# NDA/BLA Multi-Disciplinary Review and Evaluation

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| Application Type | NDA |
| Application Number(s) | 215401 |
| Priority or Standard | Standard |
| Submit Date(s) | February 22, 2021 |
| Received Date(s) | February 22, 2021 |
| PDUFA Goal Date | March 22, 2022 |
| Division/Office | Psychiatry |
| Review Completion Date | |
| Established/Proper Name | dextroamphetamine transdermal system |
| (Proposed) Trade Name | Xelstrym |
| Pharmacologic Class | CNS stimulant |
| Code name | |
| Applicant | Noven Pharmaceuticals, Inc |
| Doseage form | transdermal system |
| Applicant proposed Dosing Regimen | 4.5 mg/9 hours<br>9.0 mg/9 hours<br>13.5 mg/9 hours<br>18.0 mg/9 hours |
| Applicant Proposed Indication(s)/Population(s) | Treatment of attention deficit hyperactivity disorder in patients 6 years and older |
| Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication | 7406506008<br>Attention deficit hyperactivity disorder |
| | |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | Treatment of attention deficit hyperactivity disorder in adults and pediatric patients 6 years and older |
| Recommended SNOMED CT Indication Disease Term for each Indication (if applicable) | N/A |
| Recommended Dosing Regimen | 4.5 mg/9 hours<br>9 mg/9 hours<br>13.5 mg/9 hours<br>18 mg/9 hours |

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

# Glossary

| | |
|---|---|
| AC | advisory committee |
| ADHD | attention-deficit/hyperactivity disorder |
| ADHD-RS-IV | ADHD Rating Scale-IV |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AEDC | adverse events associated with discontinuation |
| AR | adverse reaction |
| CFR | Code of Federal Regulations |
| CGI-S | Clinical Global Impression of Severity Scale |
| CK | creatine phosphokinase |
| CSR | clinical study report |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DA | dopamine |
| d-ATS | dextroamphetamine transdermal system |
| DBP | diastolic blood pressure |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorder Fourth Edition: Text Revision |
| ECG | electrocardiogram |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| HD | high dose |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| ISS | integrated summary of safety |
| LD | low dose |
| LOU | limitation of use |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MD | mid dose |
| NDA | new drug application |
| NE | norepinephrine |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| PD | pharmacodynamic |
| PERMP | Permanent Product Measure Performance |
| PK | pharmacokinetics |
| PMR | post-marketing requirement |
| PREA | Pediatric Research Equity Act |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SI | suicidal ideation |

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|---|---|
| SI/B | suicidal ideation/behavior |
| SKAMP | Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale |
| TEAE | treatment emergent adverse event |
| WBC | white blood cell |

# 1 Executive Summary

## 1.1. Product Introduction

The Applicant has developed dextroamphetamine transdermal system (d-ATS), a central nervous system stimulant medication, for the treatment of attention-deficit/hyperactivity disorder (ADHD). d-ATS is designed to be an alternative to current oral formulations of amphetamine and as a means of providing sustained levels of dextroamphetamine while the patch is worn. The first amphetamine product was approved in 1943 for the treatment of ADHD in adults; amphetamine products are currently available in the United States and internationally in multiple oral formulations. The proposed dosage strengths formulated in a transdermal system are 4.5 mg/9 hours, 9 mg/9 hours, 13.5 mg/9 hours, and 18 mg/9 hours.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The open-label, dose-optimization and crossover, double-blind treatment, laboratory classroom study design of the submitted phase 2 efficacy and safety trial in children and adolescents ages 6 to 17 years is problematic and complicated the review of efficacy. Ultimately, however, data from the submitted study for the primary ADHD endpoint SKAMP total score was statistically significantly superior to placebo and supports an efficacy finding. Furthermore, this application relies, in part, upon the Agency's findings of efficacy for the listed drug, Vyvanse. Together, substantial evidence of effectiveness was demonstrated.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

d-ATS is a central-nervous-system (CNS) stimulant-class drug; there are multiple effective marketed stimulant drugs, including approved products with the same active moiety as d-ATS. The Applicant has submitted adequate data to establish a scientific bridge to two listed drugs, Adderall XR and Vyvanse, and can rely in part on the previous Agency finding of safety for Adderall XR and Vyvanse, and effectiveness for Vyvanse, both of which are approved for the treatment of ADHD in the entire proposed age range. In addition, the Applicant submitted one efficacy study that demonstrated a benefit in patients aged 6 to 17 years with ADHD. The systemic safety evaluation of d-ATS largely relies on the listed drugs as no long-term safety data were submitted. The Applicant submitted local safety data that revealed formulation-specific clinically significant irritation and contact sensitization, which will be described in the prescribing information. There were use errors identified in the originally submitted human factors (HF) validation study that necessitated changes to the user interface and an additional HF validation study to be conducted and submitted prior to product approval. The benefits of this product for patients aged 6 and older with ADHD outweigh the risks. Like the listed drug, use in 4 and 5-year olds is not recommended based on systemic safety concerns.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood, with a lifetime prevalence in the pediatric population of around 11%.<br>• ADHD typically presents in early school years and is characterized by in attention, hyperactivity, and impulsivity.<br>• Symptoms often continue into adulthood with a current estimated prevalence of 4%.<br>• To meet diagnostic criteria, symptoms must impair academic, social, or occupational activities. | • ADHD is a prevalent condition that can substantially compromise academic and work performance and can impair social development and relationships without treatment. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Current Treatment Options | • Behavioral interventions are preferred to medication as the initial intervention for preschool children with ADHD and are adjuncts to medication for school-aged children and adolescents.<br>• There are drug products approved for the treatment of ADHD in several drug classes: stimulants, selective norepinephrine reuptake inhibitors, and alpha-2-adrenergic agonists.<br>• There is one approved transdermal system product for the treatment of ADHD: Daytrana (methylphenidate transdermal system).<br>• Stimulant products vary by time to therapeutic onset, duration of action, or both; these differences are tightly linked to differences in their PK profiles.<br>• Some products require more than one dose per day because of a short duration of action.<br>• Response rates to currently available stimulants are high (estimated to be 70 to 80 percent).<br>• There are important risks associated with stimulants including nonmedical use, abuse, and addiction, serious cardiovascular. events, and growth suppression and weight loss in pediatric patients<br>• In addition to the other risks of stimulants, Daytrana carries formulation-specific warnings for chemical leukoderma and contact sensitization. | • There are effective treatments available for the treatment of ADHD, including approved drug products from multiple drug classes and many drug products in the stimulant drug class. |
| Benefit | • The Applicant submitted data to demonstrate that d-ATS was efficacious in reducing ADHD symptoms in a single laboratory classroom study in pediatric patients 6 to 17 years of age.<br>• The Applicant is relying, in part, on the previous Agency finding of effectiveness for the listed drug Vyvanse based on the results of a comparative bioavailability study between d-ATS and | • The benefit of d-ATS in the treatment of ADHD in pediatric patients age 6 and older and in adults has been established through efficacy data from a single clinical trial and pharmacokinetic data bridging to a listed drug. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | Vyvanse. Vyvanse is approved for the treatment of ADHD in the entire proposed age range: pediatric patients ages 6 and up and adults.<br>• The initial onset of efficacy of d-ATS was observed at 2 hours post dose.<br>• The primary efficacy analysis, which demonstrated superiority to placebo, included mean SKAMP scores up to 12 hours after patch application.<br>• The proposed starting dose in pediatric patients is supported by the submitted d-ATS efficacy data.<br>• The proposed starting dose in adults is comparable to Vyvanse. | • d-ATS adds a new route of administration and dosage form of dextroamphetamine (also referred to as d-amphetamine in this review) to the armamentarium for the treatment of ADHD.<br>• The onset and duration of effect observed in the clinical trial and based on the observed PK data are acceptable to provide a benefit for typical waking hours and support a daily dosing regimen.<br>• The proposed starting doses are acceptable for this product, which can be titrated to effect based on clinical assessments, and are supported by the submitted efficacy and pharmacokinetic data. |
| Risk and Risk Management | • The Applicant is relying on the Agency's findings of safety for the two listed drugs—Adderall XR and Vyvanse.<br>• The Applicant referenced the labeling of the listed drugs for nonclinical data including fertility and reproduction, embryofetal development, juvenile animal studies, genotoxicity, and carcinogenicity.<br>• Important risks with the stimulant class are serious cardiovascular events, increases in blook pressure, psychotic and manic symptoms, long-term suppression of growth, lowering the seizure threshold.<br>• The safety database contained no long-term safety data<br>• There is an adequate PK bridge to support reliance on the previous systemic safety findings for Vyvanse. | • Because systemic toxicities of amphetamine have been well characterized, no nonclinical toxicity studies evaluating systemic safety of d-ATS were required.<br>• The Applicant conducted nonclinical studies to evaluate product-specific safety concerns (e.g., dermal safety).<br>• The clinical safety evaluation largely relies on the previous safety finding for the listed drug Vyvanse.<br>• Considering the systemic and local safety profile of d-ATS the benefits of the |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • In short-term studies, the adverse reactions observed were consistent with the known safety profile of d-amphetamine.<br>• There was formulation-specific clinically significant irritation and contact sensitization observed in the clinical studies; there was no evidence of chemical leukoderma in the safety data.<br>• Based on the PK bridge, safety findings from the Vyvanse studies in 4- and 5-year-old patients with ADHD can be relied upon for d-ATS.<br>• The human factors validation study submitted in the original application revealed use errors that could result in much higher exposures; in response to a discipline review (DR) letter, the Applicant conducted and submitted a new HF validation study. | product outweigh the risks.<br>• The local safety findings will be described in the label.<br>• Based on the safety findings in 4- and 5-year-old patients with ADHD treated with Vyvanse, d-ATS is not recommended for this age group.<br>• Remaining areas of vulnerability identified in the new HF validation study were addressed through changes to proposed packaging, label, and labeling. |

## 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

| | | | | |
|---|---|---|---|---|
| X | **The patient experience data that were submitted as part of the application include:** | | | Section of clinical study report where discussed, if applicable |
| | X | Clinical outcome assessment (COA) data, such as | | |
| | | X | Patient reported outcome (PRO) | N25-006 CSR: 9.5.2.4. CPRS-R:S;<br>9.5.3 Dermal;<br>9.5.5. Safety Assessments (Spontaneous AE)<br>N25-002 CSR: 9.5.1.3. Dermal Evaluations;<br>9.5.1.4 Safety (Spontaneous AE)<br>N25-004 CSR: 9.5.1.14 Safety Assessments;<br>9.5.1.15 Adverse Events (Spontaneous AE)<br>N25-005 CSR: 9.5.1.4 Dermal Evaluations (Spontaneous reporting);<br>9.5.1.5 Safety Assessments (C-SSRS, Spontaneous AE)<br>N25-010 CSR: 9.5.1.7 Dermal Evaluations (Spontaneous complaints);<br>9.5.1.6 Safety Variables (C-SSRS, Spontaneous AE)<br>N25-012 CSR: 9.5.1.5 Dermal Evaluations (Spontaneous reporting)<br>N25-015 CSR: 9.5.1.7 Safety Variables<br>9.5.1.7.1 Dermal Evaluations in Clinic (Spontaneous Reaction);<br>9.5.1.7.2 Dermal Evaluations at Home<br>N25-018 CSR: 9.5.4.7. Dermal Evaluations;<br>9.5.4.12. Assessment of Adverse Events; (Spontaneous Reporting Dermal Safety);<br>9.5.2 & 11.3 Actual Use Assessments |

| | | | | |
|---|---|---|---|---|
| | | | | N25-007 CSR Section 9.5.1.1;<br>9.5.1.4 Adhesion/Water Exposure;<br>Section 11.1. Usability Assessments;<br>9.5.2 Dermal Assessments (Spontaneous reporting)<br>N25-013 CSR Section 13.1.3 Usability Assessments;<br>9.5.2/11.2 Dermal Assessments (Spontaneous reporting)<br>N25-017A CSR: Appendix D Subjective Feedback<br>N25-017B CSR: Appendix B Detailed Results and Root Cause Analysis |
| | | X | Observer reported outcome (ObsRO) | N25-006 CSR: #9.5.2.1. SKAMP;<br>9.5.2.4. CPRS-R:S<br>N25-004 CSR 9.5.1.7 SKAMP Attention and Deportment Scale<br>N25-007 CSR Section 9.5.1.1;<br>9.5.1.4 Adhesion/Water Exposure;<br>Section 11.1. Usability Assessments<br>N25-013 CSR Section 13.1.3 Usability Assessments<br>N25-017A CSR: Results<br>N25-017B CSR: Section 4 Results<br>N37-001 CSR Section 8.3 Questionnaire Results |
| | | X | Clinician reported outcome (ClinRO) | N25-006 CSR: 9.5.2.3. ADHD-RS-IV (Home Version);<br>9.5.2.5. CGI;<br>9.5.3 Dermal;<br>9.5.5. Safety Assessments<br>N25-002 CSR: 9.5.1.3. Dermal Evaluations; 9.5.1.4 Safety<br>N25-004 CSR: 9.5.1.9 Dermal Assessments;<br>9.5.1.14 Safety Assessments; |

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|---|---|---|---|---|
| | | | | 9.5.1.15 Adverse Events;<br>9.5.1.6 ADHD Rating Scale<br>N25-005 CSR: 9.5.1.4 Dermal Evaluations;<br>9.5.1.5 Safety Assessments<br>N25-010 CSR: 9.5.1.7 Dermal Evaluations<br>9.5.1.6. Safety Assessments<br>N25-012 CSR: 9.5.1.5 Dermal Evaluations;<br>9.5.1.4 Safety Variables<br>N25-015 CSR: 9.5.1.7 Safety Variables<br>9.5.1.7.1 Dermal Evaluations in Clinic;<br>9.5.1.7.3/4/5/6/7/8 Adverse Events, etc.<br>N25-018 CSR: 9.5.4.7. Dermal Evaluations<br>9.5.4.12. Assessment of Adverse Events;<br>9.1.2.3. Challenge Period<br>N25-007 CSR: 9.5.2 Dermal Evaluations<br>N25-013 CSR: 9.5.2 Dermal Assessments |
| | | X | Performance outcome (PerfO) | N25-006 CSR: 9.5.2.2. PERMP<br>N25-004 CSR 9.5.1.8 PERMP Derived Measures Test<br>N25-007 CSR 9.5.2 & 11.3 Actual Use Assessments<br>N25-013 CSR Section 13.1.3 Usability Assessments |
| | X | | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | N25-007 CSR Section 11.1 Usability Assessments;<br>9.5.2 & 11.3 Actual Use Assessments<br>N25-013 CSR Section 13.1.3 Usability Assessments<br>N25-017A and 17B Result;<br>Subject feedback<br>N25-017A CSR: Methodology; Results<br>N25-017B CSR: Methodology; Section 4 Results<br>N37-001 CSR Section 8.3 Questionnaire Results |
| | □ | | Patient-focused drug development or other stakeholder meeting summary reports | Not applicable |
| | X | | Observational survey studies designed to capture patient experience data | N25-007 CSR Section 11.1 Usability Assessments;<br>9.5.2 & 11.3 Actual Use Assessments<br>N25-013 CSR Section 13.1.3 Usability Assessments<br>N25-017A CSR: Section 3 Methodology;<br>Section 4 Results<br>N25-017B CSR: Section 3 Methodology;<br>Section 4 Results<br>N37-001 CSR Section 8.3 Questionnaire Results |
| | □ | | Natural history studies | Not applicable |
| | □ | | Patient preference studies (e.g., submitted studies or scientific publications) | Not applicable |
| | □ | | Other: (Please specify): | Not applicable |
| □ | **Patient experience data that were not submitted in the application but were considered:** | | | |
| | □ | | Input informed from participation in meetings with patient stakeholders | Not applicable |
| | □ | | Patient-focused drug development or other stakeholder meeting summary reports | Not applicable |
| | □ | | Observational survey studies designed to capture patient experience data | Not applicable |
| | □ | | Other: (Please specify): | Not applicable |
| □ | **Patient experience data was not submitted as part of this application.** | | | |

Source: Study N25-006 CSR; Study N25-007 CSR; Study N25-013 CSR; Study N25-018 CSR; Study N25-002 CSR; Study N25-004 CSR; Study N25-005 CSR; Study N25-010 CSR; Study N25-012 CSR; Study N25-015 CSR; N25-017A Pre Summative Report; N25-017B Human Factors Report; N37-001 Label Comprehension Study

Source: Applicant information amendment submitted September 7, 2021

# 2 Therapeutic Context

## 2.1. Analysis of Condition

ADHD is one of the most common psychiatric disorders affecting children and adolescents (approximately 9% or over 6 million in the United States according to a CDC survey[1]), and it affects a significant number of adults as well (anywhere from 2 to 4%).[2] The symptoms of ADHD are defined in the DSM-5 as part of two main clusters—inattention (distractibility, trouble finishing tasks, daydreaming, frequent carelessness/errors, forgetfulness) and hyperactivity/impulsivity (fidgeting, restless, chatty, always moving, blurts out answers, interrupts others, trouble waiting). There are three diagnostic subtypes of ADHD accordingly—inattentive, hyperactive/impulsive, and combined types. The condition significantly impairs daily functioning with regard to behavior, learning, and organizational skills. The symptoms contribute to low self-esteem, poor academic and work performance, and relationship stressors. Adults with ADHD have a higher risk of increased risk-taking behaviors and higher rates of criminal behavior and incarceration, driving accidents, and substance abuse.[3]

ADHD is diagnosed across all demographic groups, although more often in males and in younger children.[4] Diagnosis occurs after a careful clinical assessment of the patient that also includes additional history from parents/guardians and teachers, use of diagnostic scales and neuropsychological assessment, and a standard medical examination to rule out other factors. ADHD is diagnosed less frequently in adults than children and typically with fewer hyperactivity cluster and more inattentive cluster symptoms. Issues of psychiatric comorbidity can make ADHD diagnosis and treatment more complex in adults. ADHD is not believed to typically start in adulthood, although it may remain undiagnosed until then and there are some rare late-onset cases.[5] Adult ADHD is usually considered a continuation of a chronic syndrome that begins in childhood.[6]

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[1] https://www.cdc.gov/ncbddd/adhd/data.html
[2] Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, 2005;62(6):617-27.
[3] Goodman D. The consequence of attention-deficit/hyperactivity disorder in adults. *Journal of Psychiatric Practice*. 2007;13:318-327.
[4] http://www.chadd.org/understanding -adhd/about-adhd/data-and-statistics/general-prevalence/aspx
[5] Sibley MH, Rohde LA, et al. Late-onset ADHD reconsidered with comprehensive repeated assessments between ages 10 and 25. *Am J Psychiatry*. 2018;175(2):140-149.
[6] Li D, Sham PC, et al. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum Mol Genetics*. 2006;15:2276-2284.

Overall, ADHD has a significant impact on afflicted individuals' daily functioning, level of socioeconomic and educational attainment, and productivity and income throughout the lifespan. Although the condition is not usually acutely life-threatening, ADHD can seriously impair overall quality of life and is associated with risk-taking behaviors.

## 2.2. Analysis of Current Treatment Options

Current treatment guidelines for ADHD consider psychopharmacologic therapy to be first-line management, with psychotherapy and behavior management training as needed.

FDA has already approved numerous drugs for the treatment of ADHD, usually approved for children and adolescents ages 6 years and above. Most are not specifically labeled for adults, although they are often used off-label for that population. Only six drugs have been FDA-approved for adult ADHD: Adderall XR, Concerta, Focalin XR, Strattera, Vyvanse, and Mydayis.

The majority of FDA-approved drugs for ADHD are methylphenidate or amphetamine compounds with different formulations which yield different pharmacokinetic profiles. Amphetamine and methylphenidate-based drugs are in the stimulant class; their action is thought to be mediated via actions on dopamine (DA) and norepinephrine (NE) receptors in the brain. Methylphenidate inhibits DA and NE transporters, thereby increasing synaptic concentrations of DA and NE; amphetamine inhibits the transporters and also increases release of DA and NE from neurons.

Current stimulant-class treatments for ADHD are noted to have rapid and marked efficacy, with treatment effect sizes[7] typically larger than those for other psychiatric conditions.[8] However, symptoms in turn may also reappear once drugs are metabolized and eliminated, which is an ongoing concern with these relatively short-acting drugs and has led to the development of extended-release formulations of several stimulant-class drugs.

The main concerns and limitations with stimulant-class treatments, particularly with chronic administration, are the potential for tolerance, dependence, and waning effects over time; stimulant-class medical adverse reactions (cardiovascular and growth retardation concerns); and in some cases, concerns over variable or withdrawal effects during the course of daily administration (addressed in part by the various pharmacokinetic reformulations of previously approved drugs on the market). This class of drugs is also associated with nonmedical use, abuse, and addiction. All currently marketed stimulant-class drugs for ADHD are classified as

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[7] Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *European Child and Adolescent Psychiatry*. 2010;19(4):353-364.
[8] Huhn M, et al. Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders. *JAMA Psychiatry*. 2014; 71(6);706-715.

controlled substances under DEA Schedule II. Pemoline was Schedule IV but was removed from the United States market because of concerns about liver toxicity in 2005.

FDA-approved non-stimulant drugs for ADHD include the alpha-2 agonists such as Intuniv (guanfacine) and Kapvay (clonidine), and the NE reuptake inhibitors Strattera (atomoxetine) and Qelbree (viloxazine). Because of their mechanism of action, atomoxetine and viloxazine typically take somewhat longer to reach full effect than the stimulant-class drugs and alpha-2 agonists.

All FDA-approved ADHD drugs are available as oral formulations except for Daytrana, which is a transdermal system. Warnings and precautions specific to Daytrana's transdermal system formulation include chemical leukoderma, contact sensitization, and heat effect.

Several of these approved drugs have been or are currently being studied for preschool age populations down to age 4 years, as there is significant off-label drug use in that age group for ADHD.

Table 1: Summary of FDA-Approved Therapeutics for ADHD

| Drug | Approval Date |
|---|---|
| Desoxyn (methamphetamine hydrochloride)* | 12/31/1943 |
| Ritalin (methylphenidate hydrochloride) | 12/5/1955 |
| Adderall (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate) | 1/19/1960 |
| Cylert (pemoline)** | 1/27/1975 |
| Dexedrine Spansule (dextroamphetamine sulfate)*** | 8/2/1976 |
| Ritalin SR (methylphenidate hydrochloride) | 3/30/1982 |
| Concerta (methylphenidate hydrochloride) | 8/1/2000 |
| Metadate CD (methylphenidate hydrochloride) | 4/3/2001 |
| Adderall XR (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate) | 10/11/2001 |
| Focalin (dexmethylphenidate hydrochloride) | 11/13/2001 |
| Ritalin LA (methylphenidate hydrochloride) | 5/6/2002 |
| Strattera (atomoxetine hydrochloride) | 11/26/2002 |
| Methylin (methylphenidate hydrochloride) | 12/19/2002 |
| Focalin XR (dexmethylphenidate hydrochloride) | 5/26/2005 |
| Daytrana (methylphenidate) | 4/6/2006 |
| Vyvanse (lisdexamfetamine dimesylate) | 2/23/2007 |

| | |
|---|---|
| Intuniv (guanfacine hydrochloride) | 5/26/2005 |
| Kapvay (clonidine hydrochloride) | 9/28/2010 |
| Quillivant XR (methylphenidate hydrochloride) | 9/27/2012 |
| Aptensio XR (methylphenidate hydrochloride) | 4/17/2015 |
| Dyanavel XR (amphetamine) | 10/19/2015 |
| Quillichew ER (methylphenidate hydrochloride) | 12/4/2015 |
| Adzenys XR-ODT (amphetamine) | 1/27/2016 |
| Mydayis (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate)**** | 6/20/2017 |
| Qelbree (viloxazine) | 4/2/2021 |

*Approved for ages 12 years and older only
**Discontinued from the United States market in 2005
***Dextroamphetamine was first marketed during the pre-NDA period in 1932 as Benzedrine and in 1935 as Dexedrine
****Approved for ages 13 years and older only
Source: Reviewer-generated

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

d-ATS has not been marketed anywhere in the world. FDA has not reviewed an NDA for any other indications for d-ATS.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

- On August 29, 2006, the Division issued Preliminary Responses to pIND 73862 and conveyed the following:
  - The Division cautioned the Sponsor that the proposed 24-hour application could result in overnight insomnia and recommended a shorter application period.
  - The Division cautioned the Sponsor that transdermal absorption concentrations may not peak or begin to decrease until a few hours after patch removal, that dose dumping may occur, and warned of the potential for differential first-pass metabolism and bioavailability relative to oral formulations.
- Sponsor opened IND 073862 for the treatment of ADHD on November 1, 2006, with the protocol for Study N26-001 (a phase 1, open-label, randomized, three-treatment, three-period, six-sequence, Adderall XR comparative bioavailability study). The Division subsequently issued a Study May Proceed letter on January 8, 2007.
- On July 27, 2010, Protocol (b) (4) was placed on a full clinical hold (b) (4) Additionally, the Division recommended (b) (4) In September 2010, the Sponsor submitted a new protocol (b) (4) In October 2010, the clinical hold was removed.
- On September 7, 2011, the Sponsor submitted Protocol N25-005 (a phase 1, open-label, single-dose, randomized, three-way crossover PK study). The Division communicated the concern for a high rate of patch adherence failures (approximately 12%) from previous study results.
- The following was communicated to the Sponsor and documented in End-of-Phase 1 Meeting Minutes issued on May 2, 2012:

- The Division voiced concern for problems with d-ATS adhesion and extent of residual drug and adhesive—the Sponsor cited investigator inexperience with an early study and intended to conduct a usability study.
- The Division voiced concern for a period effect with the crossover study design.
- The short-term safety database as presented was acceptable, but the Sponsor was informed that adequacy of the long-term safety database would be contingent upon the number of patients exposed and particular safety findings of concern (e.g., dermal safety).
- The Division emphasized that at the time of NDA submission, because ADHD predominantly occurs in children and adolescents, completion of pediatric studies was required. The Division noted that an adult ADHD indication would not be approvable without evidence to support a pediatric ADHD indication because of the age distribution of ADHD and because of the risk of off-label use.

- On June 6, 2012, the Sponsor submitted Protocol N25-006 (a phase 2, randomized, double-blind, placebo-controlled, crossover laboratory classroom study to evaluate safety and efficacy in children and adolescents with ADHD). The following non-hold recommendations were communicated to the Sponsor:
  - Conduct a usability study.
  - Adopt patient-specific scales during the double-blind period to assess patch adhesion, discomfort, irritation, and residual adhesive residue—the Sponsor did not add an adhesion assessment.
  - Patients or caregivers should apply the patches on Clinical Days 42 and 49 at the prescribed times in order to fully assess real-world use—the Sponsor continued to allow application by study site staff or patients or caregivers.
- The following concernswere discussed and documented in Type C Meeting Minutes issued on February 11, 2014 regarding the results of Study N25-006 and a usability study:
  - The (b) (4) was not a pre-specified and agreed-upon key secondary endpoint and could be considered redundant with the SKAMP so would not be included in labeling.
  - The Sponsor noted a statistically significant sequence effect and, therefore, planned to base efficacy results on Period 1 data only.
  - AEs were mostly consistent with class effects although some occurred in a higher proportion of subjects compared to rates observed with oral stimulants. Dermal site AEs were very common and relatively severe in some cases, and may have been underreported as the protocol specified that skin discomfort signs or symptoms were only to be recorded as AEs if (1) they occurred at a site different from the application

site, (2) they spread significantly beyond the application site, (3) the discomfort led to subject discontinuation, or (4) the discomfort was an AE in the opinion of the investigator. The Sponsor cited more frequent assessments over a longer duration than typical and would assess multiple application sites.

- Preliminary review issues for the classroom and usability studies were identified: adhesion failures, excessive dermal application site reactions, and problems using the patch. The Sponsor proposed addressing the adhesion issue by conducting (1) a PK study utilizing an overlay reinforcement, (2) an additional usability study utilizing a Daytrana comparator arm, and (3) a PK study evaluating multiple application sites. The Division cautioned that it is unlikely that a transdermal product with overlay would receive approval.

- In a communication with the Sponsor on July 16, 2014, the Agency agreed based on the justification provided (technical difficulties and animal welfare issues) that an animal carcinogenicity study would not be required for this product.

- The following concerns were discussed and documented in the End-of-Phase 2 Meeting Minutes issued on January 14, 2016:

  - Referring to the Daytrana label in which significant increase in exposure was observed after 4 weeks of administration, the Division recommended a d-ATS 4-week multiple dose study.

  - The Sponsor agreed to evaluate the PK-exposure relationship to dermal reactions.

  - The Agency recommended instructions for use if the patch falls off, what to expect with exposure to water, and what actions to take if the patch causes irritation.

  - The Agency agreed that, in principle, the completed double-blind, placebo-controlled, randomized, crossover design analog classroom study in children and adolescents and a similar simulated workplace study in adults would be sufficient for a safety database and for filing and registration. However, due to concern for potential dermal reactions at the site of patch applications, the overall clinical program did not represent an adequate safety and efficacy package to ultimately support registration. Additionally, the Agency confirmed that if an adequate PK bridge could be established between children, adolescents, and adults, no adult efficacy trial would be necessary.

  - A statistically significant sequence effect had been noted, but the Sponsor claimed that results based only on Period 1 data were consistent with results from both periods. The Division stated that it would be a matter of review whether data from Period 2 could be included in the efficacy evaluation.

- On August 8, 2016, the Sponsor submitted an initial Pediatric Study Plan (iPSP) seeking a waiver for patients ages 0 to 3 years and deferred PK, safety, and efficacy studies for

patients ages 4 to 6 years. After the Sponsor made some suggested revisions, the Agency agreed to the iPSP in September 2016. In November 2019, the Division accepted an amended iPSP with a modified timeline.

- On October 25, 2016, the Sponsor submitted Protocol N25-015 (a randomized, multiple-dose, open-label, 4-week PK study in adults with ADHD).
- On September 16, 2019, the Sponsor submitted Protocol N25-018 (a randomized, evaluator-blinded study to evaluate skin irritation and sensitization in healthy adults), for which the Division of Dermatology and Dentistry (DDD) provided consultation.
- The following concerns were discussed and documented in pre-NDA Meeting Minutes issued on September 30, 2020:
  - For Study N25-006, the Division voiced concern for the open-label, flexible dose period prior to randomization and for the crossover study design. The Division cautioned the Sponsor that this study may not qualify as an adequate and well-controlled trial. The Sponsor proposed an integrated population pharmacodynamic (PD)-efficacy analysis using longitudinal data from Study N25-006 and established population PK modeling using all completed PK studies to aid the interpretation of efficacy and safety data from Study N25-006.
  - If an adequate scientific bridge and substantial evidence of effectiveness in pediatric patients (including an adequate assessment of onset and duration of effect) have been demonstrated, it could be reasonable to rely upon the efficacy finding from a listed drug in adults in combination with pediatric d-ATS efficacy without the need for additional adult efficacy data.
  - Because duration of effect is expected to exceed 12 hours, a long-term evaluation of growth (i.e. a 12-month safety study) in pediatric patients would be required prior to NDA submission.
- On February 22, 2021, the Division received NDA 215401. The NDA was filed on April 23, 2021 with a user fee goal date of December 22, 2021.
- On December 6, 2021, the Applicant submitted the results of a new Human Factors validation study. The Division considered this a Major Amendment and extended the goal date by 3 months to March 22, 2022.

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

The clinical investigators Drs. Waxmonsky and Wigal were inspected in support of NDA 215401. Based on the results of these inspections, the study (Protocol N25-006) appears to have been conducted adequately, and the data generated by these sites appear to be acceptable in support of the respective indication.

## 4.2. Product Quality

d-ATS contains approximately 1 mg/cm$^2$ dextroamphetamine base that delivers d-amphetamine upon application to intact skin. Each d-ATS system is composed of the following consecutive layers: (1) an oversized protective silicone-coated polyester release liner, (2) a proprietary acrylic adhesive formulation containing dextroamphetamine, and (3) a polyester and polyurethane laminate film.

Noven has developed 4 dosage strengths (4.5 mg/9 hrs, 9 mg/9 hrs, 13.5 mg/9 hrs, and 18 mg/9 hrs) of d-ATS for a 9-hr wear time within 24 hrs. The patches are compositionally equivalent, and the difference in dose is effected through a proportional increase in the surface area (cm$^2$) of the patches.

The review team identified no quality deficiencies that preclude approval. A shelf-life of 18 months is acceptable when stored at controlled room temperature 20°–25°C (68°–77° F).]

## 4.3. Clinical Microbiology

Not applicable

## 4.4. Devices and Companion Diagnostic Issues

Not applicable

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

Noven Pharmaceuticals seeks to market d-ATS for the treatment of ADHD in patients 6 years and older via the 505(b)(2) pathway relying on Adderall XR (NDA 021303) and Vyvanse (NDA 021977) as the listed drugs. The maximum recommend human dose (MRHD) is 18 mg/9 hours of application time. The site of application is changed when a new d-ATS patch is applied. The Applicant is relying on the Agency's finding of systemic safety for the listed drugs and referenced the labeling of the listed drugs for nonclinical data including fertility and reproduction, embryofetal development, juvenile animal studies, genotoxicity, and carcinogenicity. Because systemic toxicities of amphetamine have been well characterized, no nonclinical toxicity studies evaluating systemic safety of d-ATS were required.

The dermal toxicity of d-ATS was evaluated in a pivotal 9-month minipig study. The animals were treated with d-ATS at the dose of 30 mg under clinical use conditions (9 hours with site rotation) or exaggerated conditions (9 hours without site rotation or 23 hours with site rotation). Dermal irritations (i.e., erythema, edema) with histopathology findings (i.e., hyperplasia, inflammation) were noted in the epidermis or epithelium of the skin of minipigs at all treatment groups, with less effect for the animals treated for 9 hours with rotation. Although a no observed adverse effect level (NOAEL) was not identified based on the dermal irritation noted in this study, the local irritation effects are clinically monitorable and recoverable; therefore, there were no significant safety concerns.

The dermal carcinogenicity of d-ATS was not evaluated by the Applicant. It was determined that testing the clinical patch in a carcinogenicity study in rats was not feasible due to technical limitations and animal welfare issues. Therefore, the Agency agreed that a dermal carcinogenicity study for d-ATS was not required for the approval of this patch.

Three d-ATS impurities (b) (4) (b) (4) in the product formulation were above the ICH Q3B(R2) qualification thresholds. However, these impurities were adequately qualified based on the toxicology studies provided by the Applicant and these studies support the proposed specification levels for these impurities. (b) (4) were negative in valid genotoxicity tests and had no significant safety concerns identified based on a 3-month toxicity study in rats. (b) (4) was not associated with developmental structural abnormalities in rats based on an embryofetal developmental study. (b) (4) was negative for mutagenicity in a valid mouse lymphoma assay and had no significant safety concerns based on a 15-week dermal toxicity minipig study. The details of these studies are described in the review.

Based on the review and evaluation of the nonclinical data, this application can be approved from a pharmacology/toxicology perspective.

## 5.2. Referenced NDAs, BLAs, DMFs

NDA 021303, Adderall XR
NDA 021977, Vyvanse

## 5.3. Pharmacology

The Applicant relies on the PD properties as described in the labeling of the listed drug Adderall XR to support the development of dextroamphetamine transdermal system (d-ATS) for attention deficit hyperactivity disorder (ADHD); therefore, nonclinical pharmacology studies were not conducted. According to the labeling of Adderall XR and published scientific literature, amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

## 5.4. ADME/PK

No absorption, distribution, metabolism, or excretion studies were conducted.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>TK data from general toxicology studies<br><br>A 28-day Toxicity Study of Amphetamine Transdermal System (ATS) in Minipigs with a 16-day Recovery Period (Study No. 20012270, GLP)</td><td><u>Minipig</u><br>$T_{1/2}$: approximately 4-8 hours, no sex differences.<br>Accumulation: not determined because of the variability of the data.<br>Dose proportionality: exposure more than proportional for males; less than proportional for females.<br><br>Table 2 TK Parameters of Amphetamine in the 28-Day Minipig Study
<table>
<tr><th>Dose (mg)</th><th>Day</th><th>Sex</th><th>Cmax (ng/mL)</th><th>Tmax (hr)</th><th>T½ (hr)</th><th>AUCt (ng•hr/ml)</th><th>AUC∞ (ng•hr/ml)</th></tr>
<tr><td rowspan="8">10.8</td><td rowspan="2">1</td><td>M</td><td>21.9</td><td>7.00</td><td>8.17</td><td>296.9</td><td>306.5</td></tr>
<tr><td>F</td><td>18.0</td><td>9.00</td><td>6.58</td><td>250.3</td><td>247.0</td></tr>
<tr><td rowspan="2">14</td><td>M</td><td>12.7</td><td>5.00</td><td>6.08</td><td>113.6</td><td>129.9</td></tr>
<tr><td>F</td><td>52.4</td><td>4.00</td><td>4.17</td><td>460.0</td><td>517.4</td></tr>
<tr><td rowspan="2">28</td><td>M</td><td>55.0</td><td>4.00</td><td>4.36</td><td>420.6</td><td>433.9</td></tr>
<tr><td>F</td><td>36.4</td><td>5.00</td><td>5.22</td><td>391.6</td><td>416.1</td></tr>
<tr><td rowspan="8">29.6</td><td rowspan="2">1</td><td>M</td><td>92.8</td><td>7.00</td><td>6.32</td><td>1246</td><td>1581</td></tr>
<tr><td>F</td><td>39.9</td><td>6.00</td><td>5.67</td><td>499.6</td><td>284.2</td></tr>
<tr><td rowspan="2">14</td><td>M</td><td>141</td><td>4.00</td><td>4.14</td><td>1103</td><td>1135</td></tr>
<tr><td>F</td><td>192</td><td>4.00</td><td>4.01</td><td>1143</td><td>1163</td></tr>
<tr><td rowspan="2">28</td><td>M</td><td>99.4</td><td>4.00</td><td>5.36</td><td>897.7</td><td>953.7</td></tr>
<tr><td>F</td><td>84.3</td><td>4.00</td><td>4.30</td><td>860.3</td><td>890.4</td></tr>
</table>
Source: 2.6.4. Pharmacokinetics Written Summary Table 2, p. 10</td></tr>
<tr><td>A 9-Month Study by Dermal Administration in Minipigs with a 3-Month Recovery Period (Study No. 20012717, GLP)</td><td>No TK evaluations were conducted with d-ATS in the 9-month study. Amphetamine plasma levels were measured to confirm the exposure in minipigs.</td></tr>
</table>

| Type of Study | Major Findings |
|---|---|
| TK data from reproductive toxicology studies<br><br>An Embryo-Fetal development Study of (b) (4) (b) (4) by IV Administration in Rats (Study No. 20041513, GLP) | Reproductive toxicology studies for d-ATS were not conducted.<br><br>No TK evaluations were conducted with (b) (4) in the EFD study. The plasma levels of (b) (4) were measured at gestational day (GD) 17 to confirm the exposure in rats. Highest concentration (19967 ng/ml) in plasma at a dose of 20 mg/kg was noted 0.5 hour post-dose and declined at 1 hour (16333 ng/mL) and 8 hours (2313 ng/ml) post-dose. |

## 5.5. Toxicology

### 5.5.1. General Toxicology

d-ATS was evaluated in a 9-month toxicology study in minipigs. Three impurities (b) (4) in the product formulation were above the ICH recommended limit (0.5%). (b) (4) (b) (4) were evaluated with Ames test, chromosomal aberration, a 3-month toxicity study in rat, and an embryo-fetal development (EFD) study (b) (4) (b) (4) was evaluated in a mouse lymphoma assay and a 15-week toxicity study in minipigs.

Toxicity Evaluations of Amphetamine Transdermal System

Study title/ number: A 9-Month Study of Amphetamine Transdermal System (ATS) by Dermal Administration in Minipigs with a 3-Month Recovery Period / Study No. 20012717

- Gottingen minipigs (n=4/sex/group) were treated with placebo transdermal patch or d-amphetamine transdermal patch (d-ATS) at the dose of 30 mg/29 $cm^2$ for 9 hours ± 0.5 hour (with and without site rotation) or 23 hours ± 1 hour (with site rotation) once daily for 9 months with a 3-month recovery period.

- Test article-related findings in skin including erythema, edema, blanching, and desquamation were noted at all treatment groups, with less effect for the animals treated for 9 hours with rotation.
- Test article-related histopathology findings including epithelial hyperplasia, subacute inflammation, intracorneal pustules, serocellular crusts, and ulcerations were noted in all treatment groups, with the least effects in females in which patch was applied for 9 hours with rotation, and males in which patch was applied for 23 hours with rotation. Hyperplasia was limited to animals treated for 23 hours with rotation with complete reversibility after recovery period.
- A NOAEL was not identified because of the test article-related skin findings in all treatment groups.

Conducting laboratory and location: (b) (4)
(b) (4)

GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | d-Amphetamine 30 mg/29 $cm^2$ (1.05 mg/ $cm^2$), once daily for 9 hours ± 0.5 hour (with and without site rotation, 4 sites were used over the back of the animals for this rotation) or 23 hours ± 1 hour (with site rotation); placebo control, 0 mg/29 $cm^2$ for 23 hours ± 1 hour (with site rotation) |
| Route of administration: | Transdermal |
| Formulation/Vehicle: | d-Amphetamine patch/ Placebo patch |
| Species/Strain: | Gottingen minipigs |
| Number/Sex/Group: | 4/sex/group |
| Age: | 7 months |
| Satellite groups/ unique design: | Recovery (3 months) group (2 additional animals/sex/group in control and 24-hour treated groups. |
| Deviation from study protocol affecting interpretation of results: | No |

| Parameters | Major findings |
|---|---|
| Mortality | No treatment-related deaths were noted.<br><br>One female treated for 9 hours with rotation of the site was euthanized moribund on Day 78. The animal was noted with multiple dark area (petechiae) through the body which correlated with thrombocytopenia, foci of hemorrhage in the treated and untreated skin. The death seems to be related to Thrombocytopenic Purpura Syndrome (TPS) according to the Applicant. An increase of the numbers of apoptotic megakaryocytes is likely a degenerative change with TPS. The scabs noted in the treated skin from this animal were also noted in other surviving animals and it is likely that this death is not related to the skin findings. |
| Clinical Signs | Decreased activity and impaired mobility was noted in both males (1/4) and females (2/4) in animals treated for 23 hours with site rotation. Other sporadic findings (decreased food consumption, abnormal feces, hoof abnormalities, dark material around face and on the skin) were not treatment related. |
| Body Weights | No treatment-related body weight changes |
| Ophthalmoscopy | Not evaluated for test article-effects |
| ECG | Not evaluated for test article-effects |
| Hematology | No remarkable findings |
| Clinical Chemistry | No remarkable findings |
| Gross Pathology | Scabs were noted in one male and three females with d-ATS patch for 9 hours without rotation, one female with d-ATS patch for 9 hours with rotation, and one male with d-ATS patch for 23 hours with rotation. Scabs correlated with minimal to moderate serocellular crusts, intracorneal pustules, epithelial hyperplasia, ulceration, and/or subacute inflammation in histopathology. Dark areas were noted in the treated skin sites for two females (one 9 hours with rotation and one 9 hours without rotation). Refer to Table 3 below. |
| Organ Weights | Not evaluated |

| | |
|---|---|
| Histopathology<br>Adequate battery: Yes | Refer to Table 4 below.<br><br>Epithelial hyperplasia was noted in females treated with the d-ATS patch for 9 hours with and without rotation (4/4 animals: 2 minimal, 1 mild, 1 moderate), females treated for 9 hours with rotation (3/4 animals: 1 minimal, 2 mild), and females treated for 23 hours with rotation (2/4 animals: 1 minimal, 1 mild).<br><br>Epithelial hyperplasia was also noted in males with the d-ATS patch treated for 9 hours without rotation (2/4 animals: 1 minimal, 1 mild), males treated for 9 hours with rotation (4/4 animals: 4 minimal), and males treated for 23 hours with rotation (3/4 animals: 1 minimal, 2 mild). At the end of the recovery period, minimal hyperplasia was noted in 1/2 males and 2/2 females in the 24-hour treated group; however, it should be noted that no evaluation was conducted for the 9-hour treatment groups with or without rotation for either males or females.<br><br>Subacute inflammation was noted in both males and females treated with the d-ATS patch. Higher incidence and severity were observed in females treated for 9 hours without rotation (4/4 females: 1 minimal, 3 mild), compared to females treated for 9 hours with rotation (3/4 females: 1 minimal, 2 mild), and females treated for 23 hours with rotation (3/4 females: 2 minimal, 1 mild).<br><br>Higher incidence and severity of subacute inflammation were observed in males treated 23 hours with rotation (3/4 males: 1 minimal, 2 mild) compared to males treated for 9 hours without rotation (2/4 males: 1 minimal, 1 mild), and males treated for 9 hours with rotation (1/4 males: minimal).<br><br>Intracorneal pustules, serocellular crusts, and ulcerations were also noted with a similar pattern. |

| | |
|---|---|
| *Dermal Scoring* | Erythema with increased severity (up to grade 4) and edema (up to grade 2) were noted in animals treated for 23 hours with rotation and for 9 hours without rotation with comparable results, but with less severity in animals treated for 9 hours with rotation. Similar observation and trend were also noted for eschar (grades 1-3), desquamation, and blanching in the treatment groups.<br><br>Erythema (grade 1) was noted in some animals treated with the patch for 23 hours with rotation (1/2 male, 1/2 female) during the recovery period, indicating it was not completely recovered. It should be noted that animals treated for 9 hours with or without rotation were not evaluated. |

Table 3 Gross Pathological Effect of d-ATS in 9-Month Minipig Study

Summary of Gross Pathology Findings – Scheduled Euthanasia (Day 275)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| **Concentration (mg/cm$^2$)** | **0** | **1.05** | **1.05** | **1.05** | **0** | **1.05** | **1.05** | **1.05** |
| **Dose application time** | **22 to 24 hours, rotated site** | **8.5 to 9.5 hours, rotated site** | **8.5 to 9.5 hours, same site** | **22 to 24 hours, rotated site** | **22 to 24 hours, rotated site** | **8.5 to 9.5 hours, rotated site** | **8.5 to 9.5 hours, same site** | **22 to 24 hours, rotated site** |
| **No. Animals Examined** | **4** | **4** | **4** | **4** | **4** | **3[a]** | **4** | **4** |
| **Skin, treated (No. Examined)** | **4** | **4** | **4** | **4** | **4** | **3[a]** | **4** | **4** |
| Area dark | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Scab | 0 | 0 | 1 | 1 | 0 | 1 | 3 | 0 |

[a] Female Animal No. S5299382 euthanized moribund on Day 78 excluded from this table.

*Source: Applicant's Table, Study No. 20012717, p. 29*

Table 4 Histopathological Effect of d-ATS in 9-Month Minipig Study (Treatment Phase)

Summary of Microscopic Findings – Scheduled Euthanasia (Day 275)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| **Concentration (mg/cm$^2$)** | **0** | **1.05** | **1.05** | **1.05** | **0** | **1.05** | **1.05** | **1.05** |
| **Dose application time** | **22 to 24 hours, rotated site** | **8.5 to 9.5 hours, rotated site** | **8.5 to 9.5 hours, same site** | **22 to 24 hours, rotated site** | **22 to 24 hours, rotated site** | **8.5 to 9.5 hours, rotated site** | **8.5 to 9.5 hours, same site** | **22 to 24 hours, rotated site** |
| **No. Animals Examined** | **4** | **4** | **4** | **4** | **4** | **3[a]** | **4** | **4** |
| **Treated skin (No. Examined)** | **4** | **4** | **4** | **4** | **4** | **3[a]** | **4** | **4** |
| Hyperplasia, epithelial | (0)[b] | (4) | (2) | (3) | (0) | (3) | (4) | (2) |
| Minimal | 0 | 4 | 1 | 1 | 0 | 1 | 2 | 1 |
| Mild | 0 | 0 | 1 | 2 | 0 | 2 | 1 | 1 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Inflammation, subacute | (0) | (1) | (2) | (3) | (0) | (3) | (4) | (3) |
| Minimal | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 2 |
| Mild | 0 | 0 | 1 | 2 | 0 | 2 | 3 | 1 |
| Pustules, intracorneal | (0) | (1) | (1) | (2) | (0) | (1) | (3) | (2) |
| Minimal | 0 | 1 | 1 | 2 | 0 | 1 | 3 | 2 |
| Serocellular crusts | (0) | (0) | (0) | (1) | (0) | (1) | (3) | (1) |
| Mild | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 3 | 0 |
| Ulceration | (0) | (0) | (0) | (1) | (0) | (1) | (2) | (0) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |

[a] Female Animal No. S5299382 euthanized moribund on Day 78 excluded from this table.
[b] Numbers in parentheses represent the number of animals with the finding.

*Source: Applicant's Table, Study No. 20012717, p. 30*

Study title/ number: A 28-Day Toxicity Study of Amphetamine Transdermal System (ATS) in Minipigs with a 16-Day Recovery Period/ Study No. 20012270

- Gottingen minipigs (n=4/sex/group) were treated with placebo transdermal patch or d-amphetamine transdermal patch (d-ATS) at doses of 10.8 mg (11 cm$^2$ patch), 29.6 mg (29 cm$^2$ patch) for 22 hours ± 1 hour once daily for 28 days with a 16-day recovery period. The dose selection was based on 1-5 times the clinical pediatric doses.
- Test article-related clinical signs including increased activity and rubbing/ scratching were noted at 29.6 mg and 10.8 mg.
- Dermal tox: Dermal irritation observed for d-ATS at 10.8 mg and 29.6 mg. Gross pathology findings of darkened areas, flaking, and scabs at the site of d-ATS application were correlated to erythema, desquamation, and/or eschar, and dose-related microscopic changes of minimal to moderate subacute inflammation, parakeratotic hyperkeratosis, erosion, ulceration, epithelial

necrosis, and/or edema at the end of the main phase. The NOAEL was not determined for local toxicity.

Conducting laboratory and location: [redacted], [redacted]

GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 10.8 mg/11 $cm^2$, 29.6 mg/29 $cm^2$ (1.05 mg/ $cm^2$) once daily; placebo control, 0 mg/29 $cm^2$ |
| Route of administration: | Transdermal |
| Formulation/Vehicle: | d-Amphetamine patch/ Placebo patch |
| Species/Strain: | Gottingen minipigs |
| Number/Sex/Group: | 4/sex/group |
| Age: | 7 months |
| Satellite groups/ unique design: | Recovery (16 days) group (2 additional animals/sex/group in control and HD groups). |
| Deviation from study protocol affecting interpretation of results: | No |

Toxicity Evaluation of Impurities

Study title/ number: A 28-day Study of [redacted] by Intravenous Administration in Rats with a 14-Day Recovery Period/ Study No. 20041221

- Sprague Dawley rats (n=10/sex/group) were intravenously treated with vehicle phosphate buffered saline or [redacted] at the doses of 2 (LD; low dose), 10 (MD; mid dose), 20 mg/kg/day (HD; high dose) once daily for 28 days with a 14-day recovery period.
- A test article-related increase of the average severity of hyaline droplet accumulation in kidney was noted in MD and HD males and without recovery.
- Acute perivascular inflammation, subacute perivascular inflammation, and endothelial necrosis of the vein were noted for HD animals.
- A NOAEL was determined to be 2 mg/kg/day based on the kidney findings at ≥10 mg/kg.

Conducting laboratory and location: [redacted], [redacted]

GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 0, 2, 10, 20 mg/kg/day |

| | |
|---|---|
| Route of administration: | Intravenous |
| Formulation/Vehicle: | [redacted] (b) (4) (batch AN 209-57, 100% purity) / Phosphate Buffered Saline |
| Species/Strain: | Sprague Dawley rats /Crl:CD |
| Number/Sex/Group: | 10/sex/group |
| Age: | months |
| Satellite groups/ unique design: | Recovery group (5 additional animals/sex/group in control and the HD group; Tk group (3/sex/group) |
| Deviation from study protocol affecting interpretation of results: | No (test article characterization by manufacture following by the GMP) |

Observations and Results: changes from control

| Parameters | Major findings |
|---|---|
| Mortality | No treatment-related deaths were noted. |
| Clinical Signs | No treatment-related clinical signs were noted. |
| Body Weights and Food Consumption | An increase in body weight was noted in the LD males (12%), MD males (8%), LD females (7%), and MD females (8%). This correlated to increased food consumption in LD and MD males and females. However, no significant effect was noted for HD rats. |
| Clinical Chemistry | No remarkable findings |
| Gross Pathology | No remarkable findings |
| Organ Weights | Not remarkable findings |
| Histopathology<br>Adequate battery: Not full battery | A test article-related increase in the average severity of hyaline droplet accumulation in kidney was noted in MD and HD males (refer to Table 5). According to the Applicant, the possibility of α2u-globulin nephropathy was excluded because the accumulated material did not stain for α2u-globulin protein by immunohistochemistry. In addition, this lesion was not fully recovered after the recovery phase (5/5 in HD males: 2 minimal, 3 mild). It is not clear why such a finding was seen only in males and not in females if it was related to the impurity. As such, the significance of this finding to humans is not clear. Acute perivascular inflammation, subacute perivascular inflammation, and endothelial necrosis of the vein were noted for HD animals. |

Table 5 Effect of [redacted] on Kidney in 28-Days Study

| | Males | | | |
|---|---|---|---|---|
| **Group** | 1 | 2 | 3 | 4 |
| **Dose (mg/kg/day)** | 0 | 2 | 10 | 20 |
| **No. Animals Examined** | 9 | 10 | 10 | 10 |
| **Kidney (No. Examined)** | 9 | 10 | 10 | 10 |
| Accumulation, hyaline droplet | (9)[a] | (10) | (10) | (10) |
| Minimal | 9 | 10 | 2 | 1 |
| Mild | 0 | 0 | 4 | 3 |
| Moderate | 0 | 0 | 4 | 6 |

[a] Numbers in parentheses represent the number of animals with the finding.

*Source: Applicant's Table, Study No. 20041221, p.30*

Study title/ number: A 90-day Study of Amphetamine Transdermal System (ATS) Degradants by Dermal Administration in Rats with a 28-day Recovery Period/ Study No. 20033401

- Sprague Dawley rats (n=10/sex/group) were treated with vehicle control or d-ATS degradant mixture [redacted] at a dose level of 0.5, 5, 7.5 mg/day once daily for 90 days with a 28-day recovery period.
- Test article-related decreases in body weight gain (11-15%) were noted at MD and HD males and females.
- Local irritation or trauma were noted in the treated skin at MD and HD groups although there was no clear dose-response relationship.
- A NOAEL was considered to be 0.5 mg/day [redacted] used in the study based on local irritation and decreases in body weight gain at 5 mg/day.

Conducting laboratory and location: [redacted]

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0.5, 5, 7.5 mg/day, once daily for degradant mix [redacted] (or 50, 150, 500 mg/g of total weight of the mixture)

Route of administration: Dermal by applying 0.5 ml of the dosing material on the dorsal surface of animals for 9 hours

| | |
|---|---|
| Formulation/Vehicle: | 1.5% Test Article (7.5 mg/day; a mixture of [redacted] (b) (4) and vehicle, as specified here: [redacted] (b) (4) 28.9875% Polyethylene Glycol (PEG) 300, and 67.6375% PEG 400 (by weight)<br><br>1% Test Article (5 mg/day) [redacted] (b) (4) 29.325% Polyethylene Glycol (PEG) 300, 68.425% PEG 400 (by weight)<br><br>0.1% Test Article (0.5 mg/day) [redacted] (b) (4) 29.9325% Polyethylene Glycol (PEG) 300, 69.8425% PEG 400 (by weight)<br><br>Control Article<br>70% PEG 400, 30% PEG 300 (by weight) |
| Species/Strain: | Sprague Dawley Crl:CD(SD) rats |
| Number/Sex/Group: | 10/sex/group |
| Age: | 8 weeks |
| Satellite groups/ unique design: | Recovery group (5 additional animals/sex/group in control and HD groups). |
| Deviation from study protocol affecting interpretation of results: | No |

Observations and Results: changes from control

| Parameters | Major findings |
|---|---|
| Mortality | No treatment-related deaths were noted. |
| Clinical Signs | Treatment-related excessive licking at HD in both males and females and increased activity at HD in females only. Treatment-related thin fur covering along with forepaws and forelimbs was noted at MD and HD in both males and females. |

| | |
|---|---|
| Body Weights | Treatment-related decrease in body weight gain occurred throughout the study at MD and HD starting the first week of the study in males and females. At MD in females and at HD in both males and females, an 11% to 15% decreases in body weight compared to controls was observed on Day 90. |
| Ophthalmoscopy | No test article-related findings |
| Hematology | No remarkable findings |
| Clinical Chemistry | No remarkable findings |
| Urine Analysis | No remarkable findings |
| Gross Pathology | No remarkable findings |
| Organ Weights | No remarkable findings |
| Histopathology<br>Adequate battery: Yes | Refer to Table 6 below.<br><br>Local irritation or trauma were noted in the treated skin for MD and HD groups. Mild ulceration, minimal to mild mononuclear cell inflammation, minimal to moderate acanthosis, and minimal to mild serocellular crust were noted for both males and females. |
| *Dermal Scoring* | Erythema (Grade 1) was noted throughout the dose groups with higher incidences/numbers at MD and HD groups. |

Table 6 Effect of Degradants [redacted] (b) (4) in 3-Month Rat Study

Noteworthy Findings in the Treated Skin

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| **Dose (mg/g)** | **0** | **50** | **150** | **500** | **0** | **50** | **150** | **500** |
| **No. Animals Examined** | **10[b]** | **10** | **10** | **10** | **10** | **10** | **10** | **10** |
| **Treated Skin (No. Examined)** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Ulceration | (0)[a] | (0) | (0) | (1) | (0) | (0) | (1) | (0) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Inflammation; Mononuclear cell | (0)[a] | (0) | (2) | (1) | (0) | (0) | (2) | (1) |
| Minimal | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 1 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 |
| Inflammation; Mixed cell | (0)[a] | (0) | (0) | (1) | (0) | (0) | (1) | (0) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Acanthosis | (0)[a] | (0) | (1) | (1) | (0) | (0) | (2) | (1) |
| Minimal | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Crust; Serocellular | (0)[a] | (0) | (0) | (2) | (0) | (0) | (2) | (1) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 1 |

[a] Numbers in parentheses represent the number of animals with the finding.
[b] Includes male rat (Animal No. 3472) that was found dead on Day 41.

*Source: Applicant's Table, Study No. 20033401, p. 31*

Study title/ number: A 10-day Study of Amphetamine Transdermal System (ATS) Degradants by Dermal Administration in Rats/Study No. 20035393

- Sprague Dawley rats (n=3/sex/group) were treated with vehicle control or d-ATS degradants at the dose of 2, 20, 40 mg/kg/day once daily for 22 hours/day for 10 days, followed by evaluation of clinical signs, dermal scoring, body weights, body weight changes, food consumption, and gross necropsy findings.
- Test article-related decreases in body weight gain were noted at 20 mg/kg/day in both males and females and at 40 mg/kg/day in males, weight loss was noted at 40 mg/kg/day in females. Food consumption was decreased during the first week of the study in the 40 mg/kg/day animals and in the 20 mg/kg/day females compared to the control animals and correlated with the observed decreases in weight gain and weight loss.
- Dermal irritation, consisting of slight erythema (Grade 1), was noted in one 40 mg/kg/day male on Days 2-5.

- A NOAEL was considered to be at 2 mg/kg/day (b) (4) (b) (4) based on body weight loss or a reduction in body weight gain at ≥20 mg/kg/day.

Study title/number: (b) (4) A 15-Week Dermal Toxicity Study in Minipigs with a 7-Week Interim Necropsy and a 10-Day Recovery Period/ Study No. 2506-002

- Gottingen minipigs were treated with vehicle, or (b) (4) (b) (4) a degradant (b) (4) at the dose of 0.4/0.8 mg/kg (dose increased on Day 22), or 2.0 mg/kg, or amphetamine control at 1.72 mg/kg, applied to the skin once daily for 12 hours/day for 7 weeks (interim evaluation) and 15 weeks evaluation, with a 10-day recovery period.
- Test article-related local effects (hyperplasia, inflammation, hyperkeratosis, infiltration, scabs, abrasions) were noted at 2.0 mg/kg, or amphetamine control at 1.72 mg/kg.
- A NOAEL was determined to be 0.4 mg/kg based on the histopathology findings and dermal scores.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 0.4/0.8, 2.0 mg/kg, once daily |
| Route of administration: | Dermal |
| Formulation/Vehicle: | (b) (4)<br>Positive control: amphetamine (1.72 mg/kg)<br>Vehicle: mineral oil |
| Species/Strain: | Gottingen minipigs |
| Number/Sex/Group: | 3/sex/group |
| Age: | 4.5-6 months |
| Satellite groups/ unique design: | Recovery group (2 animals/sex/group) |
| Deviation from study protocol affecting interpretation of results: | No |

| Parameters | Major findings |
|---|---|
| Mortality | No mortalities were noted. |
| Clinical Signs | Treatment-related abrasions were noted at 2.0 mg/kg [redacted] (b) (4) and 1.72 mg/day amphetamine in both males and females. Treatment-related scabbed areas and discoloration were noted at 0.4/0.8 mg/kg and 2.0 mg/kg [redacted] (b) (4) and 1.72 mg/day amphetamine in both males and females during treatment and recovery period. |
| Body Weights | No test article-related findings |
| Ophthalmoscopy | No test article-related findings |
| ECG | No test article-related findings |
| Hematology | No remarkable findings |
| Clinical Chemistry | No remarkable findings |
| Urine Analysis | No remarkable findings |
| Gross Pathology | Refer to Table 32 in the Appendix.<br><br>Gross observations of abrasion and scabs were noted on the skin at [redacted] (b) (4) (2.0 mg/kg/day) and the amphetamine group (1.72 mg/kg/day) in both males and females at interim, terminal sacrifice, and recovery groups. |
| Organ Weights | No remarkable findings |
| Histopathology<br>Adequate battery: Yes | Microscopic findings related to the administration of [redacted] (b) (4) or amphetamine were limited to the treated sites on the skin as listed in Table 33 in the Appendix . |
| *Dermal Scoring* | Slight to moderate erythema was noted in 6/8 males (5/8 slight, 1/8 moderate), and 5/8 females (slight) at 2 mg/kg/day [redacted] (b) (4) throughout the study including terminal and recovery evaluations. Scabbed areas were noted.<br><br>In contrast, slight to moderate erythema was noted in 7/8 males (4/8 moderate), and slight to severe erythema for all females for amphetamine comparator. Edema and scabs were also noted in the study. Therefore, application sites were rotated. |

### 5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Bacterial Reverse Mutation Assay (b) (4) /AD59DR.502ICH (b) (4)

Key Study Findings:

- (b) (4) was negative for mutagenicity in a valid Ames assay (plate incorporation method)

GLP compliance: Yes
Test system: *Salmonella typhimurium strains* TA98, TA100, TA1535, and TA 1537 and *Escherichia coli* strain WP2 uvrA; doses ≤ 5000 µg/plate in DMSO; +/- S9.
Study is valid: Yes

Study title/number: Bacterial Reverse Mutation Assay (b) (4) HCl/AD59DP.502ICH (b) (4)

Key Study Findings:

- (b) (4) was negative for mutagenicity in a valid Ames assay (plate incorporation method)

GLP compliance: Yes
Test system: *Salmonella typhimurium strains* TA98, TA100, TA1535, and TA 1537 and *Escherichia coli* strain WP2 uvrA; doses ≤ 5000 µg/plate in DMSO; +/- S9.
Study is valid: Yes

It should be noted that the Ames test was not conducted for the impurity (b) (4) (b) (4) Quantitative Structure-Activity Relationship (QSAR) methods were used to evaluate the in vitro mutagenicity of (b) (4) (study no. AF22YC.202 (b) (4)). (b) (4) was determined to be inactive or negative for in vitro mutagenicity. Therefore, (b) (4) was considered a non-mutagenic Class 5 impurity, and there were no concerns for mutagenicity.

In Vitro Assays in Mammalian Cells

Study title/number: In Vitro Mammalian Chromosome Aberration Assay in Human Peripheral Blood Lymphocytes (HPBL) (b) (4) /AD59DR.341ICH (b) (4)

Key Study Findings:

- (b) (4) was negative for clastogenicity in a valid *in vitro* chromosome aberration assay with human peripheral blood lymphocytes (HPBL).

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes (HPBL) cells; doses ≤ 354 µg/mL in DMSO; +/- S9.
Study is valid: Yes

Study title/number: In Vitro Mammalian Chromosome Aberration Assay in Human Peripheral Blood Lymphocytes (HPBL) (b) (4)/AD59DP.341ICH (b) (4)

Key Study Findings:

- (b) (4) was negative for clastogenicity in a valid *in vitro* chromosome aberration assay with human peripheral blood lymphocytes (HPBL).

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes (HPBL) cells; doses ≤ 371 µg/mL in DMSO; +/- S9.
Study is valid: Yes

Study title/number: In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK+/- Mouse Lymphoma Assay) (b) (4)/AF22YC.704ICH (b) (4)

Key Study Findings:

- (b) (4) was negative for clastogenicity in a valid *in vitro* chromosome aberration assay with human peripheral blood lymphocytes (HPBL).

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes (HPBL) cells; doses ≤ 314 µg/mL in DMSO; +/- S9.
Study is valid: Yes

### 5.5.3. Carcinogenicity

The dermal carcinogenicity of d-ATS was not evaluated by the Applicant. Although there were hyperplastic findings observed in the 9-month minipig study (Study #20012717), hyperplasia of the epithelium of the epidermis is not considered preneoplastic findings per the NTP non-neoplastic lesions Atlas. These histological findings are typically characterized by increased thickness of the nonkeratinized layers of the epidermis due to an increased number (layers) of the epithelial cells. This observation has been reported by a pathologist's Letter of Opinion provided by the sponsor for study 20012717. In addition, based on previous discussion with the Applicant it was determined that the use of the clinical patch for a carcinogenicity study in rats was not feasible due to technical limitations and animal welfare issues. Therefore, the Agency agreed that a dermal carcinogenicity study for d-ATS was not required for the approval of this patch.

### 5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Not conducted.

Embryo-Fetal Development

Study title/number An Embryo-fetal Development Study of [redacted] (b) (4) by Intravenous Administration in Rats /Study No. 20041513

Key Study Findings

- Sprague-Dawley pregnant rats (n=25/group) were treated with vehicle (1X phosphate buffered saline) or [redacted] (b) (4) at doses of 2 (LD), 10 (MD), and 20 (HD) mg/kg via intravenous administration once daily from day of gestation (DG) 7 to DG17. Viability, clinical signs, maternal body weights, mating performance, food consumptions, and developmental parameters [fetal sex, fetal body weights, fetal morphology (gross external, soft tissue, and skeletal abnormalities), and fetal ossification] were evaluated.
- No significant findings were noted on embryo-fetal development in the study, and the NOAEL was determined to be 20 mg/kg.

| | |
|---|---|
| Conducting laboratory and location: | [redacted] (b) (4) |
| GLP compliance: | Yes |

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 0, 2, 10, and 20 mg/kg; once daily from DG 7 to DG 17 |
| Route of administration: | intravenous injection (LD and MD group) or infusion (rate, 4 mL/min; vehicle and HD group) |
| Formulation/Vehicle: | [redacted] (b) (4) (Batch No. AN-209-57) Solution/1X phosphate buffered saline |
| Species/Strain: | Rat/Sprague-Dawley |
| Number/Sex/Group: | 25 Females/group |
| Satellite groups: | TK study- 3 females/dose |
| Study design: | Dose selection was based on a dose-range finding study in SD rats (study # 20041220) in which the NOAEL was the maximum feasible dose of 20 mg/kg (maximum concentration of the test article in the vehicle is 1 mg/ml, and the maximum allowable dose volume for intravenous administration in rats is 20 ml/kg). |
| Deviation from study protocol affecting interpretation of results: | No |

Observations and Results

| Parameters | Major findings |
|---|---|
| Mortality | No treatment-related deaths. |
| Clinical Signs | No remarkable findings. |
| Body Weights | Test article-related decrease in body weight gain was noted for HD animals, and increase in body weight gain for LD and MD animals. The decrease in body weight gain is a known effect of amphetamine; therefore, the decrease observed at the HD might be related to the pharmacological property of the test article.<br><br>LD: Body weight gains were higher at DG 7-10 (+39%) , dosing period DG 7-18 (+15%), and gestation period DG 7-21 (+9%) compared to vehicle control.<br>MD: Body weight gains were higher at DG 7-10 (+31%) , dosing period DG 7-18 (+12%), and gestation period DG 7-21 (+9%) compared to vehicle control.<br>HD: Body weight gains were lower at DG 7-10 (-18%), and gestation period DG 7-21 (-3%) compared to vehicle control. |
| Necropsy findings<br>Cesarean Section Data | There were no significant differences in the number of corpora lutea, implantation sites, percentage of preimplantation loss, litter sizes, live fetuses, dead fetuses, percentage of post implantation loss, fetal body weights (total, male or female), percentage of resorbed conceptuses per litter, and percentage of live male fetuses per litter. |
| Necropsy findings<br>Offspring | There was no effect on the percentage of fetus or litters with external, soft tissue, or skeletal abnormalities (malformation and variations) in treated animals compared to control animals. A developmental malformation in the short rib and a bifid centrum in the thoracic vertebrae were noted in one HD fetus, but these findings were considered to be of no toxicological significance due to the low incidence and they were within the historical control range. |

LD: low dose; MD: mid dose; HD: high dose

No embryofetal studies were conducted for the other impurities (b) (4)

(b) (4)

[redacted]

Prenatal and Postnatal Development
Not conducted.

### 5.5.5. Other Toxicology Studies

The Applicant conducted a dermal sensitization study in minipigs (study no. 6543-150) and primary dermal irritation studies in rabbits (Study No. 6543-145 and 6543-149) using an earlier d-ATS formulation that is different from the currently proposed clinical formulation. Sensitization reactions after a challenge were observed on the skin of minipigs with d-ATS but not the placebo patch suggesting that amphetamine is a sensitizer. Although sensitization was not tested in animals using the currently proposed clinical patch, the findings from the older version might reflect on the human experience with the currently proposed clinical patch. Both the d-ATS and placebo were slightly irritating to the skin of rabbits after 16 hours of exposure, indicating that the earlier placebo formulation likely contributes to the irritation reaction in the skin.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

d-ATS, d-amphetamine transdermal system, was submitted via a 505(b)(2) regulation pathway by Noven Pharmaceuticals for the treatment of ADHD in patients 6 years of age and older. Dextroamphetamine (also referred to as d-amphetamine in this review), a non-catecholamine sympathomimetic amine with central nervous system stimulant activity, is the active moiety. The listed drugs are Vyvanse (NDA 21977) and Adderall XR (NDA 21303). Vyvanse is a capsule formulation of lisdexamfetamine, Adderall XR is an extended-release capsule formulation of a mixture of d- and l-amphetamine. Both listed drugs are approved for the indication of ADHD in patients aged 6 years of age and older.

The safety and efficacy of d-ATS in patients with ADHD were evaluated in a laboratory classroom study (N25-006) in pediatric patients 6 to 17 years of age. The study consisted of a 5-week, open-label, stepwise dose optimization period and a 2-week, randomized, cross-over, double-blind treatment period. Given the study design deviates from the current ADHD Guidance for Developing Simulant Drugs for Treatment, pharmacokinetic (PK) bridging and population pharmacokinetic (popPK) analysis provided further support for the efficacy and safety of d-ATS.

There are a total of four pivotal clinical pharmacology studies and two popPK analyses.
*Pivotal Clinical Pharmacology Studies:*

1. A single dose relative bioavailability study comparing d-ATS to the two LDs (N25-012)
2. A single-dose dose-proportionality study in children with ADHD (N25-005)
3. A single-dose relative bioavailability study comparing five different application sites (N25-010)
4. A multiple-dose, 4-week study comparing d-ATS accumulation with/without site rotation (N25-015)

*PopPK Analyses:*

1. Population pharmacokinetic modeling and simulation of transdermal amphetamine disposition across children, adolescent, and adult patient populations (NVN0601)
2. Efficacy and safety analysis of d-ATS in children and adolescents with ADHD (NVN0601-addendum)

Note: d-Amphetamine content of d-ATS is 5 mg to 20 mg/patch; considering 90% of d-amphetamine is delivered from the transdermal system over 9 hours, the dosage strength is 4.5 mg/9 hours to 18 mg/9 hours.

Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology (OCP) has determined that there is sufficient clinical pharmacology information provided in the submission. OCP recommends the approval of d-ATS.

Per recommendation from the Office of Study Integrity and Surveillance, PK data from the pivotal relative bioavailability study can be considered acceptable.

### 6.1.1. Recommendations

| Review Issue | Recommendations and Comments |
|---|---|
| General dosing instructions | The proposed starting dose of d-ATS in pediatric patients 6 years and older is 4.5 mg/9 hours once daily in the morning. The starting dose is lower than that of the relied-upon listed drugs based on d-amphetamine equivalent dose (8.9 mg and 7.5 mg for Vyvanse and Adderall XR, respectively). The starting dose is supported by the efficacy and safety study N25-006 that 3.8 to 9.6% of the subjects stayed at 4.5 mg/9 hours after titration.<br><br>The proposed starting dose in adult patients is 9 mg/9 hours. It is comparable to the starting dose of Vyvanse (8.9 mg) and lower than the starting dose of Adderall XR (15 mg) based on d-amphetamine equivalent dose.<br><br>The proposed maximum dose of d-ATS in pediatrics and adults are 18 mg/9 hours, which are lower than the maximum dose of Vyvanse (20.8 mg) and Adderall XR (22.7 mg) based on d-amphetamine equivalent dose. After single doses, exposure of 18 mg/9 hours d-ATS was consistently lower than 20.8 mg Vyvanse. After repeated dose, exposure of 18 mg/9 hours d-ATS was lower than that of 20.8 mg Vyvanse (simulated) from 0 to 9 hours and comparable from 9 to 24 hours post-dose.<br><br>Therefore, it is appropriate. |
| Dosing in patient subgroups (intrinsic and extrinsic factors) | In subjects with severe renal impairment, maximum dose is 13.5 mg/9 hours; in subjects with end stage renal disease (ESRD), maximum dose is 9 mg/9 hours.<br><br>Monoamine oxidase inhibitors slow amphetamine metabolism, concomitant administration should be avoided.<br><br>CYP2D6 Inhibitors may increase exposure of d-ATS, initiate d-ATS with lower doses if co-administered.<br><br>Therapeutic individualization in geriatric patients is the same as that in Vyvanse. |
| Labeling | Pending satisfactory agreement with the Applicant |
| Bridge between the to-be-marketed and clinical trial formulations | The formulation used in the pivotal clinical trials was the same as the to-be-marketed formulation. |

### 6.1.2. Pharmacology and Clinical Pharmacokinetics

OCP's major findings are summarized as follows:

1. An adequate PK bridging has been established between d-ATS and the two listed drugs.
2. The concentrations of maximum dose for d-ATS 18 mg/9 hours appear to be within the approved concentration range of Vyvanse 30 to 70 mg, indicating the maximum dose of d-ATS may be effective from a PK perspective. The concentrations of initial dose for d-ATS 4.5 mg/9 hours are well below the approved concentration range of Vyvanse 30 to 70 mg. The efficacy of the initial dose is not supported by PK.
3. Though d-ATS will be initiated from a lower dose (4.5 mg/9 hours) compared to the two listed drugs, the efficacy study indicated approximately 4 to 10% of pediatric patients stayed at 4.5 mg/9 hours.
4. The initial dose of 9 mg/9 hours in adult patients would result in a 35% higher increase in $C_{max}$ and 43% higher increase in $AUC_{0-24h}$ at 4.5 mg/9 hours than pediatric patients. At the highest recommended dose of 18 mg/9 hours, pediatric patients would show 44% higher in $C_{max}$ and 39% higher in $AUC_{0-24h}$ compared to adults at the same dose level according to simulation results.
5. d-Amphetamine concentrations of Vyvanse after single doses (observed) or multiple doses (simulated) are expected to be higher than or comparable to those of d-ATS at any time point over the dosing interval. Therefore, this application can rely on FDA's finding of systemic safety for Vyvanse.
6. d-Amphetamine concentrations of Adderall XR after single doses (observed) are higher than those of d-ATS between 0 to 8 hours post dose and are lower than d-ATS between 8 to 36 hours post dose. d-amphetamine concentrations of Adderall XR after multiple doses (simulated) are consistently lower than those of d-ATS over the dosing interval. Therefore, the application for d-ATS cannot rely on FDA's finding of systemic safety for Adderall XR.
7. Five different sites were shown to have comparable exposure of d-amphetamine with a similar $T_{max}$. d-ATS can be applied to hip, upper arm, upper back, chest and flank.
8. After 4-week use of d-ATS, the exposure of d-amphetamine increased by 86 to 104% compared to that on day 1 for exaggerated use (no site rotation). In comparison, the exposure of d-amphetamine increased by 46 to 54% compared to that on day 1 for intended use (with site rotation). Application site rotation is recommended with a new transdermal system.
9. Exposure of d-amphetamine after single doses of d-ATS was found to be dose proportional from 4.5 mg/9 hours to 18 mg/9 hours.

### 6.1.3. General Dosing and Therapeutic Individualization

General Dosing

The recommended starting dose of d-ATS in pediatric patients ages 6 to 17 years is 4.5 mg/9 hours. Dosage may be adjusted in weekly increments of 4.5 mg up to a maximum dose of 18 mg/9 hours.

Recommended starting dose in adults (ages 18 years and older) is 9 mg/9 hours. Dosage may be adjusted up to a maximum dose of 18 mg/9 hours.

Apply d-ATS to the application site 2 hours before an effect is needed and remove within 9 hours after application. An effect may be seen for up to 3 hours after removing d-ATS. d-ATS may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.

Apply d-ATS to one of the following application sites: hip, upper arm, chest, upper back, or flank.

Apply the transdermal system to a different application site each time a new d-ATS transdermal system is applied to reduce dermal reactions.

Do not apply external heat sources (e.g., hair dryers, heating pads, electric blankets, heated water beds) over d-ATS. When heat is applied to d-ATS after application, the rate and the extent of absorption are increased.

Therapeutic Individualization

Dose titration, final dosage, and wear time should be individualized depending on clinical response and tolerability.

*Pediatric use*
Safety and effectiveness of d-ATS have been established in pediatric patients with ADHD ages 6 to 17 years. Safety and effectiveness of d-ATS have not been established in pediatric patients below the age of 6 years.

*Renal impairment*

Due to reduced clearance in patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 $m^2$), the maximum d-ATS dose should not exceed 13.5 mg/9 hours. The maximum recommended dose in end stage renal disease (GFR < 15 mL/min/1.73 $m^2$) patients is 9 mg/9 hours d-ATS. Dextroamphetamine is not dialyzable.

Outstanding Issues

None

## 6.2. Comprehensive Clinical Pharmacology Review

### 6.2.1. General Pharmacology and Pharmacokinetic Characteristics

<table>
<tr><td colspan="3">Pharmacology</td></tr>
<tr><td>Mechanism of Action</td><td colspan="2">Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mechanism of action of d-amphetamine in ADHD is unknown. However, Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extra-neuronal space.</td></tr>
<tr><td>Active Moieties</td><td colspan="2">Dextroamphetamine (also referred to as d-Amphetamine)</td></tr>
<tr><td>QT Prolongation</td><td colspan="2">N/A</td></tr>
<tr><td colspan="3">General Information</td></tr>
<tr><td>Bioanalysis</td><td colspan="2">d-Amphetamine concentrations were measured using LC-MS/MS methods in clinical trials. A summary of the respective method deployed in each study was included in the individual study review.</td></tr>
<tr><td>Drug exposure following the therapeutic dosing regimen</td><td colspan="2">
<table>
<tr><td colspan="3">Plasma Exposure of d-Amphetamine Following d-ATS 18 mg/9 hours Once Daily Dosing</td></tr>
<tr><td>PK Parameters</td><td>Single-dose</td><td>Multiple-dose</td></tr>
<tr><td>$C_{max}$ (ng/mL) (CV%)</td><td>50.7 (23.2)</td><td>68.8 (22.0)</td></tr>
<tr><td>$AUC_{0-24}$ (hr*ng/mL) (CV%)</td><td>791 (23.0)</td><td>1150 (25.8)</td></tr>
<tr><td colspan="3">Source: Study N25-015 CSR, Table 11-1 and 11-2.</td></tr>
</table>
</td></tr>
<tr><td rowspan="2">Maximum tolerated dose or exposure</td><td>Single Dose</td><td>N/A</td></tr>
<tr><td>Multiple Dose</td><td>N/A</td></tr>
<tr><td>Dose Proportionality</td><td colspan="2">Following a single 9-hour application of d-ATS in children with ADHD, the $C_{max}$ and AUC of d-amphetamine were dose-proportional over the dose range of 4.5 mg/9 hours to 18 mg/9 hours.</td></tr>
<tr><td>Accumulation</td><td colspan="2">Accumulation ratio: 1.46 ($C_{max}$), 1.54 (AUC)</td></tr>
<tr><td colspan="3">Absorption</td></tr>
</table>

| |
|---|
| - The amount of d-amphetamine absorbed systemically is a function of both wear time and transdermal system size.<br>- On average, approximately 90% of d-amphetamine is delivered from the transdermal system over 9 hours.<br>- $T_{max}$ (median): 6-9 hours after single patch application across different dose strengths, 6 hours after repeated application when worn up to 9 hours.<br>- The application of d-ATS to different sites (hip, upper arm, chest, upper back and flank) did not alter d-amphetamine PK.<br>- There was 86% increase in $C_{max}$ and 104% increase in $AUC_{0-24}$ when d-ATS was applied to the same site for 28 days.<br>- Application of a heating pad on d-ATS for 6 consecutive hours led to a faster absorption rate with $T_{max}$ shifted 2 hours earlier. Mean d-amphetamine exposure with a heat pad, calculated as $C_{max}$ and $AUC_{0-9}$, were about 116% and 150%, respectively, compared to that without a heating pad, indicating the apparent heat effect on d-amphetamine absorption. |
| Elimination |
| *Metabolism*<br>- Apparent $t_{1/2}$ 6.4 to 1.6 hours after patch removal.<br>- Enzymes are not fully identified, CYP2D6 is known to involved in the formation of 4-OH-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.<br>- Metabolites: 4-OH-amphetamine (active), α-OH-amphetamine or norephedrine (active).<br><br>*Excretion*<br>- Both renal and hepatic pathways.<br>- With normal urine pH, ~50% of amphetamine is excreted as derivatives of α-OH-amphetamine, 30-40% as parent drug. Urine recovery is dependent on pH, ranging from 1-75%. Remaining fraction is hepatically metabolized. |

Abbreviations: $AUC_{0-24}$ = area under the plasma concentration curve from time zero to 24 hours; $AUC_{0-9}$= area under the plasma concentration curve from time zero to 9 hours; $C_{max}$ = peak plasma concentration; LC-MS/MS = liquid chromatography with tandem mass spectrometry; LD = listed drug; $T_{1/2}$ = half-life; $T_{max}$ time to maximum concentration.

### 6.2.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes for the maximum dose and no for the initial dose.

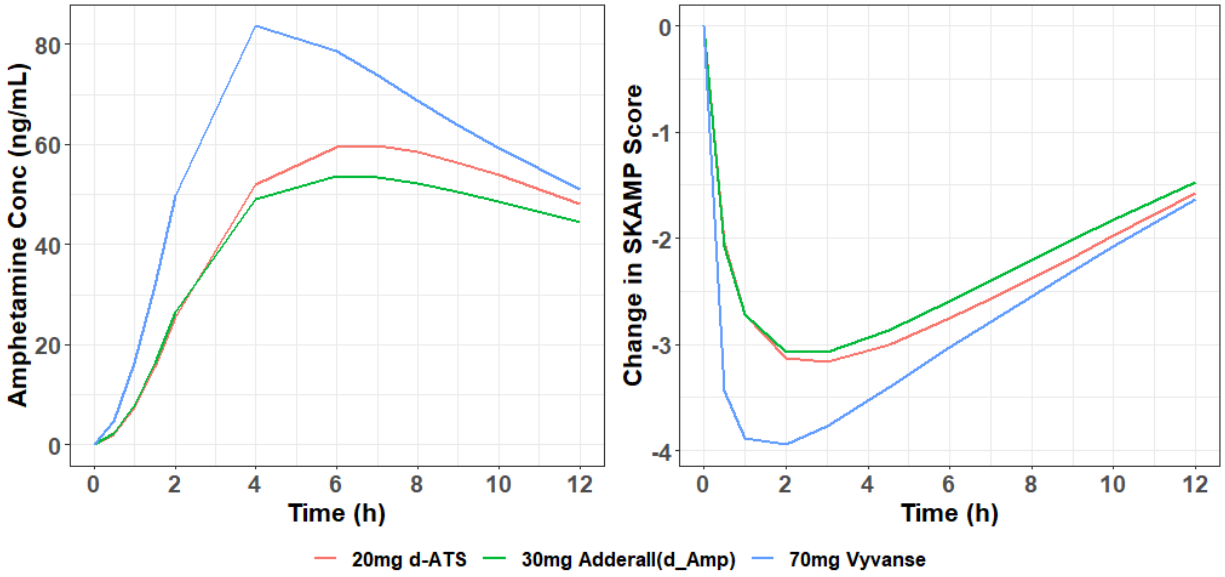
The Applicant conducted a pivotal efficacy study N25-006 that showed a statistically significant difference in decrease in mean SKAMP total score compared to placebo was observed in pediatric patients with ADHD (6 to 17 years of age). The initial onset of efficacy of d-ATS was observed at 2 hours post-dose. A carryover effect was observed, but the separation from placebo was also statistically significant in the first period. For detailed information, please refer to Statistical and Clinical Evaluation (Section 8).

The Applicant conducted an integrated population pharmacokinetic-efficacy (PK/Efficacy) analysis using d-ATS PK data from the completed clinical studies and longitudinal efficacy data from Study N25-006. The analysis was able to describe the exposure-response relationship for

d-ATS efficacy endpoint (SKAMP scores) and to characterize the onset and duration of effect in response to d-ATS administration.

The PK/Efficacy analysis suggested that Vyvanse 70 mg (eq. 20.8 mg d-amphetamine) is predicted to have the largest decrease in the SKAMP score over time, followed by d-ATS 18 mg/9 hours and Adderall XR 30 mg (eq. 22.7 mg d-amphetamine). All three products would show a maximum change in SKAMP score at 2-3 hours post dose. The maximum change in SKAMP score after administration of 18 mg/9 hours d-ATS is 80.2% of Vyvanse and 102% of Adderall XR if only d-amphetamine is considered (Figure 1). The efficacy of d-ATS is likely to be lower than Vyvanse at 70 mg but similar to Adderall XR at 30 mg considering d-amphetamine alone. It is worth noting that the efficacy of Adderall XR is attributed to both d- and l-amphetamine with exposure of 3.2:1 and based on literatures, d-amphetamine having greater or similar potency to l-amphetamine. Therefore, the efficacy of d-ATS 18 mg/9 hours cannot rely on either Vyvanse 70 mg or Adderall XR 30 mg.

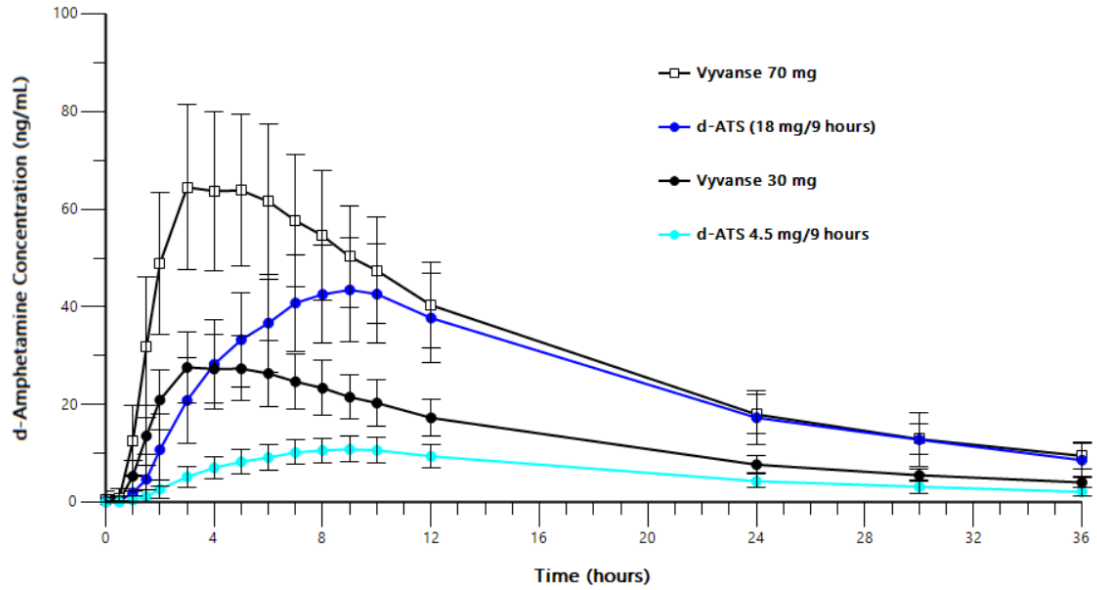
Figure 1: Simulated Concentration-time Profiles of d-Amphetamine (Left) and SKAMP Responses over Time (Right) following Single Doses of 20 mg d-ATS (18 mg/9 hours)[a], 30 mg Adderall XR (eq. 22.7 mg, d-Amphetamine) and 70 mg Vyvanse (eq.20.8 mg d-Amphetamine).




[a] d-amphetamine delivered within 9-hour wear time.
Source: Reviewer's analysis

However, d-ATS is proposed to be titrated up to the optimal dose based on individual response. The concentrations of maximum dose for d-ATS 18 mg/9 hours appear to be within the approved concentration range of Vyvanse 30 to 70 mg (Figure 2 and Table 7), indicating the maximum dose of d-ATS may be effective from a PK perspective. The concentrations of initial dose for d-ATS 4.5 mg/9 hours are well below the approved concentration range of Vyvanse 30 to 70 mg. The efficacy of the initial dose is not supported by PK. The appropriateness of proposed dosing regimen is discussed in next key question.

Figure 2: PK Profile Comparison of d-ATS 18 mg/9 hours with the Approved Dose Range of Vyvanse 30 mg to 70 mg (eq. 8.9 mg to 20.8 mg d-Amphetamine)




Source: Reviewer's analysis. Vyvanse 30 mg PK profile was generated by dose normalization of Vyvanse 70 mg and d-ATS 4.5 mg/9 hours PK profile was generated by dose normalization of d-ATS 18 mg/9 hours.

Table 7: Statistical Analysis of Mean Exposure of d-ATS Compared to the Approved Dose Range of Vyvanse 30 to 70 mg (eq. 8.9 to 20.8 mg d-Amphetamine)

| PK parameters | Vyvanse 70 mg | Vyvanse 30 mg | d-ATS 18 mg/9 hours | d-ATS 4.5 mg/9 hours |
|---|---|---|---|---|
| $AUC_{0-9}$ (ng*h/mL) | 450.3 | 193.0 | 235.8 | 58.9 |
| $AUC_{9-t}$ (ng*h/mL) | 647.0 | 277.2 | 608.6 | 152.1 |
| $AUC_{inf-obs}$ (ng*h/mL) | 1276.4 | 547.0 | 985.8 | 246.4 |
| $C_{max}$ (ng/mL) | 64.4 | 27.6 | 43.4 | 10.8 |

Source: Reviewer's analysis.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes.

d-ATS is proposed to start with 4.5 mg/9 hours in pediatrics and 9 mg/9 hours in adults. The proposed maximum dose is 18 mg/9 hours in both age groups. The equivalent d-amphetamine doses of Vyvanse and Adderall XR are shown Table 8. Vyvanse was approved from 30 to 70 mg in both pediatric and adult patients, equivalent to 8.9 to 20.8 mg d-amphetamine. Adderall XR was approved from 10 to 30 mg in pediatric patients and from 20 to 30 mg in adult patients, equivalent to 7.5 to 22.7 mg d-amphetamine and 15 to 22.7 mg, respectively. Comparing to the listed drugs, d-ATS is proposed with a relatively lower starting dose in pediatrics, while the

starting dose in adults and maximum dose in both age groups are lower than or comparable to those of Vyvanse and Adderall XR.

In Study N25-006, the pediatrics started with a dose of 4.5 mg/9 hours, may titrate up to 18 mg/9 hours based on their clinical response and tolerability. Approximtely 4 to 10% of subjects stayed at 4.5 mg/9 hours after titration and approximately 20% patients achieve the dose of 18 mg/9 hours (Table 9). Therefore, it is reasonable to initiate d-ATS from 4.5 mg/9 hours and titrate up to 18 mg/9 hours. The proposed dose range in pediatric patients is appropriate.

Table 8: Approved Doses of Listed Drugs and d-Amphetamine Equivalent Doses

| Approved/proposed doses | Pediatric Patients | | Adult Patients | |
|---|---|---|---|---|
| | Initial dose | Maximum dose | Initial dose | Maximum dose |
| Vyvanse (Lisdexamfetamine) | 30 mg (eq.8.9 mg)[a] | 70 mg (eq.20.8 mg)[a] | 30 mg (eq.8.9 mg)[a] | 70 mg (eq.20.8 mg)[a] |
| Adderall XR (*d-,l-* amphetamine) | 10 mg (eq.7.5 mg)[a] | 30 mg (eq.22.7 mg)[a] | 20 mg (eq.15.0 mg)[a] | 30 mg (eq.22.7 mg)[a] |
| d-ATS (*d*-amphetamine) | 5 mg (4.5 mg/9 hours)[b] | 20 mg (9 mg/9 hours)[b] | 10 mg (13.5 mg/9 hours)[b] | 20 mg (18 mg/9 hours)[b] |

[a] d-amphetamine equivalent dose in listed drugs.
[b] d-amphetamine dose within 9-hour wear time.
Source: Reviewer generated.

Table 9: Percentage of Pediatric Subjects at Difference Final Dose Levels (N25-006)

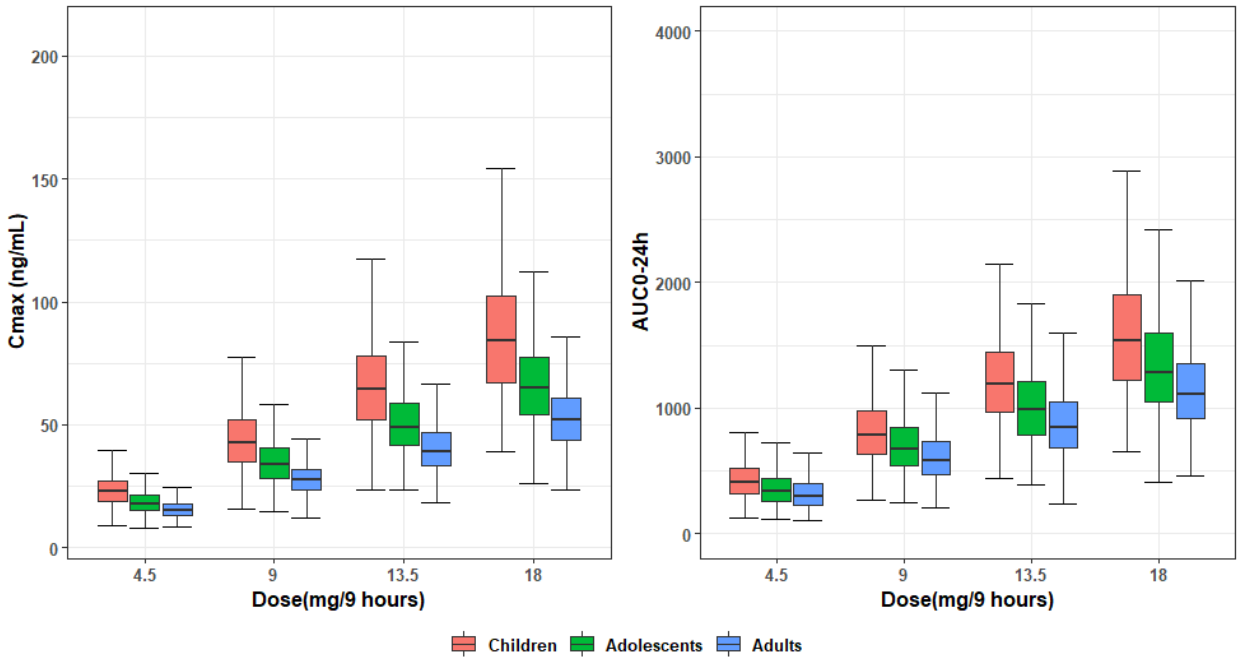
| | Percentage of subjects at different dose levels | | | |
|---|---|---|---|---|
| | 4.5 mg/9 hours | 9 mg/9 hours | 13.5 mg/9 hours | 18 mg/9 hours |
| Dose-optimization period | 6.5% | 32.7% | 39.3% | 21.5% |
| 1st Period in Double-blind phase | 3.8% | 37.7% | 37.7% | 20.8% |
| 2nd Period in Double-blind phase | 9.6% | 28.8% | 40.4% | 21.2% |

Source: Reviewer generated.

Figure 3 shows the simulated exposure for the three age groups at doses 4.5 mg/9 hours, 9 mg/9 hours, 13.5 mg/9 hours, 18 mg/9 hours. The findings suggest that an initial dose of 9 mg/9 hours in adult patients would result in 35% higher $C_{max}$ and 43% higher $AUC_{0-24h}$ than the initial dose of 4.5 mg/9 hours in pediatric patients. At the highest recommended dose of 18 mg/9 hours, pediatric patients would show 44% increase in $C_{max}$ and 39% increase in $AUC_{0-24h}$ compared to adults at the same dose level. The exposure differences are not considered significant, therefore, the proposed dose in adults is appropriate.

Overall, the PK data, efficacy and safety findings from Study N25-006, and efficacy and safety information of the two listed drugs support the recommended starting and maintenance doses in adults and pediatric patients.

Figure 3: Simulated d-Amphetamine $C_{max}$ and $AUC_{0-24h}$ with d-ATS by Dose Level in Children, Adolescents, and Adults




Source: Reviewer's analysis

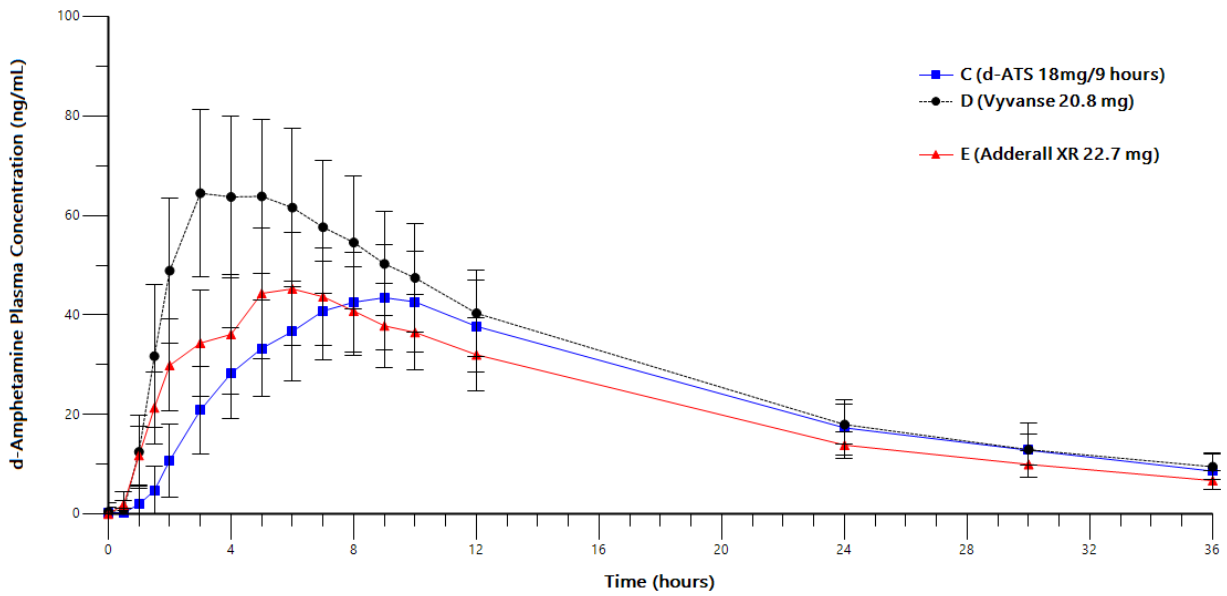
Is the safety of d-ATS supported by clinical pharmacology findings?

Yes.

The Applicant has submitted short-term safety data, but not long-term safety data, and would like to rely on the safety findings of Vyvanse and Adderall XR based on a PK bridge.

A relative bioavailability study (N25-012, part 2) was conducted to establish a PK bridge between d-ATS and Vyvanse/Adderall XR. Based on the PK profiles of d-amphetamine (Figure 4), d-ATS $AUC_{9-t}$ was 122.7% (115.5%, 130.4%) compared to that of Adderall XR (Table 10). As a CNS stimulant with a strong exposure-response relationship for systemic safety, it raises concerns as a higher exposure of d-amphetamine would probably result in a higher incidence of adverse events, such as loss of appetite and insomnia in pediatrics. There is insufficient information to conclude whether the higher exposure is clinically significant, therefore, systemic safety of d-ATS cannot rely on Adderall XR. Concentrations of d-amphetamine after d-ATS are below those of Vyvanse from 0 to 24 hours, and similar from 24 to 36 hours. Therefore, systemic safety of d-ATS may rely on Vyvanse.

Figure 4: Mean (±SD) Plasma d-Amphetamine Concentration-time Profile by Treatment (Study N25-012, Part 2)




Doses shown for Vyvanse and Adderall XR are d-amphetamine equivalent doses.
Source: Reviewer's analysis

Table 10: Summary of Statistical Analysis of Relative d-Amphetamine Exposure from d-ATS and Oral Listed Drugs at the Highest Marketed Doses (Study N25-012, Part 2)

| Exposure | Treatment | N | LS GeoMean | LS GeoMean Ratio | |
|---|---|---|---|---|---|
| | | | | Treatment Comparison | Ratio % |
| $C_{max}$ (ng/mL) | d-ATS | 15 | 43.5 | N/A | N/A |
| | Vyvanse | 17 | 65.4 | d-ATS/Vyvanse | 66.6 (62.1, 71.3) |
| | Adderall XR | 15 | 45.8 | d-ATS/Adderall XR | 94.9 (88.5, 101.8) |
| $AUC_{0-9}$ (ng.hr/mL) | d-ATS | 15 | 226 | N/A | N/A |
| | Vyvanse | 17 | 436 | d-ATS/Vyvanse | 51.9 (46.8, 57.5) |
| | Adderall XR | 15 | 293 | d-ATS/Adderall XR | 77.2 (69.4, 85.8) |
| $AUC_{9-t}$ (ng.hr/mL) | d-ATS | 15 | 598 | N/A | N/A |
| | Vyvanse | 17 | 647 | d-ATS/Vyvanse | 92.4 (87.2, 98.0) |
| | Adderall XR | 15 | 487 | d-ATS/Adderall XR | 122.7 (115.5, 130.4) |
| $AUC_{0-t}$ (ng.hr/mL) | d-ATS | 15 | 822 | N/A | N/A |
| | Vyvanse | 17 | 1070 | d-ATS/Vyvanse | 77.0 (72.5, 81.9) |
| | Adderall XR | 15 | 776 | d-ATS/Adderall XR | 105.8 (99.5, 112.6) |
| $AUC_{0-inf}$ (ng.hr/mL) | d-ATS | 15 | 963 | N/A | N/A |
| | Vyvanse | 17 | 1230 | d-ATS/Vyvanse | 78.6 (73.1, 84.5) |
| | Adderall XR | 15 | 882 | d-ATS/Adderall XR | 109.2 (101.4, 117.6) |

[a] Treatments were single dose of d-ATS 18 mg/9 hours patch, Vyvanse 70 mg (eq. 22.7 mg d-amphetamine) oral capsule, and Adderall XR 30 mg (eq. 20.8 mg d-amphetamine) oral extended-release capsule.
Source: Reviewer's analysis.

An unexplained high accumulation was observed after 28-day use for another methylphenidate transdermal product. There were concerns that d-ATS would behave similarly. Therefore, a multiple-dose PK study N25-015 was conducted. In this study, adults with ADHD received d-ATS

18 mg/9 hours for 28 days with and without site rotation. Exposure of *d*-amphetamine on Day 28 was compared with that on Day 1. Similar to another methylphenidate transdermal product, a slightly higher accumulation was observed. The theoretical accumulation ratio is 1.2 to 1.3, while the observed accumulation ratio for d-ATS with site rotation was 1.46 to 1.54 (Table 11).

Table 11: Summary Statistics of d-Amphetamine Plasma PK Parameters with Site Rotation (Group A) on Day 1 and Day 28.

| Parameter (Units) | Mean (CV%) | |
|---|---|---|
| | Day 1 | Day 28 |
| | Group A (N=15) | Group A (N=15) |
| $C_{max}$ (ng/mL) | 50.7 (23.2) | 68.8 (22.0) |
| $AUC_{0-24}$ (ng*h/mL) | 797 (23.0) | 1147 (25.8) |
| $R_{theor}$ | N/A | 1.24 (6.9) |
| AR based on $C_{max}$ | N/A | 1.46 (10.4) |
| AR based on $AUC_{0-24}$ | N/A | 1.54 (15.6) |

Source: Adopted from Study N25-015 CSR, Table 11-1 and 11-2.

We do not have multiple-dose PK information of the listed drugs in this submission. Therefore, a direct comparison to determine the relative exposure of d-amphetamine from d-ATS and Vyvanse at steady state was not available. A cross-study comparison is not optimal, but could shed some light. Exposures of Vyvanse and Adderall XR at steady state were simulated and compared with the exposure of d-ATS from study N25-012 (Figure 5 and Table 12). Adderall XR shows a lower d-amphetamine exposure than d-ATS at steady state. Exposure of Vyvanse remains higher than that of d-ATS for the first 9 hours and is similar from 9 to 24 hours post dose at steady state.

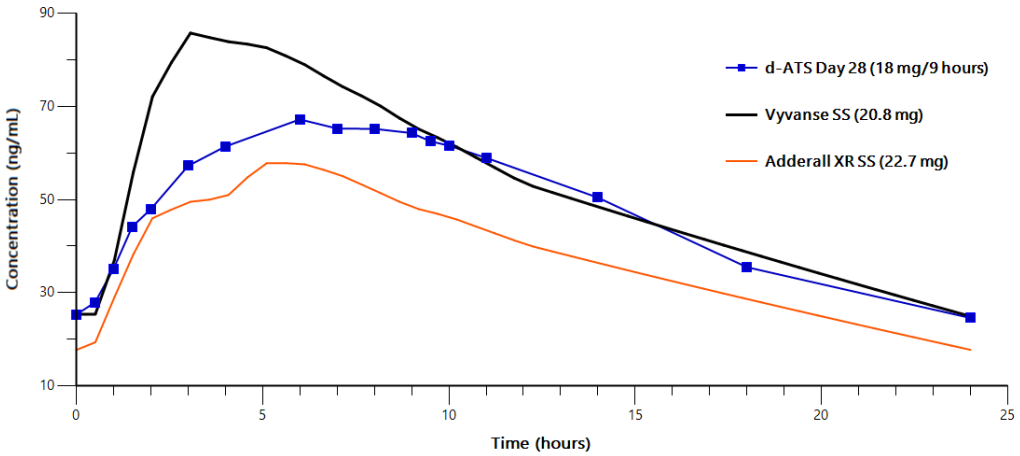
Overall, it is concluded that systemic safety of d-ATS after single or multiple doses may rely on Vyvanse from a PK perspective.

Table 12: Plasma Exposure of d-Amphetamine on Day 28 after Multiple Doses of d-ATS (N25-015, Group A), Steady State of Vyvanse (Simulated) and Steady State of Adderall XR (Simulated).

| | Vyvanse at Steady State at 70 mg[a] | d-ATS Day28 at 18 mg/9 hours[b] | Adderall XR at Steady State at 30 mg[a] |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 84.46 | 68.7 | 57.8 |
| $AUC_{0-9}$ (ng*h/mL) | 620 | 508 | 428 |
| $AUC_{9-24}$ (ng*h/mL) | 629 | 639 | 480 |
| $AUC_{12-24}$ (ng*h/mL) | 451 | 458 | 479 |
| $AUC_{0-24}$ (ng*h/mL) | 1249 | 1147 | 908 |

[a] Steady state was simulated using single-dose data from study N25-012. Vyvanse 70 mg is equivalent to 20.8 mg d-amphetamine, Adderall XR 30 mg is equivalent to approximately 22.7 mg d-amphetamine.
[b]d-Amphetamine dose with 9-hour wear time
Source: Reviewer's analysis

Figure 5: Plasma d-Amphetamine Concentration-time Profiles at Steady State after d-ATS 18 mg/9 hours (Day 28 with Site Rotation, Blue), Vyvanse 70 mg (eq. 20.8 mg d-Amphetamine, Black) and Adderall XR 30 (eq. 22.7 mg d-Amphetamine, Red)[a].




[a] d-ATS data from N25-015, Vyvanse and Adderall XR steady state were simulated with data from N25-012. Doses shown are d-amphetamine equivalent doses.
Vyvanse SS is Vyvanse at steady state, Adderall XR SS=Adderall XR at steady state
Source: Reviewer's analysis

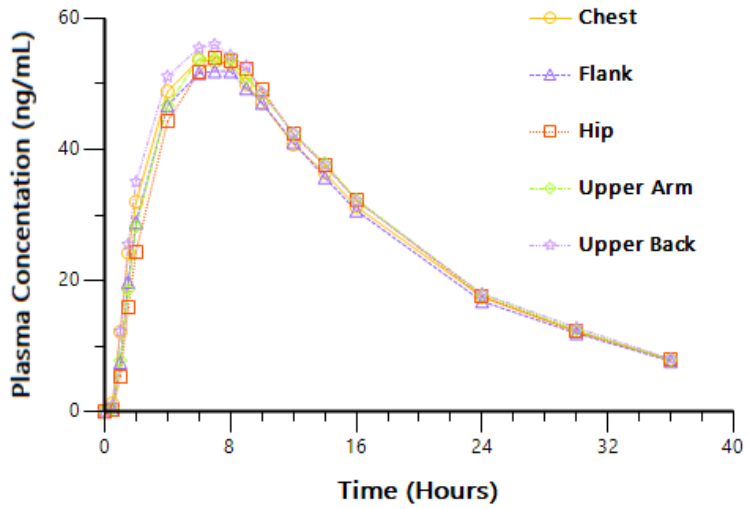
Is the proposed dosing instruction for site rotation appropriate?

Yes.

The Applicant proposed that d-ATS can be applied to one of the following sites: hip, upper arm, upper chest, upper back or flank. It is also recommended that the site of application should be rotated with a new d-ATS. The recommendation was based on a single-dose relative bioavailability study comparing five different sites (N25-010) and a multiple-dose PK study comparing d-ATS accumulation with/without site rotation (N25-015).

In Study N25-010, 18 mg/9 hours d-ATS patches were applied to five different sites. Results were summarized in Figure 6 and Table 13. The d-amphetamine exposure of specified application sites was compared with hip as the reference site, which was used in all studies but prior to Study N25-010 and study N25-006 (a pivotal efficacy and safety study). Comparable PK profiles were observed for all sites. Hence, d-ATS may be applied to any of the five sites.

Figure 6: Mean d-Amphetamine Plasma Concentration-time Profiles of d-ATS at 18 mg/9 hours by Application Site (Study N25-010)




Source: Reviewer's analysis.

Table 13: Summary of Statistical Analysis for Bioequivalence of d-Amphetamine Exposure between Application Sites (Study N25-010)

| Exposure Metric | Application Site | N | Least Squares Geometric Mean | Least Squares Geometric Mean Ratio % [90%CI][a] | Intra-subject CV% | Inter-subject CV% |
|---|---|---|---|---|---|---|
| $AUC_{0-t}$ (ng*h/mL) | Hip | 47 | 961.4 | N/A | N/A | N/A |
| | Upper Back | 47 | 1013.9 | 105 [102.0, 109.0] | 9.7 | 17.0 |
| | Chest | 47 | 978.3 | 101.8 [98.5, 105.2] | | |
| | Upper arm | 47 | 982.7 | 102.2 [98.9, 105.6] | | |
| | Flank | 47 | 946.9 | 98.5 [95.3, 101.8] | | |
| $AUC_{0-inf}$ (ng*h/mL) | Hip | 46 | 1071.5 | N/A | N/A | N/A |
| | Upper Back | 46 | 1127.2 | 105.2 [101.5, 109.1] | 10.5 | 17.9 |
| | Chest | 45 | 1096.9 | 102.4 [98.7, 106.2] | | |
| | Upper arm | 46 | 1090.1 | 101.7 [98.1, 105.5] | | |
| | Flank | 46 | 1057.2 | 98.7 [95.2, 102.3] | | |
| $C_{max}$ (ng/mL) | Hip | 47 | 55.2 | N/A | N/A | N/A |
| | Upper Back | 47 | 56.9 | 103.1 [99.7, 106.6] | 9.8 | 17.9 |
| | Chest | 47 | 55.2 | 100.1 [96.8, 103.5] | | |
| | Upper arm | 47 | 55.6 | 100.8 [97.5, 104.2] | | |
| | Flank | 47 | 53.5 | 97.0 [93.8, 100.3] | | |

[a] Reference treatment is hip application
Note: Treatment was a single dose of d-ATS at 18 mg/9 hours to specified application site.
Source: Adapted from Study N25-010 CSR, Table 14.2.2.2.

The study N25-015 evaluated exposure after multiple doses of d-ATS with (group A) and without (group B) site rotation. Participants in group B showed a 2-fold accumulation of d-

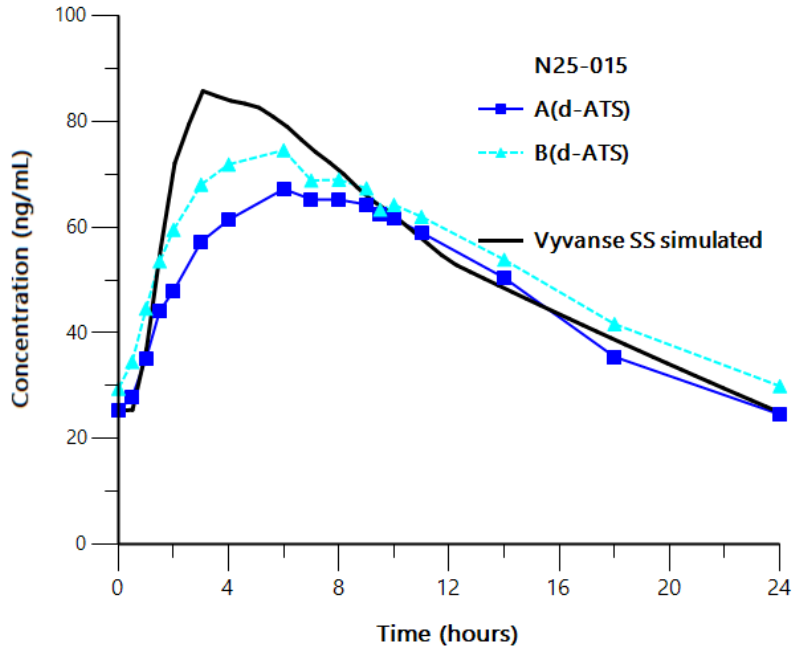
amphetamine on Day 28 compared to that on Day 1 (Table 14). Simulated exposure of Vyvanse is not likely to cover that of d-ATS at steady state, especially between 9 to 24 hours post dose (Figure 7). From a safety perspective, group B experienced a higher incidence of safety events (Refer to Section 8 for more discussion). Thus, it is recommended that d-ATS should be used with site rotation.

Table 14: Summary Statistics of d-Amphetamine Plasma PK Parameters with Site Rotation (Group A) and without Site Rotation (Group B) on Day 1 and Day 28 (N25-015).

| Parameter (Units) | Mean (CV%) | | | |
|---|---|---|---|---|
| | Day 1 | Day 28 | Day 1 | Day 28 |
| | Group A (N=15) | Group A (N=15) | Group B (N=20) | Group B (N=20) |
| $C_{max}$ (ng/mL) | 50.7 (23.2) | 68.8 (22.0) | 44.1 (23.9) | 76.5 (28.0) |
| $AUC_{0-24}$ (ng*h/mL) | 797 (23.0) | 1147 (25.8) | 665 (25.9) | 1284 (34.3) |
| $R_{theor}$[a] | N/A | 1.24 (6.9) | N/A | 1.33 (10.4) |
| AR based on $C_{max}$ | N/A | 1.46 (10.4) | N/A | 1.86 (27.2) |
| AR based on $AUC_{0-24}$ | N/A | 1.54 (15.6) | N/A | 2.04 (32.0) |

[a] Theoretical accumulation ratio
Source: Adapted from Study N25-015 CSR, Table 11-1 and 11-2.

Figure 7: Plasma d-Amphetamine Concentration-time Profiles at Steady State after d-ATS 18 mg/9 hours Day 28, with (Aqua) and without (Blue) Site Rotation, and Vyvanse 70 mg (eq. 20.8 mg d-Amphetamine, Black, Simulated)[a]




[a] d-ATS data from N25-012, Vyvanse steady state was simulated with data from study N25-012
Source: Reviewer's analysis

What is the effect of heat on the exposure of d-ATS?

The effect of extenal heat on the rate and extend of d-amphetamine absorption was evaluated in part 1 of study N25-012. Subjects received d-ATS on the hip for 9 hours with a heat patch (~40 $^{o}$C) placed on top of the patch immediately after application and kept in position for 6 hours. For the treatment group with heating, there was approximately 50% increase in AUC of d-amphetamine for the first 9 hours compared to d-ATS without heat (Table 15). $T_{max}$ shifted 2 hours ealier with a heat patch, i.e. from 8.5 hours to 6.5 hours. However, inspection of individual PK profiles did not reveal any burst of release of d-amphetamine. The ratio of peak plasma concentration $C_{max}$ and $AUC_{0\text{-}inf}$ did not increase significantly (116% and 112%, respectively) with a heat patch.

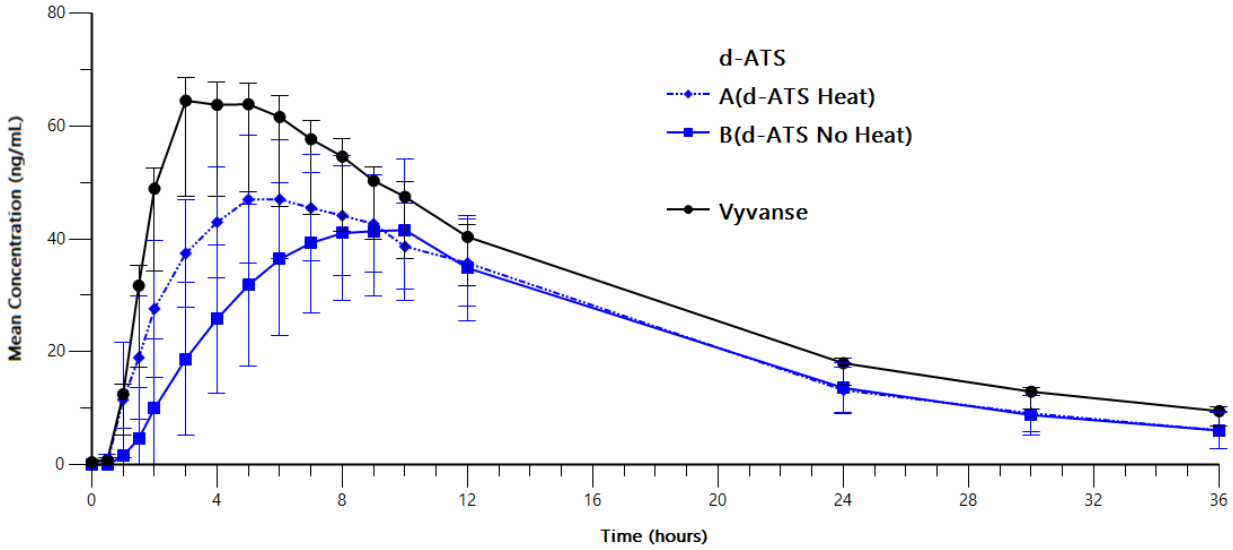
Table 15: Summary of Statistical Analysis for Effect of External Heat on d-Amphetamine Exposure from d-ATS (Study N25-012, Part 1)

| Exposure | External Heat[a] | N | LS GeoMean | LS GeoMean ratio% [90%CI][b] | Intra-subject CV% | Inter-subject CV% |
|---|---|---|---|---|---|---|
| $AUC_{0\text{-}9}$ (ng*h/mL) | Applied | 14 | 79.0 | 150 [133.5, 167.8] | 17.1 | 25.7 |
| | Not applied | 14 | 52.8 | | | |
| $AUC_{0\text{-}t}$ (ng*h/mL) | Applied | 14 | 207 | 116 [106.9, 125.2] | 11.7 | 21.6 |
| | Not applied | 14 | 179 | | | |
| $AUC_{0\text{-}inf}$ (ng*h/mL) | Applied | 14 | 223 | 112 [104.0, 120.3] | 10.4 | 24.5 |
| | Not applied | 14 | 199 | | | |
| $C_{max}$ (ng/mL) | Applied | 14 | 12.3 | 116 [108.8, 123.6] | 9.47 | 24.1 |
| | Not applied | 14 | 10.6 | | | |
| $T_{max}$[c] (h) | Applied | 14 | 6.5 (2.0, 12) | N/A | N/A | N/A |
| | Not applied | 14 | 8.5 (5.0, 10) | N/A | N/A | N/A |

[a] External heat was applied by overlaying d-ATS with a 40°C heat patch for the first 6 hrs of application.
[b] Reference treatment is external heat not applied.
[c] Median [minimum, maximum] reported for $T_{max}$.
Source: Study N25-012 CSR, Table 11-4.

Figure 8 shows the PK profile comparison between d-ATS with/without a heat patch (dose normalized to 18 mg/9 hours), along with the PK profile of Vyvanse after a single dose (Vyvanse data from N25-012 part 2). Even with a 1.5-fold increase in $AUC_{0\text{-}9}$ with a heat patch (Table 15), the exposure of 18 mg/9 hours d-ATS was projected to be 316 ng*h/mL, still well below $AUC_{0\text{-}9}$ of Vyvanse at 70 mg (436 ng*h/mL). Other key PK parameters such as $C_{max}$ and $AUC_{0\text{-}inf}$ were also lower than those from Vyvanse (Table 16).

Figure 8: Mean (±SD) Plasma d-Amphetamine Concentration-time Profiles after Single Doses of d-ATS with (Yellow) and without (Blue) Heat (Normalized to 18 mg/9 hours) and Vyvanse 70 mg (eq. 20.8 mg d-Amphetamine).




Source: Reviewer's analysis.

Table 16: Comparison of Single-dose Exposure of Vyvanse and d-ATS with Heat (N25-012).

| Exposure | LS GeoMean of d-ATS[a] (Dose normalized to 18 mg/9 hours) | LS GeoMean of Vyvanse 70 mg[b] |
|---|---|---|
| $AUC_{0-9}$ (ng*h/mL) | 316 | 436 |
| $AUC_{0-t}$ (ng*h/mL) | 828 | 1070 |
| $AUC_{0-inf}$ (ng*h/mL) | 892 | 1230 |
| $C_{max}$ (ng/mL) | 49.2 | 65.4 |

[a] External heat was applied by overlaying d-ATS with a 40°C heat patch for the first 6 hrs of application. Values from d-ATS were normalized to 18 mg/9 hours.
[b] Vyvanse 70 mg is equivalent to 20.8 mg d-amphetamine
Source: Reviewer's analysis

However, given there is an unexplained accumulation of d-amphetamine after long-term use of d-ATS based on results from study N25-015 (Table 12), and the accumulation is not observed in oral amphetamine products, if a heat patch is consistently used along with d-ATS, d-amphetamine steady state $AUC_{0-9}$ would likely increase from 508 ng*h/mL to 762 ng*h/mL (multiplied by 1.5), which is approximately 20% higher than that of Vyvanse $AUC_{0-9}$ at steady state (620 ng*h/mL). The clinical significance is unknown, hence to be conservative, use of external heat on d-ATS patch is not recommended.

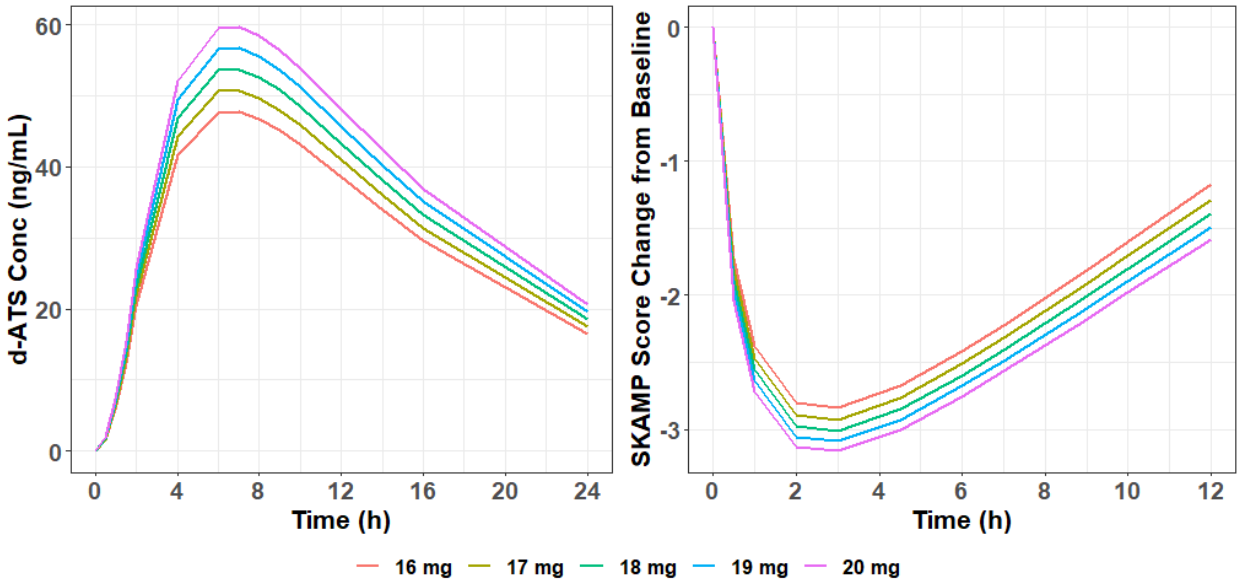
Therefore, it is appropriate to avoid exposing d-ATS to external heat sources during wear because both the rate and extent of absorption are increased.

Is a loss of up to 20% d-amphetamine, due to degradation, in d-ATS during storage expected to impact clinical efficacy?

No. A loss of up to 20% d-amphetamine, due to degradation, in d-ATS during storage will not impact clinical efficacy.

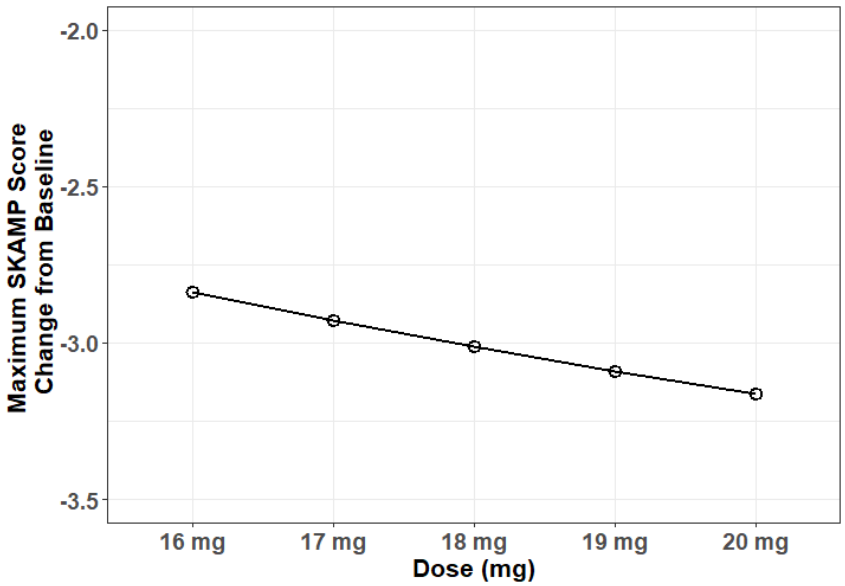
Simulations were conducted using the PK/Efficacy model to evaluate the impact of d-amphetamine degradation in d-ATS during storge on clinical efficacy (SKAMP score). The simulated SKAMP scores were plotted for each dose level (Figure 9) and the dose-response for maximum change in SKAMP score is depicted in Figure 10. Simulations suggest that no more than 10.1% difference in SKAMP score (change from baseline) would be observed over the range of d-ATS dose levels from 16 to 20 mg. Overall, a loss of up to 20% d-amphetamine, due to degradation, in d-ATS during storage is not expected to impact clinical efficacy.

Figure 9: Simulated Concentration-time Profiles of d-Amphetamine (Left) and SKAMP Responses over Time (Right) following Administration of d-ATS at Different Dose Levels




Doses shown are d-amphetamine content loaded to each patch.
Source: Reviewer's analysis

Figure 10: Relationship between Dose and Maximum Change from Baseline SKAMP Scores.




Doses shown are d-amphetamine content loaded to each patch.
Source: Reviewer's analysis

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# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

The clinical development program for d-ATS consisted of six clinical studies: five phase 1 studies and one phase 2 study (Study N25-006, an efficacy and safety trial in children ages 6 to 17 years with ADHD). The phase 1 studies consisted of PK accumulation analysis in the adult patients with ADHD under intended and exaggerated use conditions, a skin sensitization study in healthy adult subjects, a heat effect study in healthy adult subjects, an adhesion study in pediatric and adult patients with ADHD, three human factor validation studies in pediatric and adult patients with ADHD (one with d-ATS and two with placebo simulations), and a label comprehension study in adolescent and adult patients with ADHD and with healthy adult subjects.

Table 17: Listing of Clinical Trials

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | ***Controlled Studies to Support Efficacy and Safety*** | | | | | | |
| N25-006 | NCT01711021 | Phase 2, randomized, double-blind, crossover, placebo-controlled, efficacy study in 2 parts:<br>**Dose Optimization Period:** 5-week, open-label, stepwise dose optimization period<br>**Double-Blind Treatment Period:** 2-week, randomized, crossover, double-blind treatment period | **Dose Optimization Period:**<br>d-ATS 5 mg<br>d-ATS 10 mg<br>d-ATS 15 mg<br>d-ATS 20 mg<br>**Double-Blind Treatment Period (2-week crossover):**<br>d-ATS (optimized dose)<br>Placebo<br>**Route**<br>Topical placement to hip daily for 9-hour wear period | **Primary:**<br>To assess efficacy of d-ATS compared to placebo, as measured by the SKAMP total score<br>To assess the safety of d-ATS<br>**Secondary:**<br>To assess onset of efficacy of d-ATS compared to placebo, as measured by the SKAMP total score<br>To assess duration of efficacy of d-ATS compared to placebo, as measured by the SKAMP total score<br>To assess additional efficacy assessments, including the PERMP, ADHD-RS-IV, CPRS-R:S, and CGI scales | 5-week Dose Optimization Period followed by 2-week Double-blind Treatment Period | 110 subjects (in Dose Optimization Period) and 106 subjects (in Double-Blind Treatment Period) | Children and adolescents 6 to 17 years of age with ADHD | Three study sites, US-based trial |

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| | | | | **Dermal:** To assess the skin irritation, discomfort, adhesion, and adhesive residue of d-ATS<br>**Safety:** AEs, vital signs (including weight), clinical laboratory test results, 12-lead ECG, physical examination results, C-SSRS | | | | |
| | | ***Studies to Support Safety*** | | | | | | |
| N25-007 | Not registered | One-day usability study of d-ATS; Day 1 involved water exposure | **Single-dose application of:**<br>d-ATS 5 mg<br>d-ATS 10 mg<br>d-ATS 15 mg<br>d-ATS 20 mg<br>Children and adolescents were assigned a comparable strength of d-ATS as their current prescription of stimulant medication for the treatment of ADHD. Adult subjects were randomized to 1 of the 4 treatment groups | **Primary:**<br>To assess difficulty of removing d-ATS from the release liner<br>To assess adhesive transfer to the liner<br>To assess adhesive transfer to the person who was applying the patch<br>To assess adhesion after water exposure<br>To assess adhesion, discomfort, and irritation<br>To assess the amount of adhesive residue at the application site after patch removal and after | 1-day study | N=93 | Children with ADHD between 6 and 12 years of age, inclusive, and their adult caregivers with and without prior transdermal experience<br><br>Adolescents with | Single center, US-based trial |

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| | | | **Route**<br>Topical placement to hip daily for 9-hour wear period | the application site was cleaned<br>To assess that subjects and caregivers were able to apply, wear, and remove d-ATS per patient instructions in an actual-use environment<br>**Dermal:** To assess the skin irritation, discomfort, adhesion, and adhesive residue of d-ATS<br>**Safety:** AEs, vital signs, 12-lead ECG, physical examination results | | | ADHD between 13 and 17 years of age, inclusive, and their adult caregivers, if appropriate, with and without prior transdermal experience<br><br>Adults with ADHD between 18 and 65 years of age, inclusive, with and without prior transdermal | |

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| | | | | | | | experience | |
| N25-013 | Not registered | Combined usability-adhesion study to evaluate the usability (patch application, removal, disposal, wear performance, and user behavior) of d-ATS and to assess adhesion of d-ATS and Daytrana in children, adolescents, and adults with ADHD | **Treatment A:** d-ATS 5 mg patch<br>**Treatment B:** d-ATS 20 mg patch<br>**Treatment C:** Daytrana (27.5 mg methylphenidate)<br>**Treatment D:** Daytrana (82.5 mg methylphenidate)<br><br>**Route**<br>d-ATS was applied to the hip, upper arm, chest, flank, or upper back per the randomization code.<br>Daytrana was applied to the hip.<br>Products were applied for 9 hours on Days 1 and 2. | **Usability of d-ATS (Day 1)**<br>Subjects and caregivers were able to apply, remove, and dispose of the patch per subject instructions in an actual-use environment<br>Difficulty of removing the patch from the release liner<br>Adhesive transfer to the liner<br>Adhesive transfer to the person who is applying the patch<br>Discomfort, pain, and irritation<br>The amount of adhesive residue at the application site after patch removal and after the application site is cleaned<br>**Adhesion Profile of d-ATS and Daytrana (Day 1 and Day 2)**<br>In an uncontrolled setting on Day 1 | 2-day study | N=121 | Children with ADHD between 6 and 12 years of age, inclusive, and their adult caregivers<br>Adolescents with ADHD between 13 and 17 years of age, inclusive, and their adult caregivers if appropriate<br>Adults with ADHD between 18 and 65 years of | Six study sites, US-based trial |

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| | | | | In a controlled setting on Day 2<br>**Safety:** AEs, vital signs, 12-lead ECG, physical examination results, C-SSRS | | | age, inclusive | |
| N25-018 | NCT04094025 | Randomized (for patch placement), evaluator-blinded, cumulative irritation and sensitization study | Topical administration of d-ATS 5 mg patch, placebo patch, and saline patch applied simultaneously on the back of each subject once daily during Induction (21 planned applications daily) and Challenge (1 planned application) Periods. A Rechallenge Period (1 planned application) would be required if skin results from Challenge Period were suggestive of sensitization | **Primary:**<br>To evaluate skin sensitization potential after repeated exposure of d-ATS, placebo, and saline patches (the number and the proportion of subjects sensitized, and the number and the proportion of subjects potentially sensitized to each TDS unit)<br>To evaluate skin irritation after repeated exposure to d-ATS, placebo, and saline patches (mean irritation score)<br>Safety Parameters:<br>**Safety:** AEs, vital signs, 12-lead ECG, laboratory assessments, physical examination results, dermal evaluations, adhesion assessments | Induction Period of 3 weeks (21 days), a Rest Period of approximately 2 weeks (15 ± 2 days), a Challenge Period for up to 1 week (7 days), and a possible Re-challenge Period (4 weeks after Challenge Period), if required, for up to 1 week (7 days) followed by a Follow up | N=229 | Healthy adult subjects 18-65 years of age | Single center, US-based trial |

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| | | | | | Visit (7 ± 1 day) | | | |
| | | ***Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)*** | | | | | | |
| N25-002 | Not registered | Phase 1, single-dose, open-label, randomized, 2-way crossover study | **Treatment A:** d-ATS 9.38 mg patch applied to the hip for 24 hrs<br>**Treatment B:** d-ATS 9.85 mg patch applied to the hip for 24 hrs | **Pharmacokinetic parameters:** $C_{max}$, $T_{lag}$, $T_{max}$, $AUC_{0-12}$, $AUC_{0-24}$, $AUC_{0-last}$, $AUC_{0-inf}$, $K_{el}$, $t_{1/2}$, bioavailability comparison for the 2 formulations<br>**Apparent dose:** apparent amount of drug released from the system during wear time<br>**Dermal parameters:** adhesion, residue, discomfort, and irritation<br>**Safety:** AEs, vital signs, clinical laboratory test results, 12-lead ECG, physical examination results | Each single-dose treatment separated by at least 7 days | N=8 | Healthy adult males (18-30 years) | Single center, US-based trial |
| N25-004 | Not registered | Phase 1, single-center, open-label, single-dose, randomized, 3-period, 3-way crossover study | **Treatment A:** d-ATS 8.4 mg patch, hip, 9 hrs<br>**Treatment B:** d-ATS 8.4 mg patch applied to the hip for 12 hrs<br>**Treatment C:** | **Pharmacokinetic parameters:** $C_{max}$, $T_{lag}$, $T_{max}$, $AUC_{0-12}$, $AUC_{0-24}$, $AUC_{0-last}$, $AUC_{0-inf}$, $K_{el}$, $t_{1/2}$, $V_d/F$, Cl/F, relative bioavailability<br>**Pharmacodynamics:** Relationships ($E_{max}$, $E_0$, | Each single-dose treatment separated by at least 6 days | N=18 | Children 6-12 years of age with ADHD | Single center, US-based trial |

| | | | | | | | | |
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| | | | Adderall XR 10 mg capsule | $EC_{50}$, Gamma) between changes in efficacy parameters (SKAMP and PERMP scores) and plasma concentrations of d- and l-amphetamine<br>**Apparent dose:** apparent amount of drug released from the system during wear time<br>**Efficacy:** SKAMP, PERMP, ADHD-RS-IV<br>**Dermal parameters** adhesion, residue, discomfort, and irritation<br>**Safety:** AEs, vital signs, clinical laboratory test results, 12-lead ECG, physical examination results | | | | |
| N25-005 | Not registered | Phase 1, single-center, open-label, single-dose, randomized, 3-period, 3-way crossover study (N=18) | **Treatment A:** d-ATS 5 mg patch applied to the hip for 9 hrs<br>**Treatment B:** d-ATS 10 mg patch applied to the hip for 9 hrs<br>**Treatment C:** d-ATS 20 mg patch applied | **Pharmacokinetic parameters:** $C_{max}$, $T_{lag}$, $T_{max}$, $AUC_{0-24}$, $AUC_{0-last}$, $AUC_{0-inf}$, $K_{el}$, $t_{1/2}$, dose proportionality<br>**Apparent dose:** apparent amount of drug released from the system during wear | Each single-dose treatment separated by at least 7 days | N=18 | Children 6-12 years of age with ADHD | Single center, US-based trial |

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| | | | to the hip for 9 hrs | time<br>**Dermal parameters** adhesion, residue, discomfort, and irritation<br>**Safety:** AEs, vital signs, clinical laboratory test results, 12-lead ECG, physical examination results, C-SSRS | | | | |
| N25-010 | Not registered | Phase 1, single-center, open-label, single-dose, randomized, 5-period, 5-way crossover study | **Treatment A:** d-ATS 20 mg patch, applied to hip for 9 hrs<br>**Treatment B:** d-ATS 20 mg patch, applied to upper back for 9 hrs<br>**Treatment C:** d-ATS 20 mg patch applied to chest for 9 hrs<br>**Treatment D:** d-ATS 20 mg patch applied to upper arm for 9 hrs<br>**Treatment E:** d-ATS 20 mg patch applied to flank for 9 hrs | **Pharmacokinetic parameters:** $C_{max}$, $T_{max}$, $AUC_{0-7}$, $AUC_{0-9}$, $AUC_{0-t}$, $AUC_{0-inf}$, $RAUC_{0-7}$, $RAUC_{0-9}$, $\lambda_z$, $t_{1/2}$<br>**Apparent dose:** apparent amount of drug released from the system during wear time<br>**Dermal parameters:** adhesion, residue, discomfort, and irritation<br>**Safety:** AEs, vital signs, clinical laboratory test results, 12-lead ECG, physical examination results, C-SSRS | Each single-dose treatment separated by at least 7 days | N=50 | Healthy adult subjects (18-45 years) | Single center, US-based trial |
| N25-012 | Not registered | Phase 1, single-center, open-label, single-dose, | **Part 1**<br>**Treatment A:** d-ATS 5 mg patch applied to | **Primary:**<br>**Part 1** | Each single-dose treatment | Part 1: N=14<br>Part 2: N=18 | Healthy adult subjects | Single center, US-based |

| | | | | | | | | |
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| | | randomized, 2-part study<br>Part 1: 2-period, 2-way crossover<br>Part 2: 3-period, 3-way crossover | the hip for 9 hrs, overlaid with a 40°C heat patch for 6 hrs<br>**Treatment B:** d-ATS 5 mg patch applied to the hip for 9 hrs<br>**Part 2**<br>**Treatment C:** d-ATS 20 mg patch applied to the hip for 9 hrs<br>**Treatment D:** Vyvanse 70 mg oral capsule<br>**Treatment E:** Adderall XR 30 mg oral tablet | To assess the effect of external heat on the rate and extent of amphetamine absorption following application of d-Amphetamine Transdermal System (d-ATS).<br>**Part 2**<br>To compare the pharmacokinetics (PK) of amphetamine delivered by d-ATS, Adderall XR®, and Vyvanse®.<br>**Secondary:**<br>**Parts 1 and 2**<br>To assess the adhesion, discomfort, pain, irritation, and adhesive residue of d-ATS<br>To determine the residual amphetamine content after a 9-hour wear period<br>To assess the safety and tolerability of d-ATS.<br>**Pharmacokinetic parameters:** $C_{max}$, $T_{max}$, $AUC_{0-inf}$, $AUC_{0-t}$, $AUC_{0-9}$, $AUC_{0-24}$, $AUC_{ex}$, $t_{1/2}$, $\lambda_z$ | separated by at least 7 days | | between 18 and 65 years of age | trial |

| | | | | | | | | |
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| | | | | **Residual Drug and Apparent Dose**<br>**Dermal parameters** adhesion, residue, discomfort, and irritation<br>**Safety:** AEs, vital signs, clinical laboratory test results, 12-lead ECG, physical examination results | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| N25-015 | Not registered | Phase 1, single-center, open-label, multiple-dose, randomized study | **Group A** (intended use): d-ATS 20 mg patch, applied to hip, flank, chest, upper arm, or upper back for 9 hrs once daily with application site rotated every new patch<br>**Group B** (exaggerated use): d-ATS 20 mg patch applied to the hip for 9 hrs once daily with no application site rotation | **Primary:**<br>To characterize the single- and multiple-dose pharmacokinetics (PK) of amphetamine following administration of d-ATS to subjects rotating the application site daily (intended use) and subjects using the same application site daily (exaggerated use).<br>**Secondary:**<br>To assess dermal reactions (ie, type, onset, duration, and severity) to allow a direct evaluation of potential changes in exposure and PK profile in subjects experiencing various degrees of dermal reactions;<br>To assess the safety and tolerability of d-ATS<br>**Pharmacokinetic parameters:** $C_{max}$, $T_{max}$, $AUC_{0-inf}$, $AUC_{0-t}$, $AUC_{0-9}$, $AUC_{0-24}$, $AUC_{ex}$, $t_{1/2}$, $\lambda_z$<br>**Residual Drug and Apparent Dose**<br>**Dermal parameters:** adhesion, residue, | Product application daily for 28 days; total treatment duration of 31 days | Group A: 15<br>Group B: 20 | Adults 18-65 years of age with ADHD | Single center, US-based trial |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | discomfort, and irritation<br>**Safety:** AEs, vital signs, clinical laboratory test results, 12-lead ECG, physical examination results<br>**Pharmacokinetic parameters:** $C_{max}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-9}$, $AUC_{0-inf}$, , $AUC_{0-24}$, $C_{av, ss}$, $C_{min, ss}$, PTF%, $t_{1/2}$, $\lambda_z$, $ARC_{max}$, $ARAUC_{0-9}$, $ARAUC_{0-24}$, $R_{theor}$<br>**Residual Drug Analysis**<br>**Dermal parameters** adhesion, residue, discomfort, and irritation<br>**Safety:** AEs, vital signs, clinical laboratory test results, 12-lead ECG, weight, physical examination results, C-SSRS | | | | |
| ***Human Factors Studies*** | | | | | | | | |
| N25-017A | Not registered | Pre summative, simulated-use study | Placebo patches simulating d-ATS 5 mg and 20 mg patches | Explore if the final finished combination product user interface maximizes the likelihood that the product will be used safely and effectively by intended | Not applicable | Adults: 5<br>Children and adolescents: 6<br>Caregivers: 7 | Subjects with ADHD<br><br>Adult caregivers | Single center, US-based trial |

| | | | | | | | | |
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| | | | | users, for the intended uses, in the intended use environments | | | of children/adolescents with ADHD<br><br>(6 – 62 years of age) | |
| N25-017B | Not registered | Simulated-use human factor validation study | Placebo patches simulating d-ATS 5 mg and 20 mg patches | Conduct a simulated-use human factors validation study of d-ATS in order to assess whether the final finished combination product user interface maximizes the likelihood that the product can be used safely and effectively by the intended users, for the intended uses, in the intended use environments | Not applicable | Adults: 18<br>Pediatric: 16<br>Adult Caregiver: 16 | Pediatrics (10-17 years) and adults (≥18 years) with ADHD and caregivers (≥18 years)<br><br>(10 – 80 years of age) | Single center, US-based trial |
| N37-001 | Not registered | One-day label comprehension | No treatment | Determine subject ability to comprehend critical and noncritical elements contained in the Instructions for Use | Not applicable | Total: 31<br>Adolescents with ADHD: 10<br>Adults with ADHD: 10<br>Healthy adults: 11 | Subjects between 12 and 68 years of age | Single center, US-based |

Note: The N25-006 efficacy study also provided safety data. All clinical pharmacology studies also provided safety data. In addition, N25-015 had specific safety-related endpoints related to d-ATS intended use versus exaggerated use. Human Factors studies. N25-007 and N25-013 provide use safety data.

Abbreviations: d-ATS=d-amphetamine transdermal system; SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham; PERMP=Permanent Product Measure of Performance; ADHD-RS-IV=ADHD rating scale based on DSM-IV-TR criteria; CPRS-R:S=Conners' Parent Rating Scale - Revised Short Form;CGI=Clinical Global Impression; CSR=Clinical Study Report; C-SSRS=Columbia Suicide Severity Rating Scale; ADHD=attention deficit hyperactivity disorder; US=United States; $C_{max}$=the maximum plasma concentration observed; $T_{lag}$=lag time; $T_{max}$=the time of the maximum observed concentration; $AUC_{0-24}$=the area under the plasma concentration-time profile, calculated from time 0 to 24 hours by the linear trapezoidal rule; $AUC_{0-12}$=the area under the plasma concentration-time profile, calculated from time 0 to 12 hours by the linear trapezoidal rule; $AUC_{0-last}$=the area under the plasma concentration-time profile, calculated from time 0 to the last measurable concentration (Ct) by the linear trapezoidal rule; $AUC_{0-inf}$=the area under the plasma concentration-time profile extrapolated to infinity ($AUC_{0-last} + Ct/k_{el}$); $K_{el}$=elimination rate constant (slope of the concentration vs. time curve); $t_{1/2}$=elimination half-life ($\ln 2/k_{el}$); Vd/F=volume of distribution; Cl/F=clearance; $E_{max}$ =maximum effect; $E_0$ =baseline effect; $EC_{50}$ =concentration associated with 50% of the predicted maximum effect; Gamma=shape parameter; $AUC_{0-7}$=the area under the plasma concentration-time profile; calculated from time 0; hour to 7 hours (median $T_{max}$), by the linear trapezoidal rule; $AUC_{0-9}$=the area under the plasma concentration-time profile; calculated from time 0 hour to 9 hours (mean $T_{max}$ + 2 standard deviations), by the linear trapezoidal rule; $AUC_{0-t}$=the area under the plasma concentration-time profile; calculated from time 0 hour to the last measurable concentration, by the linear trapezoidal rule; $AUC_{0-inf}$=the area under the plasma concentration-time profile extrapolated to infinity ($AUC_{0-t} + C_t/k_{el}$); $RAUC_{0-7}$=test/reference ratio of $AUC_{0-7}$; $RAUC_{0-9}$=test/reference ratio of $AUC_{0-9}$; $\lambda_z$=apparent elimination rate constant (slope of the natural log of concentration vs. time curve); $C_{av,ss}$=Average plasma concentration at steady state, $C_{min,ss}$= Minimum observed plasma concentration during a dosing interval at steady state; PTF%= Peak to trough fluctuation over a dosing interval; ARCmax= Accumulation ratio for Days 28 to 1 $C_{max}$ values; $ARAUC_{0-9}$= Accumulation ratio, determined as the ratio of Days 28 to 1 $AUC_{0-9}$ values; $ARAUC_{0-24}$= Accumulation ratio, determined as the ratio of Days 28 to 1 $AUC_{0-24}$ values; $R_{theor}$= Theoretical accumulation ratio, calculated as $1/[(1 - \exp(-\lambda z \cdot \text{tau})]$ where the dosing interval tau is 24 hours (Day 28)
Source: Study N25-006 CSR; Study N25-007 CSR; Study N25-013 CSR; Study N25-018 CSR; Study N25-002 CSR; Study N25-004 CSR; Study N25-005 CSR; Study N25-010 CSR; Study N25-012 CSR; Study N25-015 CSR; N25-017A Pre Summative Study Report; N25-017B Validation Study Report; N37-001 Label Comprehension Study Report

Source: Applicant information amendment submitted September 7, 2021

## 7.2. Review Strategy

Efficacy and safety of d-ATS with regard to the proposed indication of treatment of ADHD in pediatric patients are reviewed below. The efficacy review focuses on Study N25-006, the short-term trial in pediatric patients with ADHD, with analyses performed by the Applicant and by our statistical reviewer, Dr. Katherine Meaker, presented. The clinical pharmacology team's assessment of the adequacy of PK bridging to the listed drugs, dosing, and adverse events can be found in Section 6, above. Adult efficacy is extrapolated from the pediatric data and the previous Agency findings in adults for Vyvanse.

The safety review focuses mainly on Study N25-006, with brief reviews of Study N25-015, the PK accumulation study in adult patients with ADHD which provided safety data for intended use per the proposed product label (application site rotation over five sites) and for exaggerated use (no site rotation), and Study N25-018, the skin sensitization study in healthy adult subjects.

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. N25-006: "A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Laboratory Classroom Study to Evaluate the Safety and Efficacy of d-Amphetamine Transdermal Drug Delivery System (d-ATS) Compared to Placebo in Children and Adolescents with ADHD"

Overview and Objectives
Study N25-006 was a phase 2 pediatric pivotal trial for the indication of treatment of ADHD in children ages 6 to 17 years with d-ATS.

Primary objectives:

- To evaluate the efficacy of d-ATS compared to placebo in subjects 6 to 17 years of age for ADHD symptoms as measured by the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) total score
- To evaluate the safety of d-ATS

Secondary objectives:

- To evaluate the onset and durability of effect of d-ATS compared to placebo as measured by the SKAMP
- To evaluate additional effects and functional outcomes of d-ATS compared with placebo via secondary outcome measures
- To assess the skin irritation, discomfort, adhesion, and adhesive residue of d-ATS

Trial Design

This study was an open-label, dose-optimization and randomized, double-blind, placebo-controlled, parallel-group, crossover, multicenter (United States only), laboratory classroom, outpatient study comparing doses of d-ATS (5 mg/4.76 $cm^2$ daily, 10 mg/9.52 $cm^2$ daily, 15 mg/14.29 $cm^2$, and 20mg/19.05 $cm^2$ daily) to placebo. The dose-optimization phase occurred over a 5-week period, and the crossover, double-blind phase occurred over a 2-week period (i.e., active and placebo treatments for 1 week each). The patients were children ages 6 to 17 years who were diagnosed with ADHD.

Key inclusion criteria: meeting Diagnostic and Statistical Manual of Mental Disorder Fourth Edition: Text Revision (DSM-IV-TR) criteria for ADHD combined, hyperactive/impulsive subtype, or predominately inattentive subtype with an ADHD RS-IV score $\geq$90% of the general population of children by age and gender and with an intelligence quotient of $\geq$80 on the Wechsler Abbreviated Scale of Intelligence II. Patients also had to be able to wear a patch for 9 hours.

Key exclusion criteria: any chronic or significant acute illness including serious cardiovascular disease or past seizure history within the last 2 years (excluding infantile febrile seizure); family

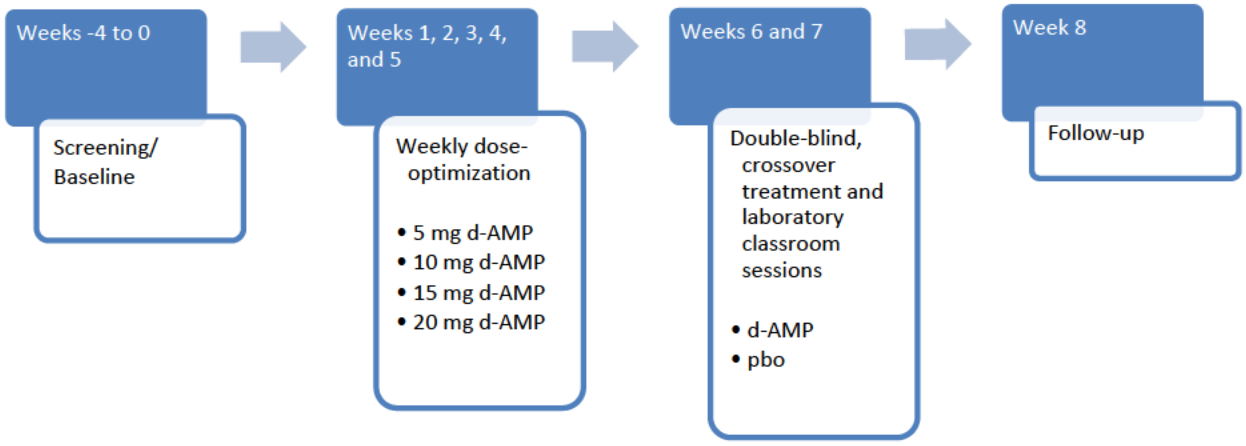
history of sudden cardiac death, any skin abnormality present at the potential application site; history of abnormal blood pressure or pulse, BMI > 95$^{th}$%, some comorbid psychiatric conditions (posttraumatic stress disorder, bipolar, severe depression, severe anxiety, severe obsessive-compulsive disorder, conduct disorder or oppositional defiant disorder with a history of prominent aggressive outbursts, psychosis, autism spectrum disorder, tic or Tourette's disorder); history of physical, sexual, or emotional abuse in the last year; known non-responder to amphetamine treatment; positive urine drug screen; currently stable on ADHD medication treatment; suicide risk; recent suicidal ideation in the last 6 months or any lifetime self-harm event. Any recent ADHD treatment medication must have been washed out at least 3 days prior to the Baseline visit.

Although the M.I.N.I. International Neuropsychiatric Interview was used to rule out exclusionary comorbid psychiatric conditions, it does not appear that ADHD diagnosis was confirmed using a structured or semi-structured clinical interview. There was no ECG exclusion criterion although patients with serious cardiovascular disease including serious heart rhythm abnormality or other problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug were prohibited. Additionally, screening ECGs were obtained. A history of substance abuse was not specifically exclusionary although a positive urine drug screen was. These omissions are notable but are unlikely to have significantly impacted overall study safety or efficacy results.

Randomization and Blinding:
The initial phase of the study was open-label. Subsequently, in the double-blind treatment phase, subjects were randomized in a 1:1 ratio to two treatment arm sequences of their optimized dose of d-ATS and placebo. Randomization occurred via an interactive response system. Placebo and d-ATS were all supplied as identical-appearing transdermal systems. Transdermal samples were not provided for inspection.

Study Schematic:
There were screening, dose-optimized treatment, double-blind treatment (including laboratory classroom sessions), and follow-up phases.

**Figure 11: Study N25-006 Design Schematic**




Source: Reviewer-generated

Dosing:

One dose of study drug was to be applied to alternating hips daily for a 9-hour wear time each day. During the dose-optimization phase, patients received the lowest strength dose of d-ATS (5 mg/4.76 $cm^2$) for 1 week, followed by titration to the next highest strength dose (10 mg/9.52 $cm^2$, 15 mg/14.29 $cm^2$, or 20 mg/19.05 $cm^2$) weekly based upon the ADHD Rating Scale-IV (ADHD-RS-IV) score, the Clinical Global Impression of Severity Scale (CGI-S) score, and tolerability. An optimal dose was considered reached with a $\geq$30% reduction in the ADHD-RS-IV score, a 1- to 2-point improvement in the CGI-I score, and tolerable side effects. After an optimal dose was reached, investigators were allowed to increase the dose to provide additional symptom control, and one dose reduction was permitted. After Visit 4 (end of Week 4), no dose changes were permitted. Any patients who were unable to reach an optimal dose (including those who were unable to tolerate d-ATS) were discontinued from the study. During the double-blind treatment phase, patients received their optimized d-ATS dose for 1 week and placebo for 1 week (the crossover sequence was randomized).

Study Schedule:

Study visits occurred at Screening (up to 24 days) and on Day 0/Baseline, Day 7, Day 14, Day 21, Day 28, Day 35 (half-day laboratory classroom practice), Day 42 (laboratory classroom), Day 49

(laboratory classroom and end of treatment), and Day 56 (follow-up). The assessment schedule was as follows:

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Table 18: Study N25-006 Assessment Schedule

| | Screening | | Baseline | Assessment Period | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Dose Optimization Period | | | | | | | | | | Double Blind Treatment Period | | | | | Safety Follow-Up |
| | | | | Week 1 | | Week 2 | | Week 3 | | Week 4 | | Week 5 | | Week 6 | | Week 7 | | Early Termination | Week 8 |
| Visit | Visit -1 | | Visit 0 | | Visit 1±3 days | | Visit 2±3 days | | Visit 3±3 days | | Visit 4±3 days | | Visit 5±2 days | | Visit 6 | | Visit 7/End of Study | | Visit 8 |
| Study Day | -28 to -4 | -3 to -1 | 0 | 1-6 | 7 | 8-13 | 14 | 15-20 | 21 | 22-27 | 28 | 29-34 | 35 | 36-41 | 42 | 43-48 | 49 | | 56 |
| Clinic Visit | X | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Laboratory classroom | | | | | | | | | | | | | X[a] | | X | | X | | |
| Telephone Contact | | | | X (Day 4) | | X (Day 11) | | X (Day 18) | | X (Day 25) | | X (Day 32) | | X (Day 39) | | X (Day 46) | | | X |
| Home | | X | | X | | X | | X | | X | | X | | X | | X | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | |
| Assign Subject Number | X | | | | | | | | | | | | | | | | | | |
| Inclusion/ Exclusion Criteria | X | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Physical Examination | X | | | | | | | | | | | | | | | | X | X | |
| Height | X | | | | | | | | | | | | | | | | | | |
| Weight | X | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Vital Signs | X | | X | | X[b] | | X[b] | | X[b] | | X[b] | | X[b] | | X[c] | | X[c] | X[d] | |

| | Screening | | Baseline | Assessment Period | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Dose Optimization Period | | | | | | | | | | Double Blind Treatment Period | | | | | Safety Follow-Up |
| | | | | Week 1 | | Week 2 | | Week 3 | | Week 4 | | Week 5 | | Week 6 | | Week 7 | | Early Termination | Week 8 |
| Visit | Visit -1 | | Visit 0 | | Visit 1±3 days | | Visit 2±3 days | | Visit 3±3 days | | Visit 4±3 days | | Visit 5±2 days | | Visit 6 | | Visit 7/End of Study | | Visit 8 |
| Study Day | -28 to -4 | -3 to -1 | 0 | 1-6 | 7 | 8-13 | 14 | 15-20 | 21 | 22-27 | 28 | 29-34 | 35 | 36-41 | 42 | 43-48 | 49 | | 56 |
| 12-lead ECG | X | | X | | | | | | | | | | X | | X | | X | X | |
| Clinical Laboratory Tests | X | | | | | | | | | | | | | | | | X | X | |
| Urine Pregnancy Test | X | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Serology and urine cotinine | X | | | | | | | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | | | | | | X | |
| Urine Drug Screen | X | | | | | | | | | | | | | | | | | | |
| Dispense Study Drug | | | X | | X | | X | | X | | X | | X | | X | | | | |
| Study Drug Administration | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Drug Accountability | | | | | X | | X | | X | | X | | X | | X | | X | X | |
| Patch Removal | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |

| | Screening | | Baseline | Assessment Period | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Dose Optimization Period | | | | | | | | | | Double Blind Treatment Period | | | | | Safety Follow-Up |
| | | | | Week 1 | | Week 2 | | Week 3 | | Week 4 | | Week 5 | | Week 6 | | Week 7 | | Early Termination | Week 8 |
| Visit | Visit -1 | | Visit 0 | | Visit 1±3 days | | Visit 2±3 days | | Visit 3±3 days | | Visit 4±3 days | | Visit 5±2 days | | Visit 6 | | Visit 7/End of Study | | Visit 8 |
| Study Day | -28 to -4 | -3 to -1 | 0 | 1-6 | 7 | 8-13 | 14 | 15-20 | 21 | 22-27 | 28 | 29-34 | 35 | 36-41 | 42 | 43-48 | 49 | | 56 |
| Visual inspection of skin at application site | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Patch Adhesion | | | | | x | | X | | X | | X | | X | | X | | X | | |
| Irritation Assessment | | | | X[e] | x | X[e] | X | X[e] | X | X[e] | X | X[e] | X | X[e] | X | | X | | |
| Discomfort Assessment | | | | X[e] | x | X[e] | X | X[e] | X | X[e] | X | X[e] | X | X[e] | X | | X | | |
| Adhesive Residue | | | | X[e] | x | X[e] | X | X[e] | X | X[e] | X | X[e] | X | X[e] | X | | X | | |
| ADHD Rating Scale | X | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Wechsler Abbreviated Intelligence Test | X | | | | | | | | | | | | | | | | | | |
| M.I.N.I.-kid 6.0 | X | | | | | | | | | | | | | | | | | | |
| Faces or VAS pain scale | | | | | | | | | | | | | X | | X | | X | | |
| SKAMP | | | | | | | | | | | | | X[a] | | X | | X | | |

| | Screening | | Baseline | Assessment Period | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Dose Optimization Period | | | | | | | | | | Double Blind Treatment Period | | | | | Safety Follow-Up |
| | | | | Week 1 | | Week 2 | | Week 3 | | Week 4 | | Week 5 | | Week 6 | | Week 7 | | Early Termination | Week 8 |
| Visit | Visit -1 | | Visit 0 | | Visit 1±3 days | | Visit 2±3 days | | Visit 3±3 days | | Visit 4±3 days | | Visit 5±2 days | | Visit 6 | | Visit 7/End of Study | | Visit 8 |
| Study Day | -28 to -4 | -3 to -1 | 0 | 1-6 | 7 | 8-13 | 14 | 15-20 | 21 | 22-27 | 28 | 29-34 | 35 | 36-41 | 42 | 43-48 | 49 | | 56 |
| PERMP A and C | X | | X | | X | | X | | X | | X | | X[a] | | X | | X | | |
| CPRS | | | X | X | | X | | X | | X | | X | | X | | X | | | |
| CGI-S | | | X | | | | | | | | | | | | | | | | |
| CGI-I | | | | | X | | X | | X | | X | | X | | X | | X | X | |
| C-SSRS | | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Dismissal from Clinic | | | X | | X | | X | | X | | X | | X | | X | | X | X | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[a] Half-day practice classroom
[b] At classroom start
[c] 30 min predose and 4 and 12 hours ± 30 min postdose
[d] Measured once
[e] Performed at home by parent/caregiver/subject

Source: Applicant Clinical Study Report (CSR) for N25-006, Table 4, pages 24-27

Study Discontinuation:

Patients could be removed from the study: for voluntary withdrawal, if the Investigator decided continuation in the study would be detrimental to the patient's well-being, for an AE, for

noncompliance, or with the Sponsor's or a regulatory authority's decision to terminate the study. Patients who discontinued study drug before study completion were asked to return for end-of-study procedures.

Prohibited Medications:
Prescription medication at a stable dose for ≥30 days for stable medical, non-psychiatric illness was permitted. The following medications were not permitted during the study: any stimulant medication, atomoxetine, clonidine, alternative ADHD treatment, antidepressants including MAOIs, mood stabilizers, antipsychotics, anticonvulsants, sedative hypnotics (unless at a stable dose ≥30 days and throughout the study), coumarin anticoagulant, halogenated anesthetics, phenylbutazone, and other investigational drugs.

Treatment Compliance:
Study personnel used patient daily dosing and skin irritation diaries to monitor appropriate dose-taking. Additionally, patients were instructed to save used and unused transdermal systems and return them to the study site during visits.

Data Quality Assurance:
The Principal Investigator and Monitor ensured appropriate staff training. Field level edit checks were conducted for protocol adherence, study progress, and data validation during the study, including quality assurance audits.

Study Endpoints

Primary Endpoint:

- The mean total SKAMP score calculated as the average of all post-dosing SKAMP total scores collected over the course of a laboratory assessment day (9 timepoints over 12 hours)

Secondary Endpoints:

- Onset of efficacy, based on the SKAMP total scores, defined as the first assessment time showing statistical significance between d-ATS and placebo
- Duration of efficacy defined as the difference in hours between the onset of efficacy and the last consecutive time point at which the difference is still statistically significant (i.e., $p \leq 0.05$) and onset of efficacy

Efficacy Assessments:

- SKAMP
    - This is a validated, observer-rated, 13-item scale measuring ADHD behavioral symptoms in a classroom setting over time (i.e., multiple ratings are conducted within a day). Each item is scored from 0 (no impairment) to 6 (maximum impairment) with total scores ranging from 0 to 78. There are three subscale groupings: deportment, attention, and quality of work.

- PERMP
    - This is an age-adjusted, written math test comprised of 5 pages of 80 math problems (400 problems total) to be completed in 10 minutes. Scoring is measured by the number of correct and attempted problems. Different versions of the test were used based on ability, which was assessed by a baseline pre-test, and to ensure that patients did not repeat the same version in the same day.
- ADHD-RS-IV
    - This is a validated, clinician-rated, 18-item scale reflecting ADHD diagnostic criteria from the DSM-IV-TR and is also consistent with DSM-5 criteria. Each item is scored from 0 (no symptoms) to 3 (severe symptoms) with total scores ranging from 0 to 54. There are two subscale groupings: hyperactivity/impulsivity (even numbered items 2 through 18) and inattentiveness (odd numbered items 1 through 17). A qualified rater at the site administered the scale to the caregiver, and repeated administration at all visits for the same patient whenever possible.
- Conners Parent Rating Scale Revised Short Form
    - This is a caregiver-rated, 27-item, standard instrument measuring ADHD behavioral symptoms. Each item is scored from 0 (not true at all) to 3 (very much true). There are four subscale groupings: oppositional, cognitive problems/inattention, hyperactivity, and ADHD index.
- CGI-S
    - This is a clinician-rated scale measuring observed and reported global ADHD symptoms, behavior, and function over the past 7 days. It is rated on a 7-point scale: 1=normal (not at all ill), 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=among the most extremely ill patients.

There are no major concerns about the choice of endpoints or outcome measures; these are typical endpoints for ADHD studies and are listed in the Agency's Clinical Outcome Assessment compendium.

Statistical Analysis Plan

The finalized statistical analysis plan is dated May 8, 2013. Analysis populations were defined as follows:

- Full Analysis Set (FAS)
  The FAS population was defined as all patients who were randomized and received at least one dose of study drug. The FAS population was used for the primary efficacy analysis.

- Completers
  The Completers population was defined as all patients in the FAS population who received full prescribed doses of study medication at both laboratory classroom sessions, completed the full classroom tests at both laboratory classroom sessions, did not miss more than 4 consecutive days of treatment during the double-blind treatment period, and did not use prohibited concomitant medication during the double-blind treatment period. The Completers population was used for supportive efficacy analysis.

- Safety Population
  The Safety population included patients who had received at least one dose of study drug and had at least one post-dose safety measurement (including dermal assessments). Patients were analyzed based on the treatment they actually received. All safety analyses were performed in the safety population.

The primary efficacy endpoint was the mean total SKAMP score calculated as the average of all post-dosing SKAMP total scores collected over the course of a laboratory assessment day (9 timepoints over 12 hours). The applicant planned to use last observation carried forward (LOCF) imputation for subjects who started a classroom day but did not complete all the assessments, for the primary and secondary efficacy analyses. The pre-dosing score for each classroom day was used to calculate change from baseline in mean total SKAMP. Subjects were observed during one classroom day at the end each of the weeks of double-blind crossover treatment (Weeks 6 & 7).

The Applicant planned to use a likelihood-based Mixed Model Repeated Measures (MMRM) approach to compare the d-ATS and placebo results. This was a 2-period 2-treatment crossover study with subjects randomized to one of two sequence arms: d-ATS/Placebo or Placebo/d-ATS. At the end of each treatment period, subjects attended a classroom day to assess efficacy. The model used to analyze the SKAMP total score for each timepoint included fixed effects for sequence (two levels), period (two levels), treatment (two levels) and time (10 levels, one for each of 30 minutes prior and 1, 2, 3, 4.5, 6, 7, 9, 10, and 12 hours post dosing); the repeated measures effect for timepoint within subject. The Applicant's primary model specified the "Variance Components (VC)' covariance structure. The four possible dose levels (5, 10, 15, 20 mg) allowed during dose-optimization were combined for a single d-ATS treatment level, compared to blinded placebo. The sequence effect (treatment x period interaction) was tested at the significance level of 0.10. The protocol specified that if significant differences are detected between sequences, data would be reviewed to investigate the crossover effect, and data from Week 6 only would be presented to assess the treatment effect.

Subgroup analyses were conducted by gender, age group, site, baseline ADHD type, Baseline ADHD severity, and optimized dose level. Subgroup analysis by race was not included by the Applicant but was conducted by the statistical reviewer.

An advice letter was sent to the Applicant on July 1, 2013, with comments on the statistical analysis plan. The letter advised that use of LOCF for imputation should not be applied in the primary analyses (MMRM model) but could serve as sensitivity analyses. The letter further advised that the primary analyses should use the unstructured covariance matrix (TYPE=UN) instead of the proposed variance component (TYPE=VC) in the MMRM model, unless there is convincing evidence supporting the use of VC. The Sponsor did not modify the statistical analysis plan according to the advice letter. The statistical reviewer's results reported here are based on MMRM analysis on the observed data (no LOCF imputation) and the unstructured covariance matrix, as advised in the letter. There were no convergence problems. The calculated results vary only slightly and the conclusion of superiority of d-ATS to placebo for the mean total SKAMP primary endpoint did not change when only Week 6 results were included. The Week 6 results support the onset of effect by 2 hours post-dose, with duration through 9 hours post-dose.

### Protocol Amendments

Four protocol amendments were made after the original protocol submission on May 25, 2012. Two sites reported patient discomfort within the first 3 hours after transdermal system application at Week 2 of the study, so on December 11, 2012, the protocol was amended to include administration of pain scales for any patients endorsing any transdermal system-related discomfort at the laboratory classroom visits. No other major changes were noted.
There are no major concerns with the amendment changes.

### Study Results

### Compliance with Good Clinical Practices

An attestation that this study was conducted in accordance with Good Clinical Practices, according to the ICH Harmonized Tripartite Guideline, and that this study received IRB approval prior to commencement was provided in Section 5.2 of the CSR.

### Financial Disclosure

This study was conducted at three sites in the United States. Four investigators had no financial disclosures to report. See Appendix 13.2 for more details.

### Patient Disposition

One hundred ten patients were enrolled in this study. Four of these patients entered the dose-optimization phase but were not randomized to double-blind treatment. In the double-blind treatment phase, the treatment sequences were evenly distributed. Although rates of discontinuation were evenly distributed between treatment sequence arms, overall, during the double-blind treatment phase, more patients on placebo discontinued than patients on d-ATS: one patient (1%) on d-ATS due to non-compliance, two (2%) on placebo were due to

withdrawal of consent, and two (2%) on placebo were due to other reasons (unable to attend Week 6 and final visits, respectively).

Table 19: Study N25-006 Patient Disposition

| Variable [n(%)] | Treatment Sequence: d-ATS - Placebo (N=53) | Treatment Sequence: Placebo - d-ATS (N=53) | Total [1] (N=110) |
|---|---|---|---|
| Enrolled in Dose Optimization (Baseline) | | | 110 |
| Receive study medication [1] | | | 110 (100%) |
| Safety Population [1] | | | 110 (100%) |
| Reason for Discontinuation from Dose Optimization [1] | | | |
| Adverse event | | | 3 (2.7%) |
| Subject withdrew consent | | | 1 (0.9%) |
| Randomized into Double Blind | 53 | 53 | 106 |
| Reason for Discontinuation from Double Blind Phase [2] | | | |
| Non-compliance with study drug | 0 (0%) | 1 (1.9%) | 1 (0.9%) |
| Subject withdrew consent | 1 (1.9%) | 1 (1.9%) | 2 (1.9%) |
| Other | 2 (3.8%) | 0 (0%) | 2 (1.9%) |

[1] Percentages calculated out of number enrolled.
[2] Percentages calculated out of number randomized.

Source: CSR for N25-006, Table 10, page 43

Protocol Violations/Deviations

The Applicant identified 86 patients (78%) who had major protocol deviations. The most frequent type involved dosing non-compliance: 58 patients (53%) during dose-optimization and, during double-blind treatment, 23 patients (22%) with d-ATS treatment and 19 patients (18%) with placebo treatment. Upon further analysis, the majority of dosing non-compliance involved one or two missed doses: during the 5 weeks of dose-optimization, 21 patients (19%) reported 37 instances of a missed dose; during double-blind treatment of 1 week each on d-ATS and placebo, six patients receiving d-ATS (6%) reported seven instances of a missed dose, and seven patients receiving placebo (7%) reported 10 instances of a missed dose. (The remaining dosing non-compliance major protocol deviations were two patients who removed the transdermal system the next day and three patients (five instances) who did not alternate hip application site.) Additionally, despite the high occurrence rate of dosing non-compliance deviating from the protocol, the overall mean rate of treatment compliance throughout the study was greater than 86%. Similarly, during the double-blind treatment phase, the mean rates of treatment compliance for the two groups were similar at 87%. Additional major protocol deviations were two patients (2%) with deviations from visit windows and one patient (1%) with a violation of subject enrollment criteria. The major protocol deviations are unlikely to affect the overall efficacy results.

Table of Demographic and Baseline Characteristics

There was a higher percentage of males overall, but this is typical for a population with ADHD. Representation of black patients in the study was reasonable, but Asian, American Indian, or Alaskan Native, and Native Hawaiian or Pacific Islander minorities' representation was

inadequate and lower than their rates in the general population of the United States, so this study's findings may be of limited generalizability to these groups.

Table 20: Study N25-006 Demographic and Baseline Characteristics (FAS Population)

| | d-ATS-Placebo N=53 | Placebo-d-ATS N=53 | Total N=106 |
|---|---|---|---|
| Sex (n/%) | | | |
| Female | 17 (32%) | 16 (30%) | 33 (31%) |
| Male | 36 (68%) | 37 (70%) | 73 (69%) |
| Age (Years/SD) | | | |
| Mean | 10.1 (3.2) | 10.8 (3.0) | 10.5 (3.1) |
| Median | 9 | 11 | 10 |
| Min, max | 6, 17 | 6, 17 | 6, 17 |
| Age Group (n/%) | | | |
| 6-12 years | 39 (74%) | 37 (70%) | 76 (72%) |
| 13-17 years | 14 (26%) | 16 (30%) | 30 (28%) |
| Race (n/%) | | | |
| White | 36 (68%) | 45 (85%) | 81 (76%) |
| Black or African American | 9 (17%) | 6 (11%) | 15 (14%) |
| Black or African American / White | 2 (4%) | 1 (2%) | 3 (3%) |
| Asian | 2 (4%) | 0 | 2 (2%) |
| Asian / Black or African American | 1 (2%) | 0 | 1 (1%) |
| Asian / White | 2 (4%) | 0 | 2 (2%) |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| American Indian or Alaskan Native / White | 1 (2%) | 0 | 1 (1%) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| Caribbean Islander | 0 | 1 (2%) | 1 (1%) |
| Ethnicity (n/%) | | | |
| Hispanic or Latino | 19 (36%) | 20 (38%) | 39 (37%) |
| Not Hispanic or Latino | 34 (64%) | 33 (62%) | 67 (63%) |
| Mean Weight/Height/BMI Parameters | | | |
| Baseline Weight (kg/SD) | 38.9 (14.9) | 42.9 (15.0) | 40.9 (15.0) |
| Baseline Height (cm/SD) | 142.9 (16.6) | 147.7 (16.4) | 145.3 (16.6) |
| Baseline BMI ($kg/m^2$/SD) | 18.3 (3.1) | 19.0 (3.7) | 18.7 (3.4) |
| Baseline ADHD Parameters | | | |
| ADHD-Inattentive (n/%) | 33 (62%) | 24 (45%) | 57 (54%) |
| ADHD-Combined (n/%) | 20 (38%) | 29 (55%) | 49 (46%) |
| ADHD-RS-IV total score (mean/SD) | 39.7 (9.0) | 37.2 (8.2) | 38.4 (8.7) |

Source: Reviewer-generated

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

It is noteworthy that ADHD diagnosis was not confirmed with a structured clinical interview. Nonetheless, because patients had to meet DSM criteria for enrollment, the study populations are likely adequate. ADHD disease severity is probably comparable to the general population with ADHD requiring pharmacological treatment, as verified by scale score cutoffs. Baseline ADHD disease severity as measured by the ADHD-RS-IV total score was similar between the treatment sequence groups (d-ATS/placebo 39.7 (SD 9.0) compared to placebo/d-ATS 37.2 (SD 8.2)). As shown in Table 14, the two groups were not balanced by type of ADHD at baseline, with the d-ATS/placebo group having a higher rate of ADHD-Inattentive (62%) subjects and the placebo/d-ATS group having a higher rate of ADHD-Combined (55%) subjects. This imbalance is investigated in the reviewer's subgroup analyses (see Table 19) and did not impact the efficacy results. Rates of baseline medical and psychiatric morbidity were unremarkable.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:
During the dose-optimization phase, the weekly mean percent compliance with d-ATS was 86% to 92%. During the double-blind treatment phase, the mean percent compliance with d-ATS and with placebo were similar at a rate of 87% each.

Prior Medications:
Similar numbers of patients across treatment sequence groups had a recent history of ADHD medication use requiring washout (d-ATS/placebo 23% compared to placebo/d-ATS 25%). The most common prior medications were methylphenidate, dexmethylphenidate, lisdexamfetamine, dextroamphetamine mixed salts, and guanfacine.

Concomitant Medications:
During dose optimization, 77% of patients took a concomitant medication. During double-blind treatment, 74% of patients took a concomitant medication. These medications are not expected to impact safety analysis.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the mean total SKAMP score during the classroom day at the end of each double-blind treatment week. The Applicant's results (Table 15) show a significant carryover effect (p=0.009), indicating that treatment effect size was related to the order in which subjects received the double-blind treatment. The Applicant provided further analyses to investigate this (permutation test), and concluded that the strength of evidence for the first DB treatment period (Week 6) was sufficient to conclude that d-ATS was superior to placebo on mean total SKAMP.

Table 15: Mean SKAMP Total Score by Visit – Carryover Effect (Full Analysis Set; MMRM)

| | | | | Treatment | | | Carryover | |
|---|---|---|---|---|---|---|---|---|
| Visit | Statistics | d-ATS (N = 106) | Placebo (N =106) | LS Mean Difference | 95% CI | P-value | Sequence p-value | Period p-value |
| Double Blind Phase | n | 100 | 101 | | | | | |
| | Mean (SD) | 12.55 (6.831) | 19.29 (10.804) | | | | | |
| | Median | 10.33 | 16.44 | | | | | |
| | Min, Max | 4.2, 35.7 | 6.2, 49.1 | | | | | |
| | LS Mean (SE) | 12.81 (0.320) | 18.67 (0.322) | -5.87 | (-6.76, -4.97) | <0.001 | 0.009 | <0.001 |
| 6 | n | 50 | 51 | | | | | |
| | Mean (SD) | 12.20 (6.519) | 17.63 (10.511) | | | | | |
| | Median | 10.50 | 13.78 | | | | | |
| | Min, Max | 4.6, 35.7 | 6.8, 49.1 | | | | | |
| | LS Mean (SE) | 12.47 (0.451) | 17.14 (0.454) | -4.67 | (-5.92, -3.42) | <0.001 | | |
| 7 | n | 50 | 50 | | | | | |
| | Mean (SD) | 12.91 (7.178) | 20.98 (10.941) | | | | | |
| | Median | 10.11 | 17.17 | | | | | |
| | Min, Max | 4.2, 32.6 | 6.2, 48.6 | | | | | |
| | LS Mean (SE) | 13.15 (0.455) | 20.21 (0.458) | -7.06 | (-8.33, -5.79) | <0.001 | | |

Note: For the double blind phase output LS Means, 95% CI and p-value are from a mixed model repeated measures (MMRM) analysis, including the SKAMP total scores, fixed effects of sequence, period, treatment, timepoint, and the treatment x timepoint interaction and repeated effect of timepoint defined for subject within sequence using a variance components correlation structure.

Source: CSR Table 14.2.1.2.1

For pediatric ADHD studies, a parallel arm study is typically preferred instead to the crossover design used in this study. The significant sequence effect observed here demonstrates one of the reasons. Although the Applicant decided it was acceptable to present results using the combined data from both DB treatment periods, the statistical reviewer investigated the treatment effects for each period separately.

Table 16shows the results for the mean total SKAMP score for each DB period separately. In both periods, the mean total SKAMP for the group who received d-ATS was better (lower value) than for the group who received placebo, so the direction of the treatment effect was consistent. However, the treatment effect size was greater in the second DB period (-4.7 for Week 6; -7.1 for Week 7). Including the Week 7 results in the analysis model overestimates the size of the treatment effect in the presence of the sequence effect.

Table 16: Mean SKAMP Total Score by Visit Separately (Full Analysis Set; MMRM)

| Double-Blind Period | | Received d-ATS | Received Placebo | Between-Group Difference |
|---|---|---|---|---|
| Period 1 | SEQUENCE: | d-ATS/Pbo | Pbo/d-ATS | d-ATS - Pbo |
| Week 6 | N | 50 | 51 | |
| | Mean (SD) | 12.4 (1.2) | 17.1 (1.2) | -4.7 |
| | 95% CI | (10.2, 14.7) | (14.8, 19.4) | (-8.0, -1.4) |
| | P-value | | | p = 0.0049 |
| Period 2 | SEQUENCE: | Pbo/d-ATS | d-ATS/Pbo | |
| Week 7 | N | 50 | 50 | |
| | Mean (SD) | 13.1 (1.2) | 20.2 (1.3) | -7.1 |
| | 95% CI | (10.6, 15.5) | (17.7, 22.7) | (-10.6, -3.6) |
| | P-value | | | P < 0.001 |

Source: Statistical Reviewer

During the last week of the dose-optimization period (Week 5), prior to randomization, subjects attended a short classroom day to get them accustomed to the process. They were on their optimized dose of d-ATS treatment at that time. The visit included a pre-dose total SKAMP score, and 2 hours of classroom observation. I used this data, along with the pre-dose total SKAMP scores from Weeks 6 and 7, to look at a potential source for the sequence effect. The results (Table 17) show that the pre-dose score was consistent across the three classroom visits for the group randomized to the d-ATS/Placebo sequence, but fluctuated for the group randomized to the Placebo/d-ATS sequence. These are descriptive results only, and do not give conclusive evidence of the source of the sequence effect. This suggests that subjects did not start the classroom day assessments at the same level, which impacts the observed treatment effect size.

Table 17: Pre-dose Total SKAMP scores – Classroom visits (FAS)

| SEQUENCE (Randomized Order Of DB Treatment) | | Week 5 (End Of Titration; Pre-Rand.) | Week 6 (First DB Trmt Period) | Week 7 (Second DB Trmt Period) |
|---|---|---|---|---|
| d-ATS/Pbo | Trmt | d-ATS | d-ATS | Placebo |
| | n | 52 | 51 | 49 |
| | Mean (SD) | 13.3 (6.9) | 13.6 (5.9) | 13.3 (8.9) |
| | Min, Max | 0, 32 | 1, 29 | 0, 40 |
| Pbo/d-ATS | Trmt | d-ATS | Placebo | d-ATS |
| | n | 52 | 50 | 49 |
| | Mean (SD) | 14.4 (8.3) | 12.7 (7.9) | 16.1 (9.9) |
| | Min, Max | 0, 40 | 3, 36 | 4, 48 |

Source: Statistical reviewer

Data Quality and Integrity

All datasets and documentation were provided in the electronic submission ( \\CDSESUB1\evsprod\NDA215401\0001). The statistical reviewer was able to reproduce the Applicant's results and to conduct independent analyses without discrepancies.

Efficacy Results – Secondary and other relevant endpoints

The Applicant prespecified two key secondary endpoints: Onset and Duration of treatment effect. A hierarchical testing approach was applied to control overall Type I error for multiplicity. The onset of efficacy, based on the SKAMP total scores, was defined as the first assessment time showing statistical significance between d-ATS and placebo. Onset of efficacy will be analyzed using the same MMRM model as for the primary analysis. The closed testing procedure starts from the time-point of 1 hour post-morning dose, then 2, 3, 4.5, 6, 7, 9, 10 and 12 hours post-dose. The duration of efficacy will be claimed as the difference in hours between the onset of efficacy and the last consecutive time point at which the difference is still statistically significant (i.e., $p \leq 0.05$) and onset of efficacy.

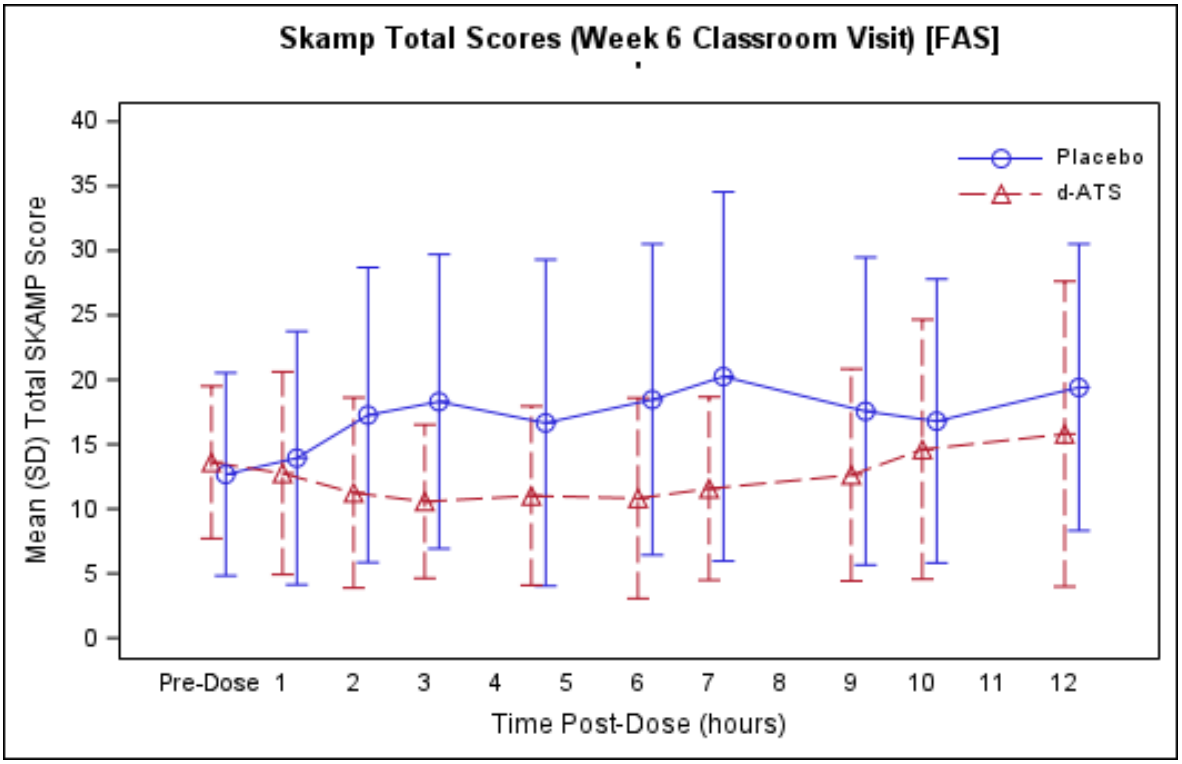
The statistical reviewer performed the ordered testing using the MMRM model using only the Week 6 data. The results indicate that d-ATS had statistically significantly lower mean SKAMP by 2 hours post-dose (onset) through 9 hours post-dose. The two treatment groups were not statistically significantly different at Hour 10 post-dose. The Applicant's analyses of onset and duration (CSR Section 11.2.1) included data from Week 6 and Week 7. Their conclusion was that onset was observed at 2 hours post-dose and continued through hour 12 (all p-values ≤ 0.003). Because the treatment effect size observed was larger in Week 7 and the statistical reviewer did not include those data, the different conclusion beyond 9 hours is not unexpected.

Table 18: Mean Total SKAMP Score by Timepoint at Week 6 (MMRM model; Full Analysis Set)

| | d-ATS-Placebo n=50 TRMT = d-ATS | Placebo-d-ATS n=51 TRMT = Pbo | LS Diff {d-Ats – Pbo} | p-value |
|---|---|---|---|---|
| Timepoint | | | | |
| Pre-dose | 13.5 | 12.5 | 0.97 | 0.6211 |
| Post-dose: 1 hr | 13.0 | 13.9 | -0.98 | 0.6168 |
| Post-dose: 2 hrs | 11.3 | 17.3 | -6.02 | 0.0021 † |
| Post-dose: 3 hrs | 10.6 | 18.3 | -7.74 | <.0001 |
| Post-dose: 4.5 hrs | 11.0 | 16.7 | -5.65 | 0.0039 |
| Post-dose: 6 hrs | 10.8 | 18.5 | -7.64 | <.0001 |
| Post-dose: 7 hrs | 11.6 | 20.3 | -8.68 | <.0001 |
| Post-dose: 9 hrs | 12.5 | 17.6 | -5.04 | 0.0102 ‡ |
| Post-dose: 10 hrs | 14.5 | 16.8 | -2.29 | 0.2417 |
| Post-dose: 12 hrs | 15.7 | 19.4 | -3.70 | 0.0586 |

† Time of Onset of treatment effect
‡ Duration of treatment effect
Source: Statistical Reviewer

Figure 12: Mean SKAMP Scores: First Double-blind Treatment Only (Week 6)




Source: Statistical Reviewer

The study design included a dose-optimization phase. At the end of the dose-optimization phase, seven patients (7%) were optimized to d-ATS 5 mg/4.76 $cm^2$, 35 patients (33%) were optimized to d-ATS 10 mg/9.52 $cm^2$, 42 patients (39%) were optimized to 15 mg /14.29 $cm^2$, and 23 patients (22%) were optimized to 20 mg/19.05 $cm^2$.

Additional Analyses Conducted on the Individual Trial

The statistical reviewer produced exploratory analyses for the primary efficacy endpoint by age group, gender, race, and Baseline ADHD Type (see Table 19). For the subgroup analyses, only the results for Week 6, the first period in the double-blind treatment, were included. The efficacy results for this period are not impacted by the carryover effect. These are descriptive analyses only and are not intended for inferential purposes.

In all the subgroups, the placebo group had consistently higher least squares mean total SKAMP scores than the d-ATS group. In general, least squares mean total SKAMP scores were higher in the younger age (6-12 yrs), males, whites, and ADHD-Combined type subgroups.

As mentioned regarding demographics, the distribution of subjects in the two ADHD types was imbalanced across the two treatment arms. The consistent results across the subgroups indicate this did not impact the results.

Table 19. Subgroup Analyses - Reviewer's Results (FAS; MMRM model)

| Primary: | Week 6 Visit | |
|---|---|---|
| Mean Total SKAMP | d-ATS | Placebo |
| LSMean (SE) | N=50 | N=51 |
| Age group | | |
| 6-12 years | n=37 | n=37 |
| | 13.6 (1.4) | 19.3 (1.4) |
| 13-17 years | n=13 | n=14 |
| | 9.2 (1.2) | 11.4 (1.2) |
| Gender | | |
| Female | n=16 | n=16 |
| | 8.8 (2.0) | 18.3 (2.0) |
| Male | n=34 | n=35 |
| | 14.1 (1.4) | 16.6 (1.4) |
| Race | | |
| White | n=34 | n=43 |
| | 12.9 (1.5) | 18.1 (1.4) |
| People of Color | n=16 | n=8 |
| | 11.5 (1.5) | 11.8 (2.1) |

| | | |
|---|---|---|
| Baseline ADHD Type | | |
| Inattentive | n=20 | n=28 |
| | 10.0 (1.4) | 14.1 (1.2) |
| Combined | n=30 | n=23 |
| | 14.0 (1.6) | 20.8 (1.9) |

Source: Statistical Reviewer

Statistical Reviewer overall conclusions for Study N25-006:
The goal of using a crossover study design is that each subject serves as their own control. This enables estimation of the within-subject variability, reducing unexplained variability, and potentially increasing the precision to detect a treatment effect. This relies on the assumption that subjects return to the same starting level during each period in the study (i.e., no carryover effect). If this assumption is not met the carryover effect is confounded with the treatment effect. This is what was discovered in Study N25-006. The Applicant used permutation test simulations to reach the conclusion the carryover effect did not impact the results of the hypothesis test between treatments. However, we are concerned with accurately estimating the effect size. By investigating the pre-dose Total SKAMP scores prior to randomization and during each of the double-blind treatment periods I determined the subjects did not return to the same starting level, and that the results in the second double-blind period gave a larger estimate of the treatment effect size. Therefore, I conducted my analyses on the two treatment periods separately. The direction of the treatment effect is consistent, with d-ATS superior to placebo, thus providing sufficient evidence to support efficacy for d-ATS in this study. I conclude that only the results for the first double-blind period should be report in Section 14 of the label representing treatment effect size.

### 8.1.2. N25:015: "A Multiple-Dose, Open-Label, 4-Week, Phase 1 Study to Characterize the Pharmacokinetics, Safety, and Tolerability of d-Amphetamine Transdermal System (d-ATS) in Adult Subjects Diagnosed with ADHD"

Overview and Objective
Study N25-015 is a phase 1 study in adult patients with ADHD presented along with Study N25-006 to provide pharmacokinetics (PK) accumulation data over 4 weeks of d-ATS administration and safety data regarding intended use with application site rotation as instructed in the proposed label.

Primary Objective:

- To assess the PK of d-ATS doses administered as intended use (rotating application site daily, Group A) and as exaggerated use (same application site daily, Group B) over 4 weeks

Secondary Objective:

- To evaluate dermal reactions in relation to exposure and PK profile

- To evaluate the safety and tolerability of d-ATS

Trial Design
This was an open-label study comparing doses of d-ATS 20 mg/19.05 $cm^2$ daily (9-hour wear time) with intended use (Group A) and with exaggerated use (Group B) over a 4-week treatment period. The patients were adults ages 18 to 65 years who were diagnosed with ADHD.

Key inclusion criteria included: meeting DSM-5 criteria for ADHD and otherwise healthy

Key exclusion criteria included: any significant illness history including serious cardiovascular disease or seizures; abnormal blood pressure, pulse, or clinically significant ECG finding; history or presence of significant skin disorder; some comorbid psychiatric conditions (severe depression, psychosis, bipolar disorder, aggression, severe anxiety, agitation, tension, tic or Tourette's disorder); history of alcohol or controlled substance abuse or positive drug/alcohol screen; prescription medication (except for ADHD treatment) within 30 days or over-the-counter medication within 7 days (with the exception of acetaminophen and hormonal therapies/contraception)

It does not appear that ADHD diagnosis was confirmed using a structured or semi-structured clinical interview. This is unlikely to have significantly impacted overall study safety or efficacy results. Otherwise, these inclusion and exclusion criteria appear reasonable.

Randomization and Blinding:
Patients were randomized to intended use (Group A) or exaggerated use (Group B). This was an open-label study.

Study Schematic:
The study was comprised of a 4-week screening phase, a 4-week treatment phase, and a telephone contact follow-up. During the treatment phase, patients were confined on Days 0 to 2 then on Days 27 to 30.

Dosing:
Patients were to apply d-ATS 20 mg/19.05 $cm^2$ at approximately the same time each morning for 9 hours of wear-time. The highest dose was selected as appropriate to meet the objectives of this PK and dermal irritation study. Patients randomized to Group A were instructed to apply the transdermal system to the left or right side of one of five different application sites (hip, flank, chest, upper arm, and upper back) in a rotating fashion. Patients randomized to Group B were instructed to apply the transdermal system to either the left or the right hip with no site rotation. During screening, patients had to washout from all prior ADHD medications over the 7 days prior to initiation of the treatment phase.

Study Schedule:

Confinement occurred on Days 0 to 2 and Days 27 to 30. Outpatient study visits occurred at Screening and on Day 7, Day 14, and Day 21. Telephone follow-up occurred on Day 35. The assessment schedule was as follows:

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Table 21: Study N25-015 Schedule of Assessments

| Study Procedures | Screening | Washout Period Days -7 to -1 | Clinic Admission 1 Day 0 | Treatment Period | | | | End of Treatment Day 30/Early Termination | Safety Follow-Up Day 35 + 3 Days |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Confinement Period 1 Days 1-2/ Confinement Period 2 Days 28-30 | Group A: Home Days 3-27/ Group B: In Clinic Days 3–26 | Clinic Visits Days 7, 14, and 21 | Clinic Admission 2 Day 27 | | |
| Informed consent | X | | | | | | | | |
| Assign subject number | X | | | | | | | | |
| Review inclusion/exclusion criteria | X | | X | | | | X | | |
| Medical/psychiatric history | X | | | | | | | | |
| Prior medications | X | | X | X[1] | | | | | |
| Medical history update | | | X | X[1] | | | | | |
| Physical examination | X | | X | | | | | X | |
| Body temperature | X | | X | | | | X | X | |
| Weight | X | | X | | | | | X | |
| Height and BMI | X | | | | | | | | |
| Sitting BP, HR, and RR | X | | X | X[2] | | X | X | X | |
| Orthostatic hypotension | X[3] | | | | | | | | |
| Serum chemistry, hematology, and urinalysis | X[4] | | X[5] | | | X[5] | | X[5] | |
| Serum/urine pregnancy[6] | X | | X | | | X | X | | |
| Hepatitis B and C, HIV antibodies | X | | | | | | | | |
| Alcohol screen | X | | X | | | X | X | | |
| Urine drug screen | X | | X | | | X[7] | X[7] | | |
| Cotinine screen | X | | | | | | | | |
| 12-lead ECG | X | | X | | | X[8] | X | X | |
| DSM-5 score | X | | | | | | | | |
| C-SSRS (baseline/ screening version) | X | | | | | | | | |
| C-SSRS (since last visit version) | | | X | X[9] | | | X | | |
| Clinic admission | | | X | | | | X | | |
| Confirm subject eligibility | | | X | | | | X | | |
| Overnight fast | | | X | X[10] | | | X | | |
| Assign randomization number | | | | X[11] | | | | | |
| Patch application in clinic[12] | | | | X | | | | | |
| Patch removal in clinic | | | | X[13] | X[14] | X | X[13] | | |
| Patch removal at home | | | | X[15] | X[16] | | | | |
| Patch application at home | | | | | X[16] | X | | | |
| PK sample collection | | | | X[17] | X[18] | X | | X | |
| Adverse events and concomitant medications | | | | X | X[19] | X | X | X | X |
| Adhesion | | | | X[20] | X[22] | | | | |

| Study Procedures | Screening | Washout Period Days -7 to -1 | Clinic Admission 1 Day 0 | Treatment Period | | | | End of Treatment Day 30/Early Termination | Safety Follow-Up Day 35 + 3 Days |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Confinement Period 1 Days 1-2/ Confinement Period 2 Days 28-30 | Group A: Home Days 3-27/ Group B: In Clinic Days 3–26 | Clinic Visits Days 7, 14, and 21 | Clinic Admission 2 Day 27 | | |
| evaluation | | | | | | | | | |
| Discomfort and pain | | | | X[21] | X[22] | | | | |
| Irritation evaluation/photo | | | | X[23] | X[23] | X | X | | |
| Irritation evaluation | | | | | X[22] | | | | |
| Adhesive residue evaluation | | | | X[24] | | X | | | |
| Dispense daily dosing and dermal diary | | | | X | | X | | | |
| Subject completes daily dosing and dermal diary | | | | | X | | | | |
| Review daily dosing and dermal diary | | | | | | X | X | | |
| Dispense study drug | | | | X[25] | | X | | | |
| Perform drug accountability | | | | | | X | X | | |
| Discharge subjects | | | | X[26] | | | | X[27] | |
| Telephone safety F/U | | | | | | | | | X |

Abbreviations: BMI = body mass index; BP = blood pressure; HR = heart rate; RR = respiratory rate; ECG = electrocardiogram; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; C-SSRS = Columbia Suicide Severity Rating Scale; PK = pharmacokinetic; F/U = follow-up.

1. Data were collected only before the first dose.
2. Confinement Period 1: Sitting BP, HR, and RR within 30 minutes prior to patch application and at 2, 4, 6, 8, 10, 18, and 24 hours post Day 1 patch application. When a vital sign was scheduled at the same timepoint as a PK sample collection, the blood collection was conducted at the exact time specified by the protocol and vital sign assessments were made within 10 minutes prior to the scheduled timepoint.
   Confinement Period 2: Sitting BP, HR, and RR within 30 minutes prior to patch application and at 2, 4, 6, 8, 10, 18, 24, 36, and 48 hours post-patch application.
3. After supine position, BP was measured again after standing for 2 minutes to test for orthostatic hypotension.
4. Blood samples were collected under fasting conditions.
5. Blood samples were collected under non-fasting conditions at Days 0 and 14.
6. Serum pregnancy test for WOCBP at screening, Day 0, and Day 27. Urine pregnancy test for WOCBP at Days 7, 14, and 21.
7. During the treatment period, subjects applied d-ATS (amphetamine) patches daily for 4 weeks. When confirming eligibility during this period, subjects tested positive for amphetamine; however, they were allowed to continue treatment until the end of the study.
8. Obtained ECG on Day 14 only.
9. Day 2 only, prior to discharge.
10. Confinement Period 1 and 2.
11. Randomization number assigned sequentially as per randomization schedule.
12. d-ATS was applied in the clinic on Days 1, 2, and 28.
13. d-ATS was removed in the clinic on Days 1, 7, 14, 21, 27, and 28.
14. Subjects in Group B only had their patches removed in the clinic.
15. For Group A only, patches applied in the clinic on Day 2 were removed at home by the subjects.
16. Subjects in Group A only, applied and removed their patches at home. Exception: Day 27 when patches were removed in the clinic.
17. Confinement Period 1: Collected blood sample (4 mL) for PK analysis within 30 minutes prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 9 (prior to patch removal), 9.5, 10, 11, 14, 18, and 24 hours post-patch application on Day 1.
    Confinement Period 2: Collected blood sample (4 mL) for PK analysis within 30 minutes prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 9 (prior to patch removal), 9.5, 10, 11, 14, 18, 24, 30, 36, and 48 hours post-patch application.
18. A blood sample for PK was collected if study personnel assessed irritation with a score of 2 or greater (Group B only) (see Section 9.5.1.7.1.1).
19. Subjects in Group A were to call the clinical site to report any AEs, including those leading to an early patch removal.
20. Assessed patch adhesion during patch wear at 1, 2, 4, 6, and 9 hours (immediately prior to patch removal) on Days 1 and 28 (see Section 9.5.1.7.1.3).
21. Assessed discomfort and pain at the patch site during patch wear at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, and 9 (immediately prior to patch removal) on Days 1 and 28 (see Section 9.5.1.7.1.2).

| Study Procedures | Screening | Washout Period Days -7 to -1 | Clinic Admission 1 Day 0 | Treatment Period | | | | End of Treatment Day 30/Early Termination | Safety Follow-Up Day 35 + 3 Days |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Confinement Period 1 Days 1-2/ Confinement Period 2 Days 28-30 | Group A: Home Days 3-27/ Group B: In Clinic Days 3–26 | Clinic Visits Days 7, 14, and 21 | Clinic Admission 2 Day 27 | | |

22. For subjects in Group A, adhesion, discomfort, pain, and irritation at the patch application site were assessed daily and recorded in the patient diary. For subjects in Group B, discomfort, pain, and irritation were assessed in clinic after patch removal.
23. Confinement Period 1: Irritation was assessed immediately after PK sampling (ie, at the following timepoints: prior to patch application; immediately after patch application; during patch wear at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, and 9 hours [immediately prior to patch removal]; and at 0.5, 1, 2, 5, 9, and 15 hours after patch removal on [ie, 9.5, 10, 11, 14, 18, and 24 hours after patch application] Day 1). A photograph of the application site was to be taken for any irritation reaction(s) scored ≥3 (see Section 9.5.1.7.1.1). For Group B only, on Days 3 to 26, irritation was assessed 30 minutes after patch removal; a photograph of the application site was to be taken for any irritation reaction(s) scored ≥3.
Confinement Period 2: Irritation was assessed immediately after PK sampling (ie, at the following timepoints: prior to patch application; immediately after patch application; during patch wear at 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, and 9 hours [immediately prior to patch removal]; and at 0.5, 1, 2, 5, 9, 15, 21, 27, and 39 hours after patch removal [ie, 9.5, 10, 11, 14, 18, 24, 30, 36, and 48 hours after patch application] on Days 28 to 29). A photograph of the application site was to be taken for any irritation reaction(s) scored ≥3 (see Section 9.5.1.7.1.1).
24. Assessed adhesive residue immediately following patch removal on Days 1, 7, 14, 21, and 28 (see Section 9.5.1.7.1.4).
25. Dispensed 1-week supply of patches to subjects prior to discharge on Day 2 and at weekly visits on Days 7, 14, and 21.
26. Subjects discharged after completion of all evaluations and procedures on Day 2.
27. Subjects discharged after completion of all 48-hour evaluations and procedures on Day 30.

Source: CSR for N25-015, Table 9-2, pages 35-39

Study Endpoints

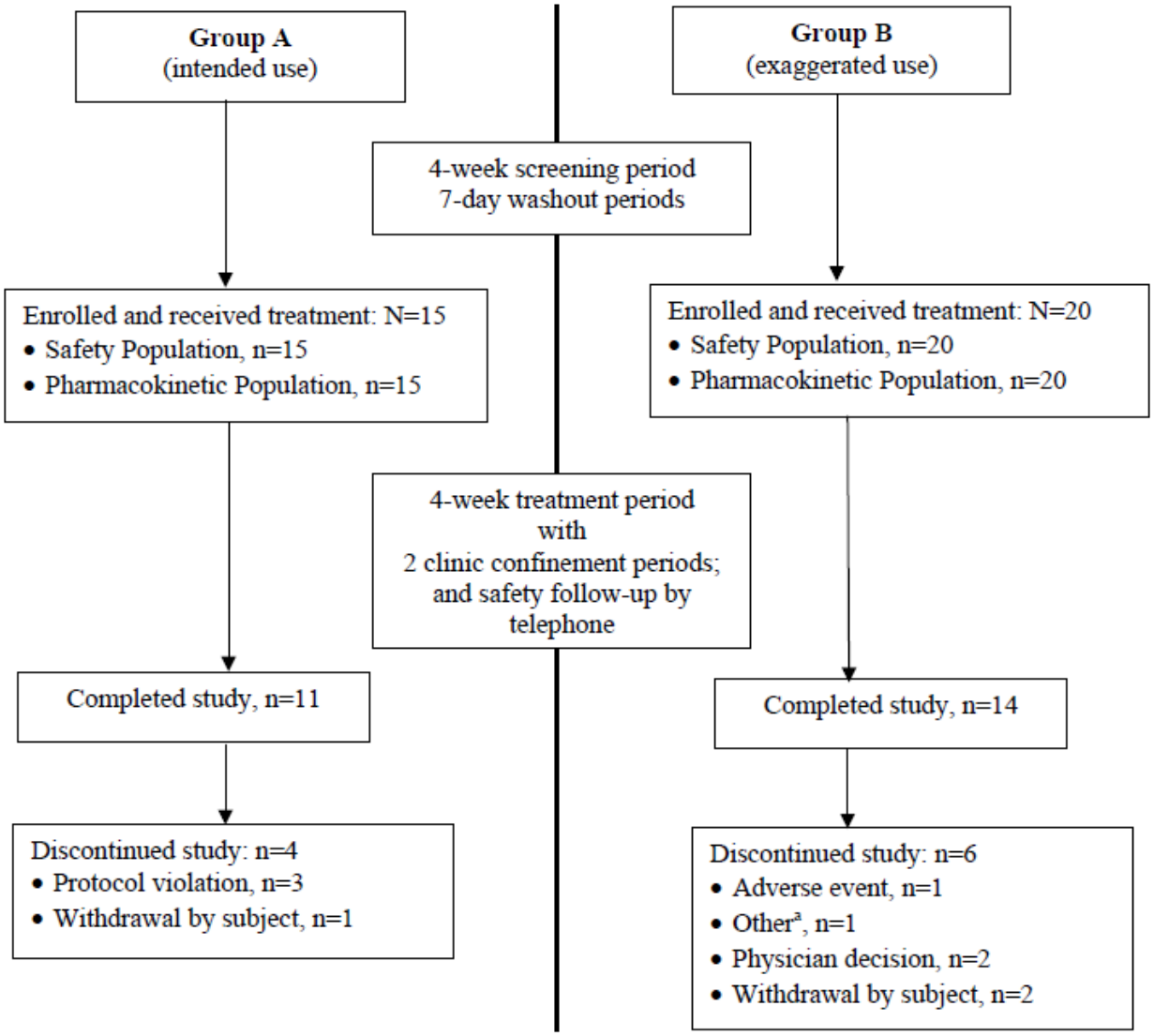
PK endpoints for d-ATS included: maximum plasma concentration; area under the curve from time 0 to the last measurable sample, from 0 to 9 hours, and from 0 to 24 hours; average plasma concentration at steady state; minimum plasma concentration during steady state; peak to trough fluctuation; time of maximum concentration; terminal eliminiation half-life; theroretical accumulation ratio; accumulation ratio determined as the ratio of Days 28 to 1 $C_{max}$ values, $AUC_{0-9}$ values, and $AUC_{0-24}$ values; mean plasma amphetamine concentrations over time for patients in Group A compared to those in Group B; relationship between plasma amphetamine PK parameters and dermal reactions (irritation, discomfort, pain, and adverse events (AEs); residual amphetamine content; residual drug percentage; apparent dose delivered; and drug released.

Safety assessments included: vital signs, physical examination, serum chemistry and hematology, urinalysis, ECG, C-SSRS, and dermal assessments of adhesion, discomfort, irritation, and adhesive residue. See Section 8.2.3 for descriptions of dermal assessments. There are no major concerns about the study endpoints; the safety endpoints are adequate.

Patient Disposition

Thirty-five patients were enrolled in this study: fifteen patients received d-ATS in Group A and twenty received d-ATS in Group B. Twenty-five patients completed the study.

Figure 12: Study N25-015 Patient Disposition




Group A: d-ATS applied daily to the left or right side of 1 of 5 different application sites of hip, flank, chest, upper arm, and upper back. The site of application was rotated every time a new patch was applied during the 4-week patch wear treatment period.
Group B d-ATS was applied daily to only the left or right hip (same site of application daily) with no application site rotation during the 4-week treatment period.
[a]Subject's score was too high on dermal assessments and was early terminated per Principal Investigator (physician decision).
Source: Post-text Table 14.1.1 (Section 14.1).

Source: CSR for N25-015, Table 10-1, page 67

### 8.1.3. N25-018: "A Randomized, Evaluator-blinded Study to Evaluate Skin Irritation and Sensitization of d-Amphetamine Transdermal System in Healthy Adults"

Overview and Objective
Study N25-018 is a phase 1 study in healthy adult subjects to assess skin irritation and contact sensitization.

Objectives:

- To assess skin sensitization potential with repeated exposure to d-ATS, placebo, and saline patches
- To assess for skin irritation with repeated exposure to d-ATS, placebo, and saline patches

Trial Design
This was a randomized, evaluator-blinded skin irritation and sensitization study. Subjects applied d-ATS 5 mg/4.76 $cm^2$, a placebo patch, and a saline patch during the induction and challenge (and as applicable, re-challenge) phases. Study duration was 10 to 16 weeks. The subjects were healthy adults ages 18 to 65 years.

Key inclusion criteria included: healthy male and non-pregnant, non-lactating females with a normal screening ECG

Key exclusion criteria included: clinically significant disease including abnormal screening investigations and history or presence of significant skin disorder (including allergy to soaps, lotions, cosmetics, adhesives, or adhesive dressings); history of severe depression, psychosis, bipolar disorder, mania, aggression, marked anxiety, agitation, tension, tics or Tourette's disorder, narcotic or drug abuse, or alcoholism; use of any prohibited medications (including at the patch application site or antihistamines within 72 hours or systemic or topical corticosteroids within 3 weeks); sunbathing within 7 days or had sunburn in the test area; foreseeable intensive solar exposure during the trial

These inclusion and exclusion criteria appear reasonable.

Randomization and Blinding:
Subjects were randomized to patch application sites. Evaluators were blinded to treatment.

Study Schematic:
The study comprised a screening period; a 3-week induction period; a 2-week rest period; a 1-week challenge period; for subjects with any sensitization during the challenge period, an up to 1-week re-challenge period 4 weeks after the challenge period; and a follow-up period.

Dosing:

Subjects applied d-ATS 5 mg/4.76 $cm^2$, a placebo patch, and a saline patch to the same sites on the left side of the back for 24 hours (+/- 3 hours) during the entire 3-week induction phase (minimum 18 days) and on the right side of the back for 48 hours during the challenge phase and, if applicable, re-challenge phase.

Study Schedule:
Subjects returned to clinic on the following schedule:

- Daily during the 3-week induction period
- 2 weeks later to initiate the challenge period, then 48 hours later, and daily thereafter for 3 days
- If applicable, 4 weeks later to initiate the re-challenge period on a schedule mirroring the challenge period

Approximately 7 days after end-of-treatment (or early termination), subjects had telephone or clinic follow-up. The assessment schedule was as follows:

Table 22: Study N25-018 Schedule of Assessments

| Phase | Screening | Treatment | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | | Induction[a] | | | Rest[b] | Challenge Days | | | | | | Re-challenge Days | | | | | | End of Treatment/ Early Termination | Follow up Visit |
| | | Clinic Days | | | | | | | | | | | | | | | | | |
| Days | Approx.-28 to -1 | 1 | 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 | 22 | 23-37 | 38 | 39 | 40 | 41 | 42 | 43 | 72 | 73 | 74 | 75 | 76 | 77 | | |
| **Procedures/Assessments** | | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | |
| Assign Subject Screening Number | X | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X[c] | | | | X[c] | | | | | | X[c] | | | | | | | |
| Medical History/Current Medical Conditions | X | X | | | | | | | | | | | | | | | | | |
| Prior/Current Medications | X | | | | | | | | | | | | | | | | | | |
| Fitzpatrick Skin Type | X | | | | | | | | | | | | | | | | | | |
| Physical Examination | X | | | | | | | | | | | | | | | | | X | |
| Vitals Signs | X[d] | X[e] | X[e] | X[e] | | X[e] | | | | | | X[e] | | | | | | X[e] | |
| Body Temperature | X | | | | | | | | | | | | | | | | | X | |
| Height, Weight, BMI | X | | | | | | | | | | | | | | | | | | |
| 12 Lead ECG[f] | X | | | | | | | | | | | | | | | | | X | |
| Alcohol Screen | X | | | | | | | | | | | | | | | | | | |
| C-SSRS | X | X | | X | | X | | | | | | X | | | | | | X | |
| Blood Chemistry, Hematology and Urinalysis | X | | | | | | | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | | | | | | X | |
| Urine Drug Test | X[g] | X[g] | | | | | | | | | | | | | | | | | |
| HBV, HCV and HIV tests | X | | | | | | | | | | | | | | | | | | |
| Pregnancy Screen (WOCBP)[h] | X | X | | | | X | | | | | | X | | | | | | X | |
| Assign Subject Enrollment Number | | X | | | | | | | | | | | | | | | | | |
| Patch Application[i] | | X | X | | | X | | | | | | X | | | | | | | |
| Patch Removal | | | X | X | | | | X | | | | | | X | | | | | |
| Adhesion Assessment[j] | | | X | X | | | X | | | | | | X | | | | | | |
| Irritation Assessment[k,l] | | X | X | X | | X | | X | X | X | X[m] | X | | X | X | X | X[n] | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X[m] | X | X | X | X | X | X[n] | X | X[p] |
| Concomitant Medications | | X | X | X | X | X | X | X | X | X | X[m] | X | X | X | X | X | X[n] | X | |
| Subject Contact | | | | | X[o] | | | | | | | | | | | | | | |
| Text visibility assessment[q] | | X[q] | X[q] | | | | | | | | | | | | | | | | |

EOT: End of Treatment; ET: Early Termination; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human Immunodeficiency virus; WOCBP: Women of childbearing potential; ECG: Electrocardiograph

**Footnotes:**

a. During the Induction Period, applications of the test articles were made to the same skin sites daily for 21 consecutive days, for a total of 21 applications. Each patch remained in place for 24 hours (± 3 hours).
b. During the Rest Period, subjects were contacted at least twice to confirm reporting of AEs or concomitant medications.
c. Inclusion/Exclusion Criteria was reconfirmed on Day 1 of the Induction, Challenge and on Day 1 of the Re-Challenge Periods (if required).
d. Screening vital signs consisted of sitting BP, HR and RR, oral body temperature, and supine BP for orthostatic hypotension.
e. Vital signs consisting of sitting BP, HR and RR were measured only on Day 1, Day 8, Day 15, and Day 22 of the Induction Period, Day 1 of Challenge and Re-challenge (if required), as well as at EOT/ ET. In addition, oral body temperature was recorded at EOT/ ET.
f. Any ECG which demonstrated a clinically significant abnormality at Screening was exclusionary and the subject was not enrolled in the trial.
g. Urine drug screen was done at Screening and Day 1 of the Induction Period.
h. Serum pregnancy test was done at Screening only. All other pregnancy tests were urine and were done prior to patch application at Day 1 of Induction, Challenge and Re-challenge Periods, if required, and at EOT/ET. Clinical Site may have performed pregnancy tests on all females if it was their standard procedure.
i. After confirmation of eligibility, the first set of three patches was applied.
j. Subjects returned to the Clinical Site post patch application for adhesion of the patches to the skin immediately prior to patch removal at 24 hours post application Day 1 assessments, and daily for patch removal and irritation assessments.
k. Subjects returned to the Clinical Site daily post patch application for adhesion assessments, patch removal and irritation assessments.
l. Irritation was assessed prior to patch application on Day 1, and 30 minutes to 1 h post-removal during Induction Period. During Challenge/Re-challenge Periods, irritation was assessed prior to patch application on Day 1 and 30 minutes to 1 h, 24h, 48h and 72h post-removal. A photograph of the application site was taken at the time of irritation assessment prior to patch application on Day 1. Additionally, photographs were taken of any irritation reaction(s) scored ≥2.
m. All EOT procedures were performed on the last Challenge visit if there was no Re-challenge.
n. All EOT procedures were performed at the last Re-challenge visit, if required.
o. Subjects had a safety visit approximately 7 days (± 1 day) after EOT/ET Visit. The Principal Investigator or qualified study staff contacted all subjects by phone for continued safety monitoring of AEs. At the discretion of the Principal Investigator, subjects may have been required to return to the Clinical Site for their Follow-up Safety Visit.
p. Subjects had a safety visit approximately 7 days (± 1 day) after EOT/ET Visit. The Principal Investigator or qualified study staff contacted all subjects by phone for continued safety monitoring of AEs. At the discretion of the Principal Investigator, subjects may have been required to return to the Clinical Site for their Follow-up Safety Visit.
q. Patch backing text visibility was evaluated 30 ± 5 minutes after patch application on Day 1 and prior to patch removal (from 30 minutes before patch removal until patch removal) on Day 2.

Source: CSR for N25-018, Table 1, pages 52-53

## Study Endpoints

Dermal endpoints included sensitization potential, irritation scores, and adhesion assessments.
Safety assessments included: vital signs, physical examination, serum chemistry and hematology, urinalysis, ECG, and C-SSRS.
There are no major concerns about the study endpoints; the safety endpoints are adequate.

## Patient Disposition

Two hundred twenty-nine subjects were enrolled in this study. Two hundred one subjects completed the study.

Figure 13: Study N25-018 Patient Disposition

| Characteristics | Overall | Population | | |
|---|---|---|---|---|
| | | Safety | PPI | PPS |
| Subjects Screened | 522 | | | |
| Screen failures | | | | |
| Did Not Meet Inclusion/Exclusion Criteria, n (%) [1] | 293 ( 56.1) | | | |
| Subjects Randomized [2] | 229 | | | |
| Qualified per Population, n (%) | 229 (100.0) | 229 (100.0) | 206 ( 90.0) | 200 ( 87.3) |
| Number of Subjects Completing the Study, n (%) [3] | 201 ( 87.8) | 201 ( 87.8) | 200 ( 87.3) | 200 ( 87.3) |
| Number of Subjects Discontinued the Study, n (%) | 28 ( 12.2) | 28 ( 12.2) | 6 ( 2.6) | 0 |
| Reason for Early Discontinuation | | | | |
| Withdrawal By Subject, n (%) | 20 ( 8.7) | 20 ( 8.7) | 6 ( 2.6) | 0 |
| Adverse Event, n (%) | 5 ( 2.2) | 5 ( 2.2) | 0 | 0 |
| Lost To Follow-Up, n (%) | 2 ( 0.9) | 2 ( 0.9) | 0 | 0 |
| Other, n (%) | 1 ( 0.4) | 1 ( 0.4) | 0 | 0 |

Notes: **Safety Population** includes all subjects who have received at least one administration of the investigational product.
**Per-protocol Cumulative Irritation (PPI) Population** includes all subjects who have all patches applied sequentially to the same site for the entire 21-day Induction Period (without any period of detachment longer than 24 hours). If a test article is moved or removed due to excessive irritation, it should be included in the PP population using Last (Worst) Observation Carried Forward (LOCF) from the original application site.
**Per-protocol Sensitization (PPS) Population** includes all subjects who have All patches worn (without any period of detachment longer than 24 hours) for the full 21-day Induction Period AND for the entire 48 hours during Challenge and Re-challenge Periods. Each subject will return for at least one of the scheduled evaluations at 24, 48 and 72 hours after removal of the Challenge/ Re-challenge patch.If a test patch is moved or removed due to excessive irritation,it should be included using LOCF.
[1] Percentage is relative to total number screened.
[2] Percentages in this section are relative to total number randomized, unless otherwise noted (see footnote 3).
[3] Percent of subjects completing the study is relative to randomized in the corresponding column.

Source: CSR for N25-018, Table 9, page 71

### 8.1.4. Assessment of Efficacy Across Trials

Not applicable

### 8.1.5. Integrated Assessment of Effectiveness

Analysis and interpretation of the pivotal pediatric study was complicated by the crossover study design. However, the statistically significant treatment effect observed on the primary efficacy endpoint (the SKAMP, which has been previously accepted for use as a clinical endpoint for ADHD) in period 1 prior to crossover ultimately meets the evidentiary standard for effectiveness for d-ATS treatment of ADHD in children and adolescents ages 6 to 17 years in combination with reliance on the Agency's finding of effectiveness for Vyvanse, via an acceptable scientific bridge.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

This safety review will examine the pediatric population (6 to 17 years of age) with ADHD in Study N25-006, a dose-optimization and randomized, double-blind, placebo-controlled, parallel-group, crossover trial. Please see Section 8.2.3 for details of the AE adjudication approach. Additionally, adults patients with ADHD in Study N25-015 and healthy adult subjects

in Study N25-018, open-label trials, were briefly reviewed for pertinent information, although there was no controlled safety data. Finally, results of the d-ATS phase 1 programs in the Integrated Summary of Safety (ISS) for any major trends or concerns were also reviewed and the safety analysis results were independently confirmed using the datasets submitted by the Applicant.

### 8.2.2. Review of the Safety Database

Overall Exposure

A total of 648 subjects (245 children (all with ADHD) and 403 adults (87 with ADHD and 316 healthy) received at least one dose of d-ATS in the entire development program.

A substantial proportion of subjects exposed in all age groups received the highest dose proposed for marketing as shown in Table 23below.

Table 23: d-ATS Exposure by Dose in All Subjects

| Age Groups | 5 mg/ 4.7 $cm^{2a}$ | 8.4 mg/ 8 $cm^2$ | 9.38 mg/ 9.38 $cm^2$ | 9.85 mg/ 9.38 $cm^2$ | 10 mg/ 9.52 $cm^{2a}$ | 15 mg/ 14.29 $cm^{2a}$ | 20 mg/ 19.05 $cm^{2a}$ | Total |
|---|---|---|---|---|---|---|---|---|
| Children with ADHD: 6-12 years | 115 | 18 | 0 | 0 | 87 | 40 | 49 | 166 |
| Adolescents with ADHD: 13-17 years | 47 | 0 | 0 | 0 | 39 | 29 | 27 | 79 |
| Adults with ADHD: ≥18 years | 19 | 0 | 0 | 0 | 8 | 8 | 52 | 87 |
| Healthy adults: ≥18 years | 243 | 0 | 7 | 8 | 0 | 0 | 65 | 316 |

a Proposed dosage strength to be listed in the USPI for d-ATS.
Source: Module 5.3.1.2, Study N25-002 CSR, Listing 16.2.1; Module 5.3.1.2, Study N25-004 CSR, Listing 16.2.7.8; Module 5.3.3.2, Study N25-005 CSR, Listing 16.2.6.1; Module 5.3.5.1, Study N25-006 CSR, Listing 16.2.5.1; Module 5.3.5.4, Study N25-007 CSR, Listing 16.2.1.1; Module 5.3.3.1, Study N25-010 CSR, Listing 16.2.5.1; Module 5.3.1.2, Study N25-012 CSR, Listing 16.2.1; Module 5.3.5.4, Study N25-013 CSR, Listing 16.2.5.1; Module 5.3.3.2, Study N25-015 CSR, Listing 16.2.3.1; Module 5.3.5.4, Study N25-018 CSR, Listing 16.2.1.
ADHD=attention deficit hyperactivity disorder; CSR=clinical study report; d-ATS= dextroamphetamine transdermal system; USPI=United States Prescribing Information.

Source: ISS, Table 7, page 28

In multiple-dose studies, the duration of d-ATS exposure ranged from 4 to 6 weeks as shown in Table 24, below. Although we recommended a long-term safety study during the IND stage, the Applicant provided an adequate scientific bridge based upon comparative bioavailability to the listed drug,

Vyvanse. Given that, the Applicant can rely upon the long-term safety data in Vyvanse labeling, so no longer-term studies were conducted.

Table 24: d-ATS Duration of Exposure

| | Number of subjects exposed to d-ATS | | |
|---|---|---|---|
| **Dose** | **≥ 1 dose** | **≥ 4 weeks** | **≥ 6 weeks** |
| **9.38 mg/9.38cm$^2$ × 24 hr** | 7 (N25-002) | n/a | n/a |
| **9.85 mg/9.38cm$^2$ × 24 hr** | **8** (N25-002) | n/a | n/a |
| **8.4 mg/8.0cm$^2$ × 9 hr** | **17** (N25-004) | n/a | n/a |
| **8.4 mg/8.0cm$^2$ × 12 hr** | **18** (N25-004) | n/a | n/a |
| **5 mg/4.76cm$^2$ × 9 hr** | 18 (N25-005)<br>110 (N25-006)*<br>23 (N25-007)<br>14 (N25-012)<br>30 (N25-013)<br>229 (N25-018)<br>**Total=424** | 7 (N25-006)* | 7 (N25-006)* |
| **10 mg/9.52cm$^2$ × 9 hr** | 18 (N25-005)<br>89 (N25-006)*<br>27 (N25-007)<br>**Total=134** | **35** (N25-006)* | **35** (N25-006)* |
| **15 mg/14.29cm$^2$ × 9 hr** | 56 (N25-006)*<br>21 (N25-007)<br>**Total=77** | **42** (N25-006)* | **41** (N25-006)* |
| **20 mg/19.05cm$^2$ × 9 hr** | 18 (N25-005)<br>25 (N25-006)*<br>22 (N25-007)<br>50 (N25-010)<br>15 (N25-012)<br>28 (N25-013)<br>35 (N25-015)<br>**Total=193** | 23 (N25-006)*<br><br><br><br><br><br>25 (N25-015)<br>**Total=48** | **22** (N25-006)* |

*Study N25-006 was the pivotal efficacy and safety study designed as a two-period study, dose optimization period and cross-over double blind period. [Source: Study N25-006 Clinical Study Report Table 14.1.4.3 Summary of

Source: Applicant information amendment submitted November 5, 2021

Relevant Characteristics of the Safety Population

Pediatric:
The safety population (defined as all patients who received at least one dose of d-ATS and had at least one post-dose safety assessment) in Study N25-006 generally shared the same demographic characteristics of the FAS population discussed in the efficacy section (see Table X). The study was conducted in the United States and enrolled a reasonably standard range of pediatric patients with ADHD. Minority representation for Black patients adequately reflected

national demographic data but was not representative for non-Black minority patients. The study population may have patients with fewer psychiatric comorbidities and with less use of concomitant medications than those who would use the drug in the general population. Medical comorbidities may be comparable, as children are a relatively healthy population. A total of 110 pediatric patients participated in Study N25-006, with 101 (92%) completers and 9 patients (8%) who discontinued.

Adult:
The demographic characteristics of the safety population in Study N25-015 was as follows:

Table 25: Study N25-015 Demographics and Baseline Characteristics (Safety Population)

| | d-ATS | |
|---|---|---|
| | **Group A (N=15)** | **Group B (N=20)** |
| Age (yrs) | | |
| Mean (SD) | 31.9 (9.55) | 29.7 (9.24) |
| Median | 31.0 | 27.5 |
| Min, Max | 20,57 | 20,51 |
| Sex, n(%) | | |
| Male | 8 (53.3) | 13 (65.0) |
| Female | 7 (46.7) | 7 (35.0) |
| Ethnicity, n(%) | | |
| Hispanic or Latino | 1 (6.7) | 5 (25.0) |
| Not Hispanic or Latino | 14 (93.3) | 15 (75.0) |
| Race, n(%) | | |
| Asian | 2 (13.3) | 1 (5.0) |
| Black or African American | 1 (6.7) | 2 (10.0) |
| White | 10 (66.7) | 17 (85.0) |
| Multiple | 1 (6.7) | 0 (0.0) |
| Other | 1 (6.7) | 0 (0.0) |
| Height (cm) | | |
| Mean (SD) | 171.57 (11.013) | 171.25 (8.732) |
| Median | 177.00 | 171.90 |
| Min, Max | 151.1,189.0 | 152.0,184.3 |
| Weight (kg) | | |
| Mean (SD) | 72.37 (16.076) | 73.04 (10.578) |
| Median | 75.60 | 72.00 |
| Min, Max | 46.6, 97.0 | 54.7,93.4 |
| BMI ($kg/m^2$)[a] | | |
| Mean (SD) | 24.38 (3.913) | 24.89 (2.907) |
| Median | 24.68 | 25.76 |
| Min, Max | 18.5,29.9 | 19.7,29.6 |

Abbreviations: BMI = body mass index; SD = standard deviation.
[a] BMI was calculated as: Weight (kg) / [Height (m)]^2.
Source: Post-text Table 14.1.2.2 (Section 14.1).

Source: CSR for N25-015, Table 10-2, page 68

The study was conducted in the United States and covered patients ages 18 to 65 years, but only patients ages 20 to 57 years enrolled thereby excluding the important 18- to 19-year-old age range treated for ADHD. Except for the Asian population, minority representation did not reflect national demographic data. The adult study population may have fewer medical and

psychiatric comorbidities and use fewer concomitant medications than those who would use the drug in the general population.

Adequacy of the safety database:

ADHD is a chronic condition and this product is intended for chronic use. Based upon comparative bioavailability, the Applicant is relying upon the previous Agency findings for the listed drug, Vyvanse, for systemic safety thereby obviating the need to meet ICH E1 drug exposure recommendations. However, the listed drug does not inform the local safety of this novel topical formulation, which needs to be supported by the submitted safety database. The treatment periods in all of the clinical trials ranged from single-dose to 7 weeks, which could be adequate to assess local safety of a novel topical formulation. However, comparison of safety findings between d-ATS and placebo based upon the only controlled trial (Study N25-006) is significantly limited due to the open-label dose-optimization and crossover double-blind treatment study design. Furthermore, dosing instructions for this study were to rotate hip application sites only in contrast to the draft label dosage and administration guidance which advises application site rotation over five sites (hip, upper arm, upper chest, upper back, and flank). Unblinded, uncontrolled safety data from Study N25-015, which was conducted with the application site rotation over five sites that is proposed for labeling, is described briefly in this safety review.

The patient demographics appear generally appropriate for a population with ADHD, although some minority populations were underrepresented. Additionally, both the pediatric and adult clinical trial population probably have fewer psychiatric comorbidities, and the adult clinical trial population is probably slightly physically healthier than the general ADHD population because of exclusion criteria for the studies.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No major concerns about data integrity were noted by the OCS Core Data Fitness team.

Categorization of Adverse Events by Primary Clinical Reviewer

For Study N25-006, AEs were recorded at each study visit. I performed some AE analysis adjustments varying from the Applicant's analyses for my tables in Section 8.2.4. I classified Treatment-Emergent AEs (TEAEs) as an AE that occurred after at least one dose of treatment and within 2 days (five half-lives) of the last treatment dose. Exclusion of AEs that occurred more than 2 days after the last treatment dose did not significantly impact AE analysis. Although AEs were collected through 30 days after the last treatment dose, the last scheduled follow-up visit was on Day 56, 1 week after the last treatment dose. The study used MedDRA Version 15.0 to code AEs. The Applicant appeared to use standard methods for AE severity coding. I used my own clinical judgment and reviewed available data for AE adjudication apart from the Applicant's included ones; some of the Applicant's AE terms were split into

subcategories that could minimize incidence rates for clinically significant safety signals. I grouped the following terms together:

- Insomnia: insomnia, delayed sleep phase, initial insomnia, middle insomnia, terminal insomnia
- Abdominal pain: abdominal pain, abdominal pain upper
- Blood pressure increased: blood pressure increased, blood pressure systolic increased
- Depression: depression, dysphoria
- Heart rate increased: heart rate increased, tachycardia
- Platelet count increased: platelet count increased, thrombocytosis
- Body temperature increased: body temperature increased, pyrexia
- Blood potassium increased: blood potassium increased, hyperkalemia
- Irritability: irritability, agitation, anger
- Fatigue: fatigue, listless
    Application site pain: application site pain, application site burn (reported terms were "burning at application site" and "burned in patch area"; the Applicant provided information that clarified that the terms were describing a burning sensation)
- Affect lability: affect lability, emotional disorder, mood swings, mood altered (reported terms were "moody" and "rebound moodiness")

The following reported terms were also re-categorized into different dictionary-derived terms: "rebound oppositionality" was changed from "negativism" to "defiant behavior," and "dulled affect (mental)" was changed from "mental impairment" to "blunted affect."

The study protocol did not include any specially prompted AE assessments for particular AEs of interest such as appetite or weight. Furthermore, signs or symptoms elicited from dermal safety assessment scales administered during the study were not to be recorded as AEs unless they occurred at a site different from the application site, they led to the patient's premature discontinuation from the study, or they were so severe that the investigator judged recording as an AE appropriate.

Safety Assessment (Scale) Descriptions are as follows:

- Berger and Bowman Scale
    - This is a clinician-rated dermal response scale of application site irritation rated on a 7-point scale with 6 additional modifiers.

Table 26: Berger Bowman Scale

| Dermal Response Scale | |
|---|---|
| **Score** | **Definition** |
| 0 | No evidence of irritation |
| 1 | Minimal erythema, barely perceptible |
| 2 | Moderate erythema, readily visible; or minimal edema or minimal papular response |
| 3 | Strong erythema; or erythema and papules |
| 4 | Definite edema |
| 5 | Erythema, edema, and papules |
| 6 | Vesicular eruption |
| 7 | Strong reaction spreading beyond test site |

| Other Effects | |
|---|---|
| **Score** | **Definition** |
| A (0) | Slight glazed appearance |
| B (1) | Marked glazed appearance |
| C (2) | Glazing with peeling and cracking |
| F (3) | Glazing with fissures |
| G (3) | Film of dried serous exudates covering all or part of the patch site |
| H (3) | Small petechial erosions and/or scabs |

Note: A score of "N" (none) for the Other Effects Scale was recorded in the eCRF when no other effects were observed.

Source: CSR for N25-006, Table 6, pages 30-31

For irritation falling between unit grades, the more severe grade was selected. Additionally, the patient or caregiver endorsed the presence or absence of any irritation in a daily diary ("Do you see any irritation?") with descriptors, as appropriate. The results are discussed in Section 8.2.5.

- Discomfort Scale

  - This is a clinician-rated scale of discomfort related to the transdermal system rated on a 4-point scale: 0=no discomfort, 1=mild discomfort, 2=moderate but tolerable discomfort, 3=severe intolerable discomfort, and 4=patch not present. Endorsement of any discomfort was further qualified by type of discomfort and, at the laboratory classroom visits, a 10-point pain scale (Wong-Baker Faces for patients 6 to 11 years of age or Visual Analog Scale for patients 12 to 17 years of age, a higher score indicates greater pain). Additionally, the patient or caregiver endorsed the presence or absence of any discomfort in a daily diary ("Are you

experiencing any discomfort?") with descriptors, as appropriate. The results are discussed in Section 8.2.5.

- C-SSRS—Children's Version

    - This is a clinician-administered tool designed to systematically assess and track suicidal ideation and behavior throughout the study. There are two subgroups of ideation and behavior that are further subdivided into five categories each. The results are discussed in Section 8.2.5.

Routine Clinical Tests

Study N25-006 included a standard array of serum chemistry and hematology, urinalysis, vital signs, and ECG assessments.

- Hematology: hematocrit, hemoglobin, platelet count, RBC count, white blood cell (WBC) total count, WBC differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
- Serum chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin (total), blood urea nitrogen, calcium, chloride, creatine phosphokinase (CK), creatinine, glucose, hemoglobin A1c, lactate dehydrogenase, phosphorous, potassium, protein (total), sodium
- Urinalysis: bilirubin, blood, glucose, ketones, pH, protein, specific gravity
- Other tests: breath alcohol test, serum and urine cotinine, urine drug screen, and urine pregnancy test (in female patients of child-bearing potential)
- Vital Signs: blood pressure, body temperature, heart rate, respiratory rate

Altough weight was measured, interpretation of growth effects in the safety data is limited because there was no accompanying monitoring of height, which is essential in assessing pediatric growth. Effects of this product on pediatric growth must therefore rely on the previous safety findings described in product labeling for Vyvanse.

### 8.2.4. Safety Results

Deaths

No deaths occurred in this development program.

Serious Adverse Events

There were no treatment-emergent serious adverse events (SAEs) in this development program.

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, when looking at AEs associated with discontinuation (AEDCs) in the entire development program, the only ones that showed potential trends (i.e., multiple cases) were dermal reactions. Eleven out of twenty discontinuations were due to application site reactions, although four of these were for subjects in exaggerated use conditions (i.e., no application site rotation). These AEDCs occurred in one- or two-dose phase 1 studies in children, adolescents, and adults with ADHD (Studies N25-007 and N25-013), in a contact sensitization study in healthy adults (Study N25-018), and in a 4-week intended use and exaggerated use PK study in adults with ADHD (Study N25-015). In Study N25-006, three patients (3%) out of 110 discontinued prematurely for adverse events during the dose-optimization phase and none during the double-blind treatment phase. The three discontinuations due to AEs were abdominal pain, irritability, and decreased appetite.

Significant Adverse Events

In Study N25-006, there were six patients who reported a total of 15 AEs rated as "severe":
During the dose-optimization phase:

- One patient reported application site pain.
- One patient reported application site pain, pruritis, and erythema; perceptual change/disturbance; depression; irritability; and nausea.
- One patient reported foot fracture.

During the double-blind treatment phase:

- One patient on d-ATS experienced hyperkalemia.
- One patient on d-ATS reported insomnia.
- One patient on placebo reported viral gastroenteritis.

Treatment Emergent Adverse Events and Adverse Reactions

The AE summary for Study N25-006 is as follows:

Table 27: Study N25-006 AEs Summary

| | d-ATS | | Placebo | |
|---|---|---|---|---|
| | Number of subjects | Proportion (%) | Number of subjects | Proportion (%) |
| Patients with any AE | Dose-optimization 105/110<br>Double-blind 41/105 | 95<br>39 | -<br>42/105 | -<br>40 |
| Patients with severe AE | Dose-optimization 3/110<br>Double-blind 2/105 | 3<br>2 | -<br>1/105 | -<br>1 |

| | | | | |
|---|---|---|---|---|
| Patients with any SAE | 0 | 0 | 0 | 0 |
| Patients with any AE leading to death | 0 | 0 | 0 | 0 |
| Patients with any AEDC | Dose optimization 3/110<br>Double-blind 0 | 3<br>0 | -<br>0 | -<br>0 |

Source: Reviewer-generated

The following TEAE tables for Study N25-006 only include the treatment period of each study up to 2 days after the last dose of treatment and only AEs that occurred on d-ATS greater than or equal to 2% incidence and, in the double-blind treatment period, greater than placebo.

Table 28: Study N25-006 Dose-optimization Phase Most Common AEs by Preferred Term

| | Number of Subjects | Proportion |
|---|---|---|
| Preferred Term | 110 | |
| Any AE | 105 | 95% |
| DECREASED APPETITE | 59 | 54% |
| INSOMNIA | 35 | 32% |
| HEADACHE | 23 | 21% |
| IRRITABILITY | 19 | 17% |
| ABDOMINAL PAIN | 18 | 16% |
| AFFECT LABILITY | 18 | 16% |
| APPLICATION SITE PAIN | 14 | 13% |
| NASAL CONGESTION | 13 | 12% |
| COUGH | 11 | 10% |
| NAUSEA | 10 | 9% |
| APPLICATION SITE PRURITUS | 8 | 7% |
| UPPER RESPIRATORY TRACT INFECTION | 8 | 7% |
| FATIGUE | 6 | 5% |
| NASOPHARYNGITIS | 5 | 5% |
| VOMITING | 4 | 4% |
| OROPHARYNGEAL PAIN | 4 | 4% |
| WEIGHT DECREASED | 4 | 4% |
| PHARYNGITIS | 4 | 4% |
| DIZZINESS | 3 | 3% |
| HEART RATE INCREASED | 3 | 3% |
| INFLUENZA | 3 | 3% |
| BODY TEMPERATURE INCREASED | 3 | 3% |
| DYSMENORRHEA | 2 | 2% |
| ARTHRALGIA | 2 | 2% |

| | | |
|---|---|---|
| APPLICATION SITE ERYTHEMA | 2 | 2% |
| TEARFULNESS | 2 | 2% |
| RASH | 2 | 2% |
| PAIN IN EXTREMITY | 2 | 2% |
| SOCIAL AVOIDANT BEHAVIOUR | 2 | 2% |
| NON-CARDIAC CHEST PAIN | 2 | 2% |
| ANXIETY | 2 | 2% |
| PSYCHOMOTOR HYPERACTIVITY | 2 | 2% |
| DEPRESSION | 2 | 2% |
| LOGORRHEA | 2 | 2% |
| MOTION SICKNESS | 2 | 2% |
| APPLICATION SITE SWELLING | 2 | 2% |

Source: Reviewer-generated

Table 29: Study N25-006 Double-blind Treatment Phase Most Common AEs by Preferred Term

| | d-ATS | | Placebo | |
|---|---|---|---|---|
| N | 105 | | 105 | |
| Preferred Term | Number of subjects | Proportion | Number of subjects | Proportion |
| ANY AE | 41 | 39% | 42 | 40% |
| DECREASED APPETITE | 11 | 10% | 1 | 1% |
| INSOMNIA | 8 | 8% | 4 | 4% |
| HEADACHE | 6 | 6% | 2 | 2% |
| VOMITING | 4 | 4% | 0 | 0% |
| ABDOMINAL PAIN | 4 | 4% | 1 | 1% |
| NAUSEA | 3 | 3% | 1 | 1% |
| NASOPHARYNGITIS | 3 | 3% | 2 | 2% |
| IRRITABILITY | 2 | 2% | 1 | 1% |
| BLOOD PRESSURE INCREASED | 2 | 2% | 1 | 1% |
| HEART RATE INCREASED | 2 | 2% | 0 | 0% |
| TIC | 2 | 2% | 0 | 0% |

Source: Reviewer-generated

The most common AEs (greater than or equal to 5% incidence) include: decreased appetite, insomnia, headache, irritability, abdominal pain, affect lability, application site pain, nasal congestion, cough, nausea, application site pruritis, upper respiratory infection, fatigue, and nasopharyngitis.

In the dose-optimization phase, some AEs occurred at higher rates compared to what is described in the prescribing information for the listed drug: decreased appetite (d-ATS 54%

versus Vyvanse 34 to 39%), insomnia (32% versus 13 to 22%), irritability (17% versus 10%), and affect lability (16% versus 3%). However, based on the variability between study designs (a 5-week dose-optimization, open-label study design with no comparator arm for d-ATS versus 3 and 4-week randomized, controlled, parallel-group, forced-titration study design for Vyvanse) and other general limitations of cross-study comparisons, the comparative AEs data are difficult to interpret.

Laboratory Findings

In Study N25-006, laboratory testing was conducted at screening and at the end of the study (Visit 7, Week 7) or early termination. Laboratory results were obtained after 1 week on either d-ATS or placebo treatment that was preceded by 1 week on the other treatment and 5 weeks on d-ATS. However, given the d-ATS half-life of approximately 10 hours, the results may be informative for the assigned treatment at the time of testing. There were clinically significant abnormal laboratory results for WBCs and neutrophils that merit inclusion in the prescribing information. There were no other significant or concerning clinical or toxicity-related issues. (All of the mean value data in this section were reviewer-generated on JMP Clinical via the ADLB.xpt dataset.)

*Serum Chemistry:*
Shifts from normal to abnormal values or mean shifts from baseline occurred with albumin, protein, CK, and potassium, but determination of clinical meaningfulness and extrapolation to the greater patient population cannot be made given absent associated abnormalities and the small patient sample size.

Overall, mean serum chemistry results showed no concerning clinical trends. No subjects met criteria for Hy's Law.

AEs during the treatment period from abnormal serum chemistry results were as follows:

- Blood potassium increased in 5 patients (5%) on d-ATS and 5 patients (5%) on placebo
- Blood CK increased in 1 patient (1%) on d-ATS during double-blind treatment
- Hepatic enzyme increased in 1 patient (1%) on d-ATS during double-blind treatment

These AEs occurred at the same rates between treatment arms or at such a low rate (i.e., one patient) that they are unlikely to be drug-related.

*Hematology:*
Hematology results showed higher rates of patients with low WBCs and neutrophil percentage in patients on d-ATS compared to placebo:

- WBC < 5.0 $x10^9$/L: d-ATS 5/48 patients (10%) versus placebo 1/47 (2%)
- Neutrophils < 40%: d-ATS 5/37 (14%) versus placebo 2/34 (6%)

None of the abnormal results were severe. Mean shifts from baseline in WBCs and neutrophil percentage were not clinically significant (d-ATS WBCs -0.9 $x10^9$/L (SD 2.1) versus placebo -0.3

$x10^9$/L (SD 2.5); d-ATS neutrophil percentage -2.8% (SD 10.9) versus placebo -0.9% (SD 11.1), and there were no reported WBC or neutrophil result-associated AEs. Of note, some methylphenidate products contain a warning for hematologic monitoring or list leukopenia as a postmarketing adverse reaction, so this is a known risk with some other stimulant products. Given these factors and the imbalance in incidence of abnormally low WBCs and neutrophils, it is plausible that these findings are drug-related and a description of these findings will be included in the ADVERSE REACTIONS section of the prescribing information.

Additional shifts from normal to abnormal patient values or mean shifts from baseline occurred with WBC differentials and hemoglobin and hematocrit, but absent associated abnormalities and given the small patient sample size, clinical meaningfulness and extrapolation to the general population are uncertain.

AEs during the treatment period from abnormal hematology results were as follows:

- Platelet count increased in 1 patient (1%) each on d-ATS and placebo during double-blind treatment
- Eosinophilia in 1 patient (1%) each on d-ATS and placebo during double-blind treatment

These AEs occurred at the same rates between treatment arms and are unlikely to be drug-related.

*Urinalysis:*
Overall urinalysis results showed no concerning clinical trends. No AEs were reported based on urinalysis results during the treatment period.

Vital Signs

In Study N25-006, vital signs were measured at Screening, Baseline, and weekly study visits. There was a trend towards increased mean shift in systolic and diastolic blood pressure and this is an expected finding in the stimulant class of drugs. (All of the mean value data in this section were reviewer-generated on JMP Clinical via the ADVS.xpt dataset.)

*Cardiovascular/Respiratory/Body Temperature:*
Systolic (SBP) and diastolic (DBP) blood pressure mean shifts were higher with d-ATS (SBP 2.7 mmHg, SD 10.4; DBP 3.2 mmHg, SD 9.2) compared to placebo (SBP 1.5 mmHg, SD 10.4; DBP 1.1 mmHg, SD 9.8). During dose-optimization, blood pressure increased AE was reported in 1 patient (1%) on d-ATS, and during double-blind treatment, in 2 patients (2%) on d-ATS and in 1 patient (1%) on placebo. However, a single patient with baseline elevated blood pressure accounted for three of these four occurrences (during dose-optimization and during both d-ATS and placebo treatment during double-blind treatment). These blood pressure findings are consistent with a known stimulant class effect.
Otherwise, mean cardiovascular, respiratory, and body temperature results did not show concerning clinical trends. AEs during the treatment period from abnormal results were as follows:

- Heart rate increased in three patients (3%) on d-ATS during dose-optimization and in two patients (2%) on d-ATS during double-blind treatment (none on placebo).
- Body temperature increased in three patients (3%) on d-ATS during dose-optimization.
- Body temperature increased in one patient (1%) each on d-ATS and placebo during double-blind treatment.

Body temperature increased in isolation is a non-specific finding, and during double-blind treatment, these AEs occurred at the same rates between the treatment arms and so are unlikely to be drug-related.

*Weight:*
Weight showed mean decreases from baseline by Week 7 in both d-ATS (-1.8 kg) and placebo (-1.5 kg) groups. There were four patients (4%) on d-ATS who reported weight decreased AEs during dose-optimization. A comparative analysis cannot be conducted due to the suboptimal study design in which all patients received open-label d-ATS treatment for 5 weeks followed by randomization into a crossover sequence of 1 week each on their dose-optimized d-ATS regimen or placebo. Furthermore, interpretation of growth effects is limited because there was no accompanying monitoring of height, which is essential in assessing pediatric growth.

Electrocardiograms (ECGs)

In Study N25-006, ECGs were obtained at Screening, Baseline, Visit 5 (Week 5), Visit 6 (Week 6), and Visit 7 (Week 7). (All of the mean value data in this section were reviewer-generated on JMP via the ADEG.xpt dataset.) Shifts from normal to abnormal patient values or mean shifts from baseline occurred with PR and QRS intervals, but absent associated abnormalities and given the small patient sample size, clinical meaningfulness and extrapolation to the general population are uncertain.

There were no ECG-related AEs, but one patient (1%) each on d-ATS in both the dose-optimization and double-blind treatment phases reported palpitations.

QT

There were no significant QT interval mean shifts from baseline or patient shifts from normal to abnormal QT intervals. No patients experienced QT prolongation > 480 msec. One patient (1%) on d-ATS during dose-optimization had an AE of ECG QT prolonged.

### 8.2.5. Analysis of Submission-Specific Safety Issues

Dermal Reactions
In Study N25-006, dermal safety was formally assessed with daily patient/caregiver diaries and, at the laboratory classroom visits, with clinician-rated scales assessing irritation and discomfort (see Section 8.2.3 for descriptions). Additionally, dermal safety was assessed by reported AEs, but this is limited because formal dermal assessment symptom criteria for AE-classification

were occurrence at a site different from the application site, associated premature study discontinuation, or symptomatic irritation that was intolerable or so severe that in the investigator's judgment it should be recorded as an AE (see Section 8.2.4). Also noteworthy is that dosing instructions for this study were to rotate hip application sites in contrast to the proposed dosage and administration section of the prescribing information, which advises application site rotation over five sites (hip, upper arm, upper chest, upper back, and flank). Rates of discomfort and irritation in the patient diaries were high.

Table 30: Study N25-006 Dermal Safety Daily Diaries

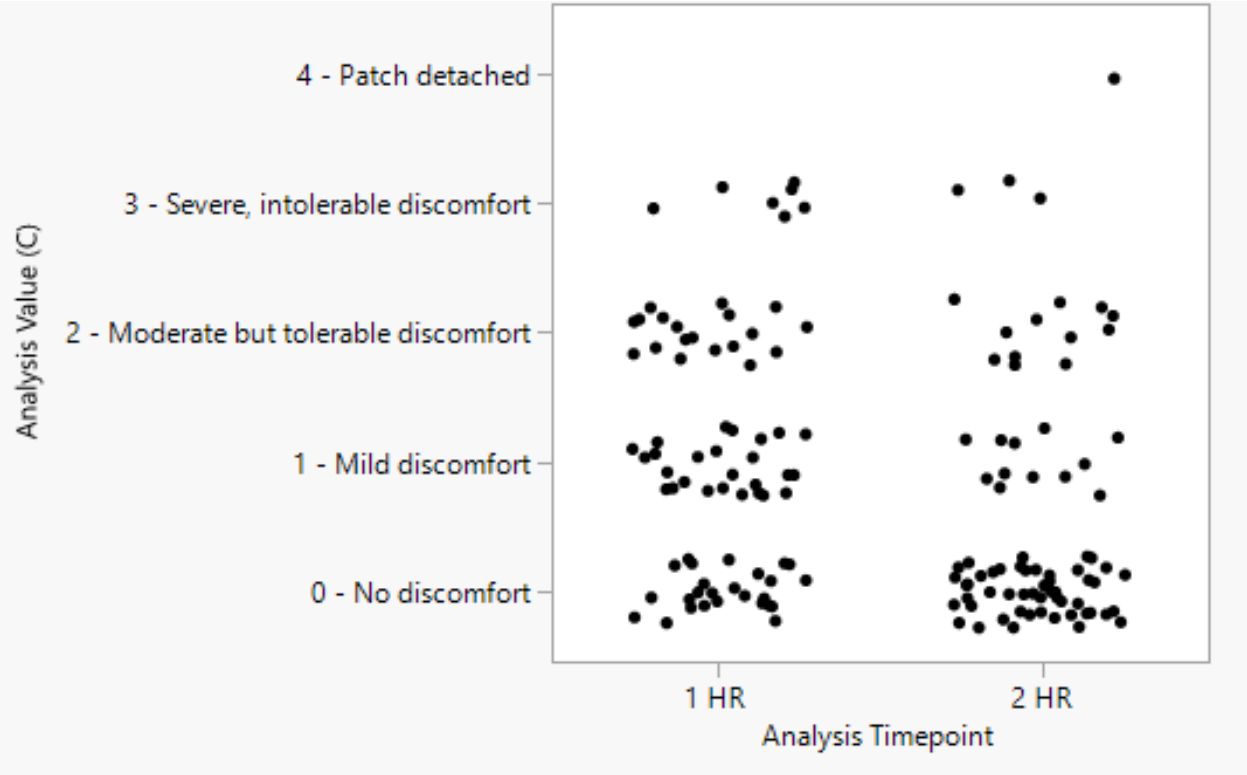
| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 |
|---|---|---|---|---|---|---|---|
| Discomfort | | | | | | | |
| d-ATS | 32/105 (30%) | 21/103 (20%) | 18/100 (18%) | 15/101 (15%) | 8/100 (8%) | 3/45 (7%) | 5/50 (10%) |
| Placebo | - | - | - | - | - | 4/50 (8%) | 4/45 (9%) |
| Irritation | | | | | | | |
| d-ATS | 61/106 (58%) | 52/107 (49%) | 48/105 (46%) | 47/105 (45%) | 39/102 (38%) | 23/50 (46%) | 31/50 (62%) |
| Placebo | - | - | - | - | - | 16/50 (32%) | 16/47 (36%) |

Source: Reviewer-generated

Based on the daily diaries, during dose-optimization, 49/108 patients (45%) reported discomfort at least once. During double-blind treatment, 8/96 patients (8%) on d-ATS and 8/98 (8%) on placebo reported discomfort at least once. During dose-optimization, 79/108 patients (73%) reported irritation at least once. During double-blind treatment, 54/101 patients (53%) on d-ATS and 32/100 (32%) on placebo reported irritation at least once.

Rates of discomfort and irritation as assessed by in-clinic scales were also high.

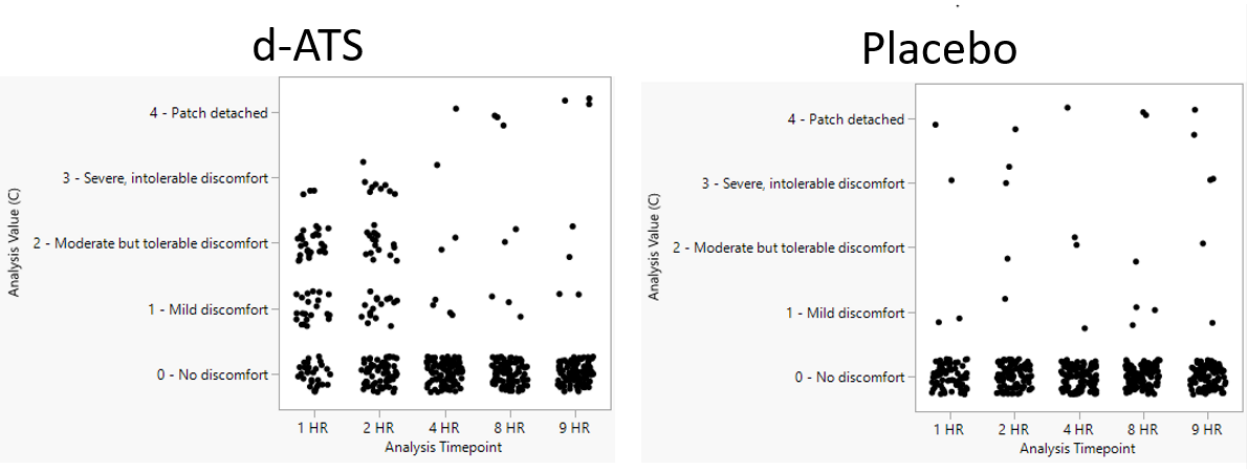
Figure 14: Study N25-006 Dermal Safety Discomfort Scale at Visit 5 (Dose-optimization Phase)




Source: Reviewer-generated

At Visit 5, 56/78 patients (72%) reported discomfort at least once; 10/78 patients (13%) graded their discomfort as severe.

Figure 15: Study N25-006 Dermal Safety Discomfort Scale at Visits 6 and 7 (Double-blind Treatment Phase)

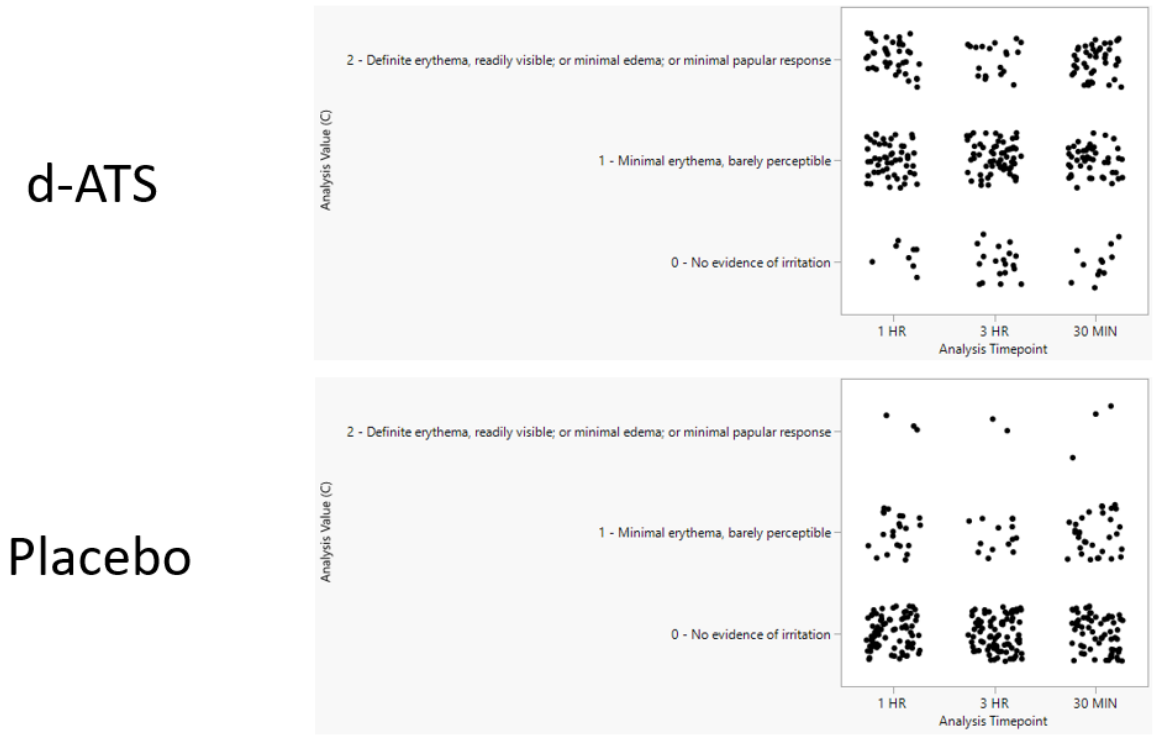



Source: Reviewer-generated

At Visits 6 and 7, 72/104 patients (69%) on d-ATS and 9/101 (9%) on placebo reported discomfort at least once; 10/104 patients (10%) on d-ATS and 4/101 (4%) on placebo graded their discomfort as severe. Reported pain scores (on a scale from 0 to 10) ranged from 2 to 10 (mostly 2 to 6) in the first 2 hours of wear (Hours 1 and 2) and from 0 to 3 in the last 2 hours of wear (Hours 8 and 9).

Across all assessments, discomfort was variably described as burning, burn, pinch, and stinging.

Figure 16: Study N25-006 Dermal Safety Irritation Scale at Visits 6 and 7 (Double-blind Treatment Phase)




Source: Reviewer-generated

At Visits 6 and 7, 97/103 patients (94%) on d-ATS and 55/101 (54%) on placebo demonstrated irritation; 55/103 patients (53%) on d-ATS had definite erythema or erythema with or without papules and 6/101 (6%) on placebo had definite erythema. Rates of dermal-related AEs are listed in Table 31, below.

Table 31: Study N25-006 Dermal Safety AEs

| | Number of Subjects | Proportion | Number of Subjects |
|---|---|---|---|
| Preferred term | | | |
| Dose-optimization | 110 | | |
| Application site pain | 14 | 13% | |

| | | | |
|---|---|---|---|
| Application site discomfort | 1 | 1% | |
| Application site pruritis | 8 | 7% | |
| Application site erythema | 2 | 2% | |
| Application site swelling | 2 | 2% | |
| Double-blind Treatment | | | |
| | d-ATS | | Placebo |
| | 105 | | 105 |
| Application site erythema | 1 | 1% | 0 |
| Application site swelling | 1 | 1% | 0 |

Source: Reviewer-generated

During dose-optimization, of the 14 patients who reported application site pain, 2 patients reported severe pain thrice, 2 patients had their d-ATS dose reduced due to pain, and 7 patients received concomitant therapy for the pain (hydrocortisone, acetaminophen, ibuprofen, or "other"). Of the 8 patients who reported application site pruritis, 1 patient reported severe pruritis twice, 3 patients had their d-ATS dose interrupted due to pruritis, and 2 patients received concomitant therapy for the pruritis. Of the 2 patients who reported application site erythema, 1 patient reported erythema as severe, and the other patient had their d-ATS dose interrupted due to erythema. Of the 2 patients who reported application site swelling, 1 patient received concomitant therapy of "other." During double-blind treatment, the patient who reported application site erythema had their d-ATS dose interrupted due to erythema. The patient who reported application site swelling had failed to rotate application sites (i.e., applied d-ATS to the same site at the time of the reported AE).

In Study N25-015 of adult patients with ADHD, dermal safety was also formally assessed with daily patient diaries and, at clinic visits, with clinician-rated scales assessing irritation and discomfort (see Section 8.2.3 for descriptions). Dosing instructions for Group A reflect intended use with rotation of five application sites (hip, upper arm, upper chest, upper back, and flank). Rates of discomfort and irritation in the patient diaries were high: 7/15 patients (47%) endorsed discomfort, and 11/15 (73%) reported irritation at least once during treatment. Rates of discomfort and irritation as assessed by in-clinic scales were also high: 12/15 patients (80%) experienced any discomfort (none described as severe), and all patients experienced irritation (2/15 patients (13%) had a combined irritation score of 1, and 13/15 patients (87%) had a score of 2). Both discomfort and irritation were transient. Onset of discomfort was within 2 hours, and mean duration was less than 1 hour with a range of 0 to 3 hours. Mean duration of irritation was 2 hours with a range of 0 to 5 hours. No application site AEs were reported in Group A. As expected, compared to dermal assessments in Group A, assessments in Group B with exaggerated use (no site rotation) generally revealed more severe discomfort and irritation with the exception of in-clinic assessments of discomfort, which were less frequent (12/20 patients (60%) experienced mild discomfort, and 8/20 (40%) experienced none compared to Group A in which 3/15 (20%) experienced none). The reason and clinical meaningfulness of this difference is unclear. One patient in Group B experienced application site-related AEs, and three patients (15%) experienced dermal safety-related AEDCs. In

comparison to Study N25-006, daily diary endorsement of discomfort and irritation in Study N25-015 Group A were similar, but clinical assessments for both were higher (Study N25-015 80% of patients experienced discomfort and 100% irritation compared to N25-006 69 to 72% and 94%, respectively). This is notable because findings from Study N25-015 Group A are based on treatment administration that follows intended use as instructed in the proposed product label in contrast to Study N26-006 in which patients were instructed to rotate application sites from right to left hips only. However, interpreting clinical meaningfulness of these differences in clinical assessments is limited because the frequency of assessments per day in Study N25-015 was nearly double that in Study N25-006. Additionally, data from Study N25-015 must be interpreted with caution because of an open-label design in a limited number of adult patients with ADHD and absent a comparator arm.

Although transdermal systems are known to be irritating, the overall rates of dermal discomfort and irritation for d-ATS were much higher than expected regardless of limited application site rotation to the hips or as intended over five sites. In Study N25-006, 10 to 13% of patients described severe discomfort. Rates of discomfort were most prominent in the first 2 hours of wear-time and tended to improve or resolve thereafter. Irritation remained prevalent over time both throughout the day and over study duration. These signs and symptoms of irritation and discomfort were not associated with treatment discontinuation. However, in Study N25-006, of the patients with relevant AEs, seven had their treatment dose interrupted or reduced as related to the AE and nine received concomitant therapy for the relevant AE. Dermal discomfort and irritation associated with d-ATS do not generally appear to be debilitating, associated with long-term sequelae, or otherwise serious. However, see Section 8.2.5 regarding the potential for contact sensitization, which is serious and has long-term implications. Of note, Daytrana, an approved methylphenidate transdermal system, includes a warning for chemical leukoderma in the label. Post-marketing reports of persistent loss of skin pigmentation at and around the application site led to the post-approval labeling addition. There were no reported AEs or other data suggesting chemical leukoderma associated with d-ATS in the development program.

In Study N25-018 of healthy adult subjects, the Applicant reported that 10 out of 200 subjects (5%) met criteria for potential sensitization: two subjects (1%) demonstrated positive sensitization confirmed by re-challenge, seven subjects (4%) demonstrated potential sensitization at challenge but did not return for re-challenge due to COVID-19 public health restrictions, and one subject did not have confirmed sensitization on re-challenge and was thus considered negative for sensitization. Contact sensitization will be included as a Warning and Precaution in the d-ATS label. (Please refer to the Division of Dermatology and Dentistry consult review for more details.) In Study N25-006, there were numerous reports of application site signs and symptoms suggesting reaction, but there was no evidence of specific hypersensitivity-related AEs.

Growth
Stimulants are known to be associated with decreased appetite, decreased weight, and negative growth impact overall. Decreased appetite was the most common AE in Study N25-

006 with the incidence during dose-optimization exceeding that which is typically seen with other stimulants as described in FDA labeling. At Week 7, patients on d-ATS experienced a 1.8 kg weight decrease and patients on placebo experienced 1.5 kg weight decrease. However, the open-label dose-optimization and double-blind crossover treatment design of the study severely confounds safety analysis. Furthermore, a head-to-head comparison with other stimulant products is difficult because of different types of studies used in stimulant trials.

Insomnia

Stimulants are known to be associated with insomnia. Insomnia was the second most common AE in Study N25-006 with the incidence rate during dose-optimization exceeding that which is typically seen with other stimulants described in FDA labeling. However, as discussed above with growth, the study design and limitations of cross-study comparison significantly confound safety analysis.

Suicidal Ideation and Behavior (SI/B)

Overall, no clear drug-related trends were evident from the SI/B events that occurred during Study N25-006, either from AE reporting or from C-SSRS monitoring. Four patients had a past lifetime history of SI reported on the C-SSRS at Baseline but remained in the study. Three patients reported SI on the C-SSRS during the study. All three patients were on d-ATS (two during dose-optimization and one during double-blind treatment). One of the patients with SI during dose-optimization reported thoughts about being dead while he was upset about rules regarding video game access. He calmed within minutes, denied SI, and did not endorse further SI since that time. The patient with SI during double-blind treatment had also reported it at baseline. There were no reported SI AEs. Four other patients endorsed SI in the d-ATS clinical development program: three were adult patients, and one was a pediatric patient for whom the AE was classified as a SAE and AEDC. All four of these SI AEs preceded d-ATS treatment initiation. The three reports of SI while on d-ATS do not indicate a new safety signal based upon narratives (one patient with conditional, transient SI and another with a history of SI prior to initiation of treatment) and baseline rates of SI in children and adolescents,[9] which are increased in those with ADHD.[10]

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable

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[9] https://www.cdc.gov/mmwr/volumes/69/su/su6901a6.htm

[10] Shoval G, et al. Evaluation of Attention-Deficit/Hyperactivity Disorder Medications, Externalizing Symptoms, and Suicidality in Children. *JAMA Netw Open*, 2021; 4(6):e2111342.doi:10.1001/jamanetworkopen.2021.11342.

### 8.2.7. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were not conducted secondary to small sample size.

### 8.2.8. Specific Safety Studies/Clinical Trials

The Applicant conducted Study N25-015 per Division recommendations to assess for increased PK exposure at 4 weeks. This study also provides safety data in adult patients with ADHD comparing intended use with application site rotation (Group A) versus exaggerated use without site rotation (Group B). (See Section 8.1.2 for further study details.) No deaths, SAEs, or severe AEs were reported. In Group A, six patients (40%) reported any TEAE. In Group B, 16 patients (80%) reported any TEAE. Common AEs were dry mouth, decreased appetite, palpitations, dizziness, nausea, and upper respiratory tract infection. In Group A, there were no AEDCs. In Group B, one patient had an AEDC of palpitations, and three were discontinued due to application site reactions. Blood pressure, heart rate, and some ECG values were increased from baseline during treatment, and two patients experienced heart rate increased AEs. Blood pressure and heart rate increases are known stimulant class effects. There were no new safety trends. Otherwise, investigations did not reveal any clinically significant safety signals. The Applicant found that the accumulation ratio for patients in Group A were as expected, but the accumulation ratio for patients in Group B was greater than expected. The Applicant did not find a clear correlation between PK exposures and dermal reactions.

Additionally, the Applicant conducted Study N25-018, which confirmed skin sensitization in healthy adults so this will be included as a warning and precaution in the d-ATS label. No deaths or SAEs were reported. Thirty-two subjects (14%) reported any AE. Common AEs included dry mouth, nausea, and headache. Five subjects (2%) experienced AEDCs: hypertension; cellulitis; tape reaction at application site; abnormal heart rate; and headache, nausea, and vomiting. Blood pressure and heart rate were increased from baseline during treatment, but these are known stimulant class effects. There were no new vital sign or ECG safety trends of clinical significance. Laboratory tests were only conducted at Screening. See Section 8.1.3and refer to the Division of Dermatology and Dentistry consult review for further details regarding Study N25-018.

### 8.2.9. Additional Safety Explorations

Human Reproduction and Pregnancy

No pregnancies were reported in the development program and the product labeling can rely on the listed drug Vyvanse.

Pediatrics and Assessment of Effects on Growth

Refer to the pediatric Study N25-006 results discussed in Section 8.2.4 and the discussion of recent new safety findings for Vyvanse in Section 10 of the review.

The stimulant drug class carries a boxed warning for abuse and dependence. The proposed draft label for d-ATS includes the same boxed warning.

### 8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no postmarketing experience with d-ATS. Vyvanse (the listed drug for which an adequate scientific bridge has been established to rely on the Agency's previous safety finding) postmarketing experience includes the following adverse reactions: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, tics, bruxism, depression, dermatillomania, alopecia, aggression, Stevens-Johnson Syndrome, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, and rhabdomyolysis.

### 8.2.11. Integrated Assessment of Safety

Safety review based upon the current pivotal trial (Study N25-006) is significantly limited due to the following: (1) the open-label dose-optimization and double-blind crossover treatment study design, (2) study dosing instructions to rotate hip application sites only in contrast to the current draft label dosage and administration guidance which advises application site rotation over five sites, and (3) the small patient sample size.

As a stimulant class drug, d-ATS has expected associations with decreased appetite, insomnia, irritability, and affect lability. However, higher than usual rates of these AEs occurred during the dose-optimization phase compared to other FDA-approved stimulants: 54%, 32%, 17%, and 16%, respectively. Limitations of cross-study comparison significantly confound analysis.

Although overall numbers were small, perhaps as a result of the sample size, laboratory findings of leukopenia and neutropenia occurred at higher rates with d-ATS (10% and 14%, respectively) compared to placebo (2% and 6%, respectively). None of these findings were severe or reported as AEs. Leukopenia and pancytopenia have also been reported with methylphenidate stimulate products. It is recommended that this finding be included in the Adverse Reactions section of labeling.

As a transdermal product, d-ATS had high rates of dermal site discomfort (up to 72%) and irritation (up to 94%). Rates of discomfort were sometimes severe (in up to 13% of patients) but tended to improve within a day of wear and over 7 weeks of use. Irritation generally remained prevalent over time both throughout the day and over study duration. These signs and symptoms of irritation and discomfort were associated with treatment discontinuation in three patients (15%) with exaggerated use (i.e., no site rotation) but not in patients who rotated site application. However, in patients who rotated site application and experienced relevant AEs,

seven (6%) had their treatment dose interrupted or reduced as related to the AE, and nine (8%) received concomitant therapy for the relevant AE. Dermal discomfort and irritation associated with d-ATS do not generally appear to be debilitating, associated with long-term sequelae, or otherwise serious. The Applicant includes discomfort and irritation described as application site reactions in the Warnings and Precautions and Adverse Reactions sections of labeling. Additionally, confirmed contact sensitization has occurred in 1% of subjects on d-ATS and potential contact sensitization not confirmed with re-challenge occurred in 4%. Due to the serious nature, it is recommended that contact sensitization be described in the Warnings and Precautions section of labeling.

The safety profile of d-ATS otherwise is similar to other drugs in the stimulant class including increased rates of blood pressure and heart rate escalation, headache, and gastrointestinal symptoms. There does not appear to be increased risk for QTc prolongation or SIB. Based upon exposures, d-ATS is relying upon the listed drug for long-term safety.

Overall, the safety profile of d-ATS comprises potentially higher rates of decreased appetite, insomnia, irritability, and affect lability AEs, increased frequency of non-severe leukopenia and neutropenia, and high occurrences of application site reactions including two confirmed cases of contact sensitization. It is recommended that these be adequately described in labeling. Again, data presented from Study N25-006 must be interpreted with caution given the limitations of study design.

## 8.3. Statistical Issues

For the cross-over study N25-006, because of the significant sequence effect, efficacy results should be derived based only on period 1 data to avoid over-estimating the treatment effect. In addition, the covariance structure in the MMRM model should be an unstructured covariance to avoid potential mis-specification of the covariance structure. For details, refer to efficacy results in Section 8.1.3. The Applicant addressed these issues in response (\\CDSESUB1\evsprod\NDA215401\0051) to our second Information Request, and subsequently submitted additional results for key secondary endpoints (\\CDSESUB1\evsprod\NDA215401\0053) upon request.

## 8.4. Conclusions and Recommendations

Although complicated by study design, efficacy of d-ATS for the treatment of ADHD was demonstrated in Study N25-006: there was a statistically significant reduction in the primary endpoint of mean SKAMP total score. Similarly, study design confounded safety assessment due to the open-label titration period that preceded the randomized, controlled, blinded period. However, the Applicant provided an adequate bridge to the listed drug, Vyvanse, such that the application can rely, in part, on the Agency's previous findings of safety (for purposes of systemic safety evaluation) and effectiveness. The combination of the bridge to Vyvanse and the results of Study N25-006 provide substantial evidence of effectiveness for d-ATS in the

treatment of ADHD in patients ages 6 years and older; Study N25-006 also provides product-specific information about onset and duration of efficacy. The following safety findings were identified and are recommended for inclusion in product labeling: clinically important incidence of decreased appetite, insomnia, irritability, and affect lability AEs, increased frequency of non-severe leukopenia and neutropenia compared to placebo, and high occurrences of application site reactions including two confirmed cases of contact sensitization.

# 9 Advisory Committee Meeting and Other External Consultations

Because there are several previously approved agents in the stimulant class of drugs, the evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and substantial evidence of effectiveness was provided via a positive study and reliance on an approved listed drug, this product was not presented at an Advisory Committee.

# 10 Pediatrics

Based on epidemiological data, the Division is in agreement with the Applicant's Pediatric Research Equity Act (PREA) waiver request for patients with ADHD ages 0 to 3 years old because studies are impossible or highly impractical. Additionally, since this application was submitted, the Division reviewed pediatric data in patients with ADHD ages 4 to 5 years who were treated with the listed drug, Vyvanse. Vyvanse did not get an indication for treatment of patients with ADHD ages 4 to 5 years and now carries a limitation of use (LOU) for this age group based on safety findings, including more severe long-term weight loss than in older pediatric patients. Because this application relies on Agency safety findings from the listed drug and because the exposures after repeat dosing with d-ATS are similar enough to the listed drug that more patients ages 4 and 5 years old should not be exposed to the risks of d-amphetamine in more clinical studies, a PREA waiver will be granted on the grounds that "The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested." The d-ATS label will contain the same LOU as the listed drug. (See Section 11.1 for details.)

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

Prescribing information

- Indications and Usage: The listed drug now carries a limitation of use (LOU) for patients with ADHD ages 4 to 5 years based on safety findings, including long-term weight loss. Because this application relies on Agency safety findings from the listed drug, the same LOU for this population was added.

- Warnings and Precautions:

  - Suppression of Growth: This section was expanded to include basic growth data and the pediatric LOU described above.

  - Contact Sensitization: This section was added as an important safety issue based upon confirmed cases in the development program.

  - Application Site Reactions: This section was truncated from the Applicant's original proposal, and reference made to Section 6 Adverse Reactions where study data is described in more detail.

- Adverse Reactions:

  - ARs during the dose-optimization phase are important given that the controlled data were obtained after several weeks of prior drug exposure and may not be representative of the full safety profile of d-ATS and were added.

  - Regarding ARs during the double-blind controlled phase, the Applicant's Table 1 differs slightly from the Division's unireview Table 29 because the latter does not include ARs that were reported after the discontinuation of Xelstrym and initiation of another medication for the treatment of ADHD.

  - Application Site Reactions: (b) (4) data were removed and replaced with dermal site reaction data from patient diaries and dermal reaction scales at clinic assessments, which more accurately describe relevant signs and symptoms.

  - Weight Loss and Slowing Growth Rate in Pediatric Patients with ADHD: More data and information were added to mirror the listed drug prescribing information.

  - Leukopenia and Neutropenia: Based upon a potential safety signal seen in the

clinical study data, this section was added.

- Use in Specific Populations:
  - Nonclinical information in Section 8 relies on findings described in labeling for the listed drug, Adderall XR.
  - Safety information for pediatric patients ages 4 to less than 6 years relies on findings described in labeling for the listed drug, Vyvanse.
- Nonclinical Toxicology:
  - Information in Section 13 relies on findings described in labeling for the listed drug, Adderall XR.
- Clinical Studies:
  - [redacted] (b) (4) removed and replaced with a summary statement.
  - [redacted] (b) (4)
  - Adhesion study data was added.

# 12 Risk Evaluation and Mitigation Strategies (REMS)

There are multiple stimulant class products currently approved without REMS. No new safety issues that would necessitate a REMS were identified during the review of this product.

# 13 Postmarketing Requirements and Commitment

Although the Agency typically issues PREA post-marketing requirements (PMRs) for stimulant drugs for studies in pediatric patients with ADHD ages 4 to less than 6 years, this application relies in part on a listed drug that has already fulfilled a PMR for such a study (see section 10 for additional details). No additional PMRs will be issued.

## 14 Division Director (Clinical) Comments

I have reviewed and provided edits to the above assessment. I agree with the conclusions of the primary review team.

# 15 Appendices

## 15.1. References

Not applicable

## 15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): N25-006

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 3 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 15.3. Nonclinical Pharmacology/Toxicology

Table 32 Pathological Effect of [redacted] (b) (4) in 15-Week Minipig Study

Summary of Gross Pathology Findings – Interim Euthanasia (Day 54/56)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| **Dose (mg/kg/day)** | **0** | **0.4/0.8** | **2.0** | **1.72** | **0** | **0.4/0.8** | **2.0** | **1.72** |
| **No. Animals Examined** | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **3** |
| **Skin, treated site 1 (No. Examined)** | (3) | (3) | (3) | (3) | (3) | (3) | (3) | (3) |
| Abrasion/scab | - | - | 1 | 2 | - | - | 1 | 3 |
| **Skin, treated site 2 (No. Examined)** | (3) | (3) | (3) | (3) | (3) | (3) | (3) | (3) |
| Abrasion/scab | - | - | 1 | 1 | - | - | - | 3 |

Summary of Gross Pathology Findings – Terminal Euthanasia (Day 106/107)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| **Dose (mg/kg/day)** | **0** | **0.4/0.8** | **2.0** | **1.72** | **0** | **0.4/0.8** | **2.0** | **1.72** |
| **No. Animals Examined** | **3** | **3** | **3** | **3** | **3** | **3** | **3** | **3** |
| **Skin, treated site 1 (No. Examined)** | (3) | (3) | (3) | (3) | (3) | (3) | (3) | (3) |
| Abrasion/scab | - | - | 2 | 2 | - | - | 2 | 2 |
| **Skin, treated site 2 (No. Examined)** | (3) | (3) | (3) | (3) | (3) | (3) | (3) | (3) |
| Abrasion/scab | - | - | 2 | 2 | - | - | 1 | 2 |
| **Skin, treated site 3 (No. Examined)** | (0) | (0) | (1) | (2) | (0) | (0) | (0) | (3) |
| Abrasion/scab | - | - | - | 1 | - | - | - | 1 |
| **Skin, treated site 4 (No. Examined)** | (0) | (0) | (1) | (2) | (0) | (0) | (0) | (3) |
| Abrasion/scab | - | - | - | 1 | - | - | - | 1 |

Summary of Gross Pathology Findings – Recovery Euthanasia (Day 117)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** |
| **Dose (mg/kg/day)** | **0** | **0.4/0.8** | **2.0** | **1.72** | **0** | **0.4/0.8** | **2.0** | **1.72** |
| **No. Animals Examined** | **2** | **2** | **2** | **2** | **2** | **2** | **2** | **2** |
| **Skin, treated site 1 (No. Examined)** | (2) | (2) | (2) | (2) | (2) | (2) | (2) | (2) |
| Abrasion/scab | - | - | - | 1 | - | - | - | 2 |
| **Skin, treated site 2 (No. Examined)** | (2) | (2) | (2) | (2) | (2) | (2) | (2) | (2) |
| Abrasion/scab | - | - | 1 | 1 | - | - | - | 2 |
| **Skin, treated site 3 (No. Examined)** | (0) | (0) | (0) | (2) | (0) | (0) | (0) | (2) |
| Abrasion/scab | - | - | - | 1 | - | - | - | - |
| Focus/foci, red | - | - | - | 1 | - | - | - | - |
| **Skin, treated site 4 (No. Examined)** | (0) | (0) | (0) | (2) | (0) | (0) | (0) | (2) |
| Abrasion/scab | - | - | - | 1 | - | - | - | - |
| Focus/foci, red | - | - | - | 1 | - | - | - | - |

*Source: Applicant's Table, Study No. 2506-002, pp. 26-28*

Table 33 Histopathological Effect of [redacted] (b) (4) in 15-Week Minipig Study

Summary of Microscopic Findings – Interim Euthanasia (Day 54/56)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Dose (mg/kg/day)** | 0 | 0.4/ 0.8 | 2.0 | 1.72 | 0 | 0.4/ 0.8 | 2.0 | 1.72 |
| **No. Animals Examined** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Skin, treated site 1 (No. Examined)** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Ulcer, squamous epithelium | (0)[a] | (0) | (0) | (2) | (0) | (0) | (1) | (2) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Marked | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Crust, suppurative | (0) | (0) | (0) | (2) | (0) | (0) | (1) | (3) |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Marked | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 |
| Fibroplasia | (0) | (0) | (0) | (2) | (0) | (0) | (0) | (0) |
| Minimal | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Hyperplasia, epidermal | (0) | (0) | (0) | (2) | (0) | (0) | (1) | (2) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mild | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 1 |
| Crust, serocellular | (0) | (0) | (1) | (1) | (0) | (0) | (1) | (1) |
| Minimal | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Infiltration, mixed leukocyte | (0) | (0) | (1) | (2) | (0) | (0) | (0) | (2) |
| Mild | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Bacterial colonies | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Skin, treated site 2 (No. Examined)** | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 3 |
| Ulcer, squamous epithelium | (0) | (0) | (1) | (1) | (0) | (0) | (0) | (3) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| Marked | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Crust, suppurative | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (3) |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Marked | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hyperplasia, epidermal | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (3) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 |
| Infiltration, mixed leukocyte | (0) | (0) | (1) | (1) | (0) | (0) | (0) | (3) |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |
| Marked | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Bacterial colonies | (0) | (0) | (1) | (1) | (0) | (0) | (0) | (1) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mild | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |

[a] Numbers in parentheses represent the number of animals with the finding.

Summary of Microscopic Findings – Terminal Euthanasia (Day 106/107)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Dose (mg/kg/day)** | 0 | 0.4/ 0.8 | 2.0 | 1.72 | 0 | 0.4/ 0.8 | 2.0 | 1.72 |
| **No. Animals Examined** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Skin, treated site 1 (No. Examined)** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Ulcer, squamous epithelium | (0)[a] | (0) | (1) | (2) | (0) | (0) | (1) | (2) |
| Mild | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| Moderate | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 1 |
| Crust, suppurative | (0) | (0) | (2) | (2) | (0) | (0) | (2) | (3) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Moderate | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 1 |
| Marked | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Fibroplasia | (0) | (0) | (2) | (1) | (0) | (0) | (1) | (2) |
| Minimal | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 2 |
| Hyperplasia, epidermal | (0) | (1) | (2) | (2) | (0) | (1) | (2) | (3) |
| Minimal | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 |
| Mild | 0 | 0 | 1 | 2 | 0 | 0 | 1 | 3 |
| Erosion/ulcer, squamous epithelium | (0) | (0) | (1) | (0) | (0) | (0) | (1) | (0) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Infiltration, mixed leukocyte | (0) | (0) | (0) | (2) | (0) | (0) | (1) | (2) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Bacterial colonies | (0) | (0) | (2) | (2) | (0) | (0) | (1) | (2) |
| Minimal | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| Mild | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| Hemorrhage | (0) | (0) | (0) | (2) | (0) | (0) | (0) | (0) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Skin, treated site 2 (No. Examined)** | 0 | 0 | 2 | 3 | 1 | 0 | 1 | 3 |
| Ulcer, squamous epithelium | (0) | (0) | (1) | (2) | (0) | (0) | (0) | (2) |
| Mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| Crust, suppurative | (0) | (0) | (2) | (2) | (0) | (0) | (1) | (3) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Moderate | 0 | 0 | 1 | 2 | 0 | 0 | 1 | 1 |
| Marked | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Hyperplasia, epidermal | (0) | (0) | (2) | (2) | (0) | (0) | (1) | (3) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Mild | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 2 |
| Infiltration, mixed leukocyte | (0) | (0) | (0) | (1) | (0) | (0) | (1) | (3) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Bacterial colonies | (0) | (0) | (2) | (2) | (0) | (0) | (1) | (2) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 |
| Moderate | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Erosion/ulcer, squamous epithelium | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hyperkeratosis | (0) | (0) | (1) | (1) | (0) | (0) | (1) | (1) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| Mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Fibroplasia | (0) | (0) | (2) | (0) | (0) | (0) | (0) | (0) |
| Minimal | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| **Skin, treated site 3 (No. Examined)** | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| Crust, suppurative | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Bacterial colonies | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Erosion/ulcer, squamous epithelium | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Infiltration, mixed leukocyte | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Skin, treated site 4 (No. Examined)** | | | | | | | | |
| Erosion/ulcer, squamous epithelium | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Crust, suppurative | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |

Summary of Microscopic Findings – Recovery Euthanasia (Day 117)

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| **Group** | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| **Dose (mg/kg/day)** | 0 | 0.4/ 0.8 | 2.0 | 1.72 | 0 | 0.4/ 0.8 | 2.0 | 1.72 |
| **No. Animals Examined** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Skin, treated site 1 (No. Examined)** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Erosion/Ulcer, squamous epithelium | (0)[a] | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Crust, suppurative | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (2) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Fibroplasia | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Hyperplasia, epidermal | (0) | (0) | (2) | (2) | (0) | (0) | (2) | (2) |
| Minimal | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Infiltration, mixed leukocyte | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (2) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Bacterial colonies | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (2) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Hyperkeratosis | (0) | (0) | (2) | (2) | (0) | (0) | (2) | (1) |
| Minimal | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 1 |
| **Skin, treated site 2 (No. Examined)** | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| Crust, suppurative | (0) | (0) | (1) | (0) | (0) | (0) | (0) | (2) |
| Mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Hyperplasia, epidermal | (0) | (0) | (1) | (1) | (0) | (0) | (0) | (2) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mild | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Hyperkeratosis | (0) | (0) | (1) | (1) | (0) | (0) | (0) | (0) |
| Minimal | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Erosion/Ulcer, squamous epithelium | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (2) |
| Minimal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Crust, serocellular | (0) | (0) | (1) | (1) | (0) | (0) | (0) | (0) |
| Minimal | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Mild | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Bacterial colonies | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) |
| Mild | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

[a] Numbers in parentheses represent the number of animals with the finding.

*Source: Applicant's Tables, Study No. 2506-00, pp. 29-32*

## 15.4. OCP Appendices (Technical documents supporting OCP recommendations)

Individual reviews of pivotal clinical pharmacology studies will be documented in a separate review.

### 15.4.1. Pharmacometric Review

**Applicant's Analysis**

**Population PK Analysis**

The final PopPK model was developed from a dataset of 6607 observed plasma concentrations from 156 subjects enrolled in six clinical studies to quantitatively describe the clinical PK of and identify sources of interindividual variability. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.3.4 (ICON, Maryland) was used for the PopPK analysis.

**Table 34: Summary of Studies Included in the Population PK Analysis**

| Protocol | Title | Subject Population | No. of Subjects | Dose |
|---|---|---|---|---|
| N25-002 | Phase 1, Open-label single-dose, randomized, 2-period, 2-way crossover | Healthy Adults (18-30 yr) | 8 | 9.38, 9.85 mg |
| N25-010 | Phase 1, Single-dose relative BA of different application sites | Healthy Adults (18-45yr) | 50 | 20 mg |
| N25-012 | Phase 1, Single-dose study<br>Part 1: PK bridge to listed drugs Effect of external heat<br>Part 2: Pivotal PK bridging study with Adderall XR and Vyvanse using the highest strength of each | Healthy Adults (18-65 yr) | Part 1: 14<br>Part 2: 16 | 5, 20 mg |
| N25-015 | Phase 1, Open-label, multiple-dose, 4-week, PK with/without application site rotation for accumulation and safety | ADHD Adults (18-65 yr) | 35<br>Intended use:15<br>Exaggerated use: 20 | 20 mg |
| N25-004 | Phase 1, Open-label, single-dose, randomized, 3-period, 3-way crossover relative bioavailability study | ADHD Children (6-12 yr) | 18 | 8.4 mg |
| N25-005 | Phase 1 Dose proportionality | ADHD Children (6-12 yr) | 18 | 5,10,20 mg |
| N25-006 | Pivotal efficacy/safety | ADHD Children<br>ADHD Adolescent | Children (n=76)<br>Adolescent (n=30) | 5,10,15,20 mg |

*Source: Adapted from applicant's Summary of Clinical Pharmacology Studies, Page 11, Table 1*

**Table 35: Categorical Covariates by Study in the Population PK Development Dataset**

| Study: | | N25-002 | N25-004 | N25-005 | N25-010 | N25-012 | N25-015 | All studies |
|---|---|---|---|---|---|---|---|---|
| Sex* | Male | 8(100%) | 10(62.5%) | 10(55.6%) | 21(42.0%) | 12(41.4%) | 21(60.0%) | 74(47.4%) |
| | Female | | 6(37.5%) | 8(44.4%) | 29(58.0%) | 17(58.6%) | 14(40.0%) | 82(52.6%) |

*Baseline data is presented as counts (percent of subjects).

*Source: Applicant's PopPK report NVN0601, Page 34, Table 3*

Table 36: Continuous Covariates by Age Group and Study in the Population PK Development Dataset

| Age Group | Study | Age (yr)* | Body weight (kg)* | Height (cm)* |
|---|---|---|---|---|
| All subjects | All studies | 29.0(6.00-62.0) | 67.3(23.1-101) | 166(122-189) |
| Adults | All studies | 33.0(18.0-62.0) | 73.2(43.8-101) | 170(150-189) |
| Children | All studies | 10.0(6.00-12.0) | 40.6(23.1-63.5) | 147(122-175) |
| Adults | N25-002 | 35.5(31.0-41.0) | 78.0(66.0-83.0) | 178(175-185) |
| Children | N25-004 | 10.0(6.00-12.0) | 40.5(23.1-63.5) | 151(122-170) |
| Children | N25-005 | 10.5(6.00-12.0) | 40.6(24.1-62.2) | 146(126-175) |
| Adults | N25-010 | 35.5(19.0-45.0) | 72.8(43.8-101) | 165(150-185) |
| Adults | N25-012 | 33.0(18.0-62.0) | 71.3(46.9-93.6) | 167(150-189) |
| Adults | N25-015 | 29.0(20.0-57.0) | 74.7(46.6-97.0) | 172(151-189) |

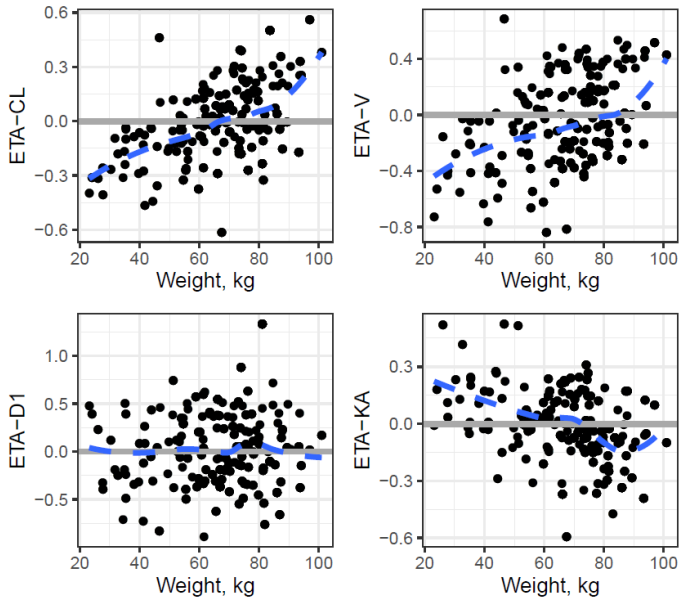
*Baseline data presented and summarized as median (range).

*Source: Applicant's PopPK report NVN0601, Page 34, Table 4*

A full covariate modeling approach was implemented for PopPK analysis. A list of covariate-parameter relationships was pre-defined based on exploratory graphics, scientific interest, mechanistic plausibility or prior knowledge. Covariates with correlation coefficients > 0.35 were not simultaneously included as potential predictors to avoid correlation or collinearity. An exploratory assessment of any remaining trends was conducted by graphical inspection of all covariate effects. Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision. No hypothesis testing was conducted.

The PK of amphetamine in the dose range (4.5 mg/9 hours-18 mg/9 hours) tested was best described by a one-compartment model with sequential zero- (D1) and first-order (ka) absorption. Plots of random effects parameters versus covariates showed trends of weight on CL/F, V/F and Ka (Figure 17). Trends of age on CL/F and V/F were apparent, but there was only a slight trend of age on Ka (Figure 18). After body weight was included as a covariate on clearance, volume and Ka, no more trend of age on CL/F, V/F, Ka or D1 were seen (Figure 19).

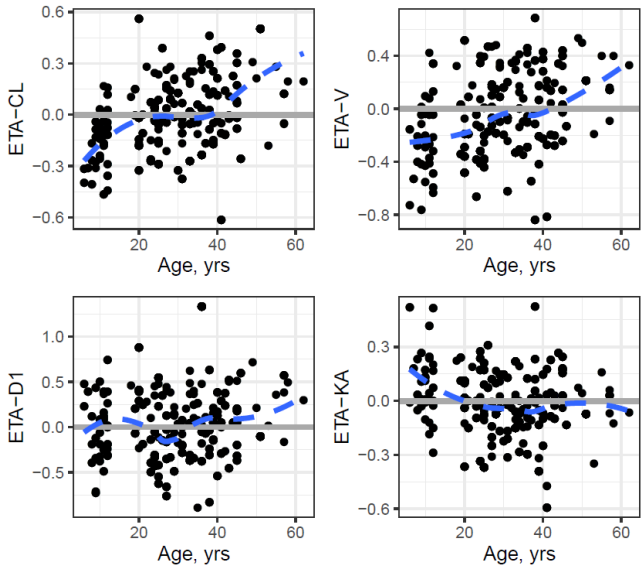
Figure 17: Individual Random Effects versus Weight for Base Model




Individual maximum a posteriori Bayes estimates of individual random effects versus body weight for base model (Run 8016). Values are indicated by points with a loess smooth trend line (dashed blue) through the data. The line of identity (solid gray) is shown as reference. Baseline body weight is presented.

*Source: Applicant's PopPK report NVN0601, Page 68, Figure 29*

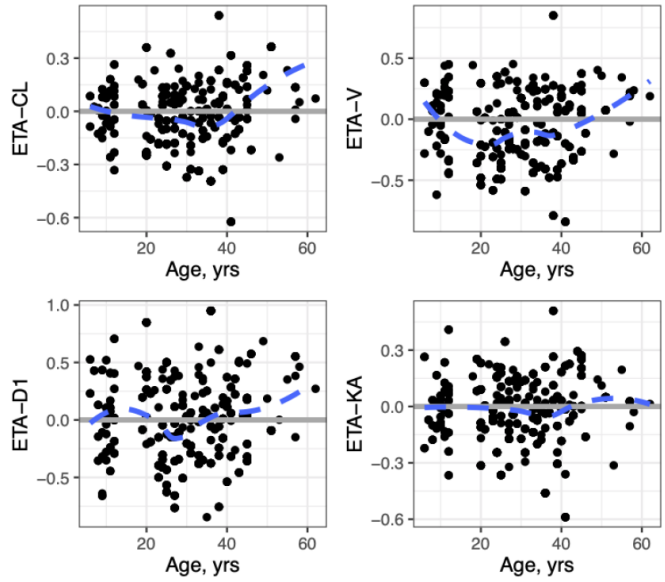
Figure 18: Individual Random Effects versus Age for Base Model




Individual maximum a posteriori Bayes estimates of individual random effects versus body weight for base model (Run 8016). Values are indicated by points with a loess smooth trend line (dashed blue) through the data. The line of identity (solid gray) is shown as reference. Baseline body weight is presented.

*Source: Applicant's PopPK report NVN0601, Page 69, Figure 30*

Figure 19: Individual Random Effects versus Age for Final Model




Individual maximum a posteriori Bayes estimates of individual random effects versus age for final model (Run 8026). Values are indicated by points with a loess smooth trend line (dashed blue) through the data. The line of identity (solid gray) is shown as reference. Baseline body weight is presented.

*Source: Applicant's PopPK report NVN0601, Page 79, Figure 40*

The model was parameterized in terms of population parameters relative clearance (CL/F), relative central volume of distribution (V/F), absorption rate constant (Ka), and zero-order absorption time (D1). Inter-individual random effects were modeled for CL/F, V/F, Ka, and D1. The PopPK model also included inter-occasion variability (IOV) on D1 and relative bioavailability (F). A combined proportional and additive residual error model described the random residual variability. The equations for the population PK final model are shown below.

$$CL/F_i = \exp(\theta_{CL/F_{pop}} + \eta_{CL/F}) * \frac{WT}{70}^{\theta_{WT,CL}}$$

$$V/F_i = \exp(\theta_{V/F_{pop}} + \eta_{V/F}) * \frac{WT}{70}^{\theta_{WT,V}}$$

$$Ka_i = \exp(\theta_{Ka_{pop}} + \eta_{Ka}) * \frac{WT}{70}^{\theta_{WT,Ka}}$$

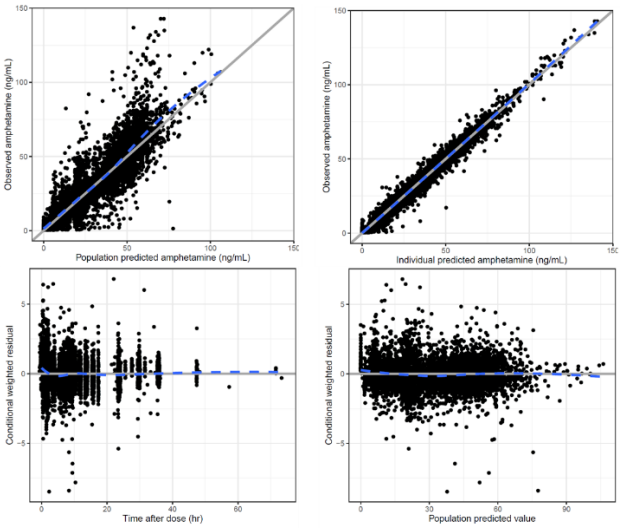
$$D1_i = \exp(\theta_{D1_{pop}} + \eta_{D1} + \eta_{IOV_{D1}})$$

$$F_i = \exp(\theta_{F_{pop}} + \eta_{IOV_F})$$

*Source: Applicant's PopPK report NVN0601, Page 24, Equation 5*

The final PK/Efficacy model for d-amphetamine was assessed with diagnostics plots including goodness-of-fit (Figure 20) and pairwise correlation of interindividual random effects (Figure 21).

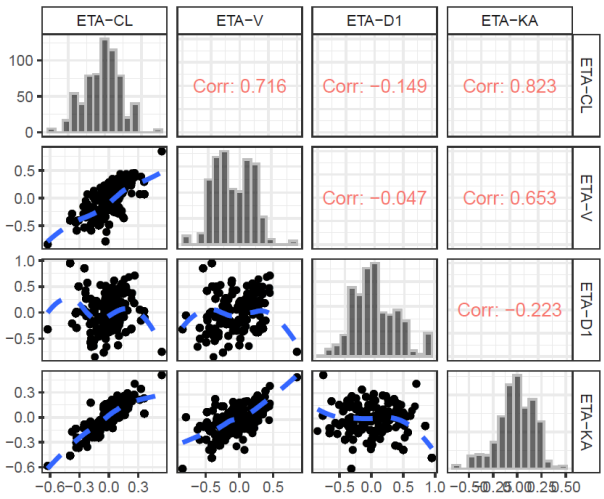
Figure 20: Goodness-of-Fit Plots for Final PopPK Model




Values are indicated by points with a loess smooth trend line (dashed blue) through the data.

*Source: Applicant's PopPK report NVN0601, Page 70,71,73 and 74, Figure 31,32,34 and 35*

Figure 21: Pairwise Correlation Plots of the Interindividual Random Effects for the Final Population PK Model.




Scatter plot matrix of interindividual random effects for the final population PK model (Run8026). The lower off-diagonal shows bivariate scatter plots where circles represent data points and dashed blue lines represent loess smoothing trend lines. The diagonal shows density plots of the ETAs, and the correlation coefficients are reported in the upper off-diagonal in red.

*Source: Applicant's PopPK report NVN0601, Page 67, Figure 28*

Parameter estimates from the final population PK model are presented in Table 37.
For a typical patient with body weight of 70 kg, the estimated CL/F was 18.4 L/hr, V/F was 51.9L, Ka was 0.0696 $hr^{-1}$, D1 was 1.92 hr. Interindividual variability on CL/F, V/F, D1 and Ka were 20.1%,37.4%, 48.6% and 20.3%, respectively. The shrinkage standard deviations for the random effects were 12.9, 17.5, 22.1, and 15.6%, for CL/F, V/F, D1 and Ka, respectively. This

suggests that the final PopPK model can adequately characterize IIV of those parameters in the final model.

Table 37: Summary of Final Population PK Parameters

| Description | Parameter | Units | Estimate | 95% CI | % RSE |
|---|---|---|---|---|---|
| Absorption rate constant | $K_a$ | 1/hr | 0.0696 | (0.0665, 0.0728) | 2.31% |
| Relative clearance | CL/F | L/hr | 18.4 | (17.6, 19.2) | 2.22% |
| Relative central volume of distribution | V/F | L | 51.9 | (48.1, 56.1) | 3.97% |
| Zero order absorption time | D1 | hr | 1.92 | (1.75, 2.11) | 4.75% |
| Weight effect on CL/F | $CL_{WT}$ | | 0.469 | (0.361, 0.577) | 11.8% |
| Weight effect on V/F | $V_{WT}$ | | 0.526 | (0.305, 0.748) | 21.4% |
| Weight effect on $K_a$ | $Ka_{WT}$ | | -0.290 | (-0.429, -0.151) | 24.4% |
| Interindividual variance of CL/F | $\omega_{CL}$ | CV % | 20.1 | (16.6, 23.1) | 7.94% |
| Correlation of $\omega_V$ and $\omega_{CL}$ | $Cor_{V-CL}$ | | 0.713 | (0.595, 0.830) | 8.44% |
| Correlation of $\omega_{D1}$ and $\omega_{CL}$ | $Cor_{D1-CL}$ | | 0.120 | (-0.171, 0.412) | 124% |
| Correlation of $\omega_{Ka}$ and $\omega_{CL}$ | $Cor_{Ka-CL}$ | | 0.796 | (0.664, 0.927) | 8.43% |
| Interindividual variance of V/F | $\omega_V$ | CV % | 37.4 | (30.3, 43.7) | 8.44% |
| Correlation of $\omega_{D1}$ and $\omega_V$ | $Cor_{D1-V}$ | | 0.121 | (-0.229, 0.470) | 148% |
| Correlation of $\omega_{Ka}$ and $\omega_V$ | $Cor_{Ka-V}$ | | 0.635 | (0.477, 0.793) | 12.7% |
| Interindividual variance of D1 | $\omega_{D1}$ | CV % | 48.6 | (40.6, 55.8) | 7.16% |
| Correlation of $\omega_{Ka}$ and $\omega_{D1}$ | $Cor_{Ka-D1}$ | | -0.0168 | (-0.332, 0.298) | 954% |
| Interindividual variance of $K_a$ | $\omega_{Ka}$ | CV % | 20.3 | (15.7, 24.1) | 10.1% |
| Interoccasion variance of D1 | $\omega_{D1\text{-}IOV}$ | CV % | 53.5 | (46.4, 60.2) | 5.80% |
| Interoccasion variance of F1 | $\omega_{F1\text{-}IOV}$ | CV % | 18.3 | (12.4, 22.8) | 13.7% |
| Proportional residual error | $\sigma_{prop}$ | CV % | 5.23 | (4.04, 6.42) | 11.6% |
| Additive residual error | $\sigma_{add}$ | SD | 2.59 | (2.33, 2.86) | 5.26% |

*Source: Applicant's PopPK report NVN0601, Page 37, Table 8*

*Reviewer's Comments*

*The applicant's population PK model appears adequate to describe amphetamine PK profiles following application of d-ATS. Therefore, this model is acceptable for PK simulation to support extrapolation of efficacy from pediatric patients to adults.*

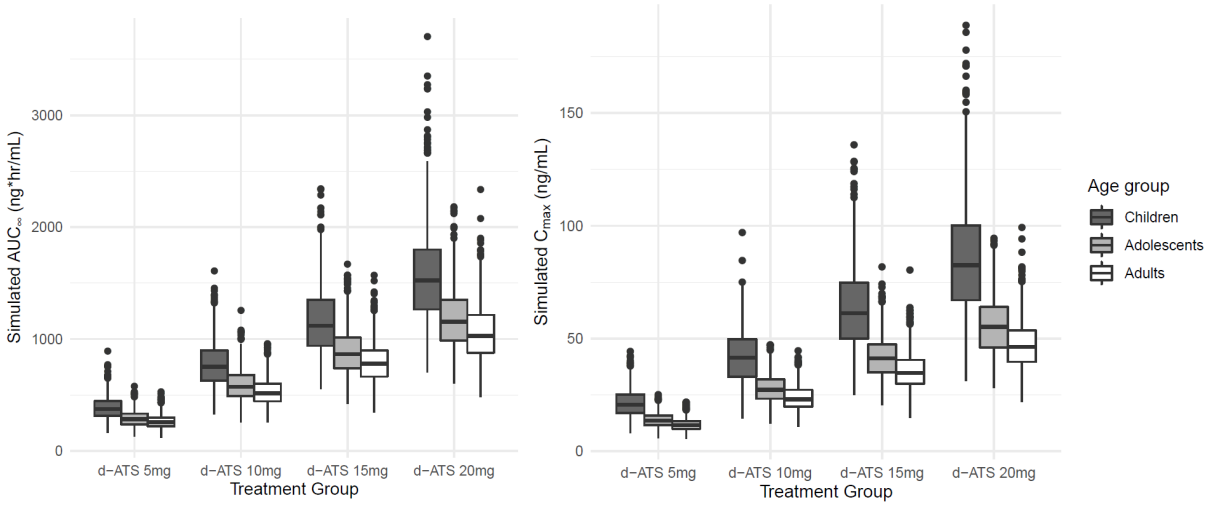
PK predictions in adults based on PopPK model

The applicant's final d-amphetamine PopPK model was used to support the PK extrapolation from children and adolescents to adults. Simulation was performed to compare adult exposures to those in children and adolescents at the effective doses (4.5 mg/9 hours,9 mg/9 hours,13.5 mg/9 hours or 18 mg/9 hours QID) in N25-006. For each age group, 1000 subjects were sampled with replacement from the National Health and Nutrition Examination Survey (NHANES) database.

The simulated exposure metrics for the three age groups at the doses administered in study N25-006 (4.5 mg/9 hours,9 mg/9 hours,13.5 mg/9 hours or 18 mg/9 hours) are compared in Figure 22.

The findings suggest that an initial dose of 4.5 mg/9 hours in pediatric patients would result in 30% lower $C_{max}$ and 34% lower in AUC when compared to 9 mg/9 hours in adult patients. At the highest recommended dose of 18 mg/9 hours, pediatric patients would show 40% increase in $C_{max}$ and 30% increase in AUC compared to adults at the same dose level.

Figure 22: Simulated Amphetamine Exposures with d-ATS by Dose Level across Age Groups




Note: d-Amphetamine content of d-ATS is 5 mg to 20 mg/patch, considering 90% of d-amphetamine is delivered from the transdermal system over 9 hours, the dose strength is 4.5 mg/9 hours to 18 mg/9 hours. Hereafter, 5 mg and 4.5 mg/9 hours, 10 mg and 9 mg/9 hours, 15 mg and 13.5 mg/9 hours, and 20 mg and 18mg/9 hours are interchangeable.

*Source: Applicant's PopPK report NVN0601, Page 121 and Page 122, Figure 63 and Figure 64*

## Population PK/Efficacy analysis

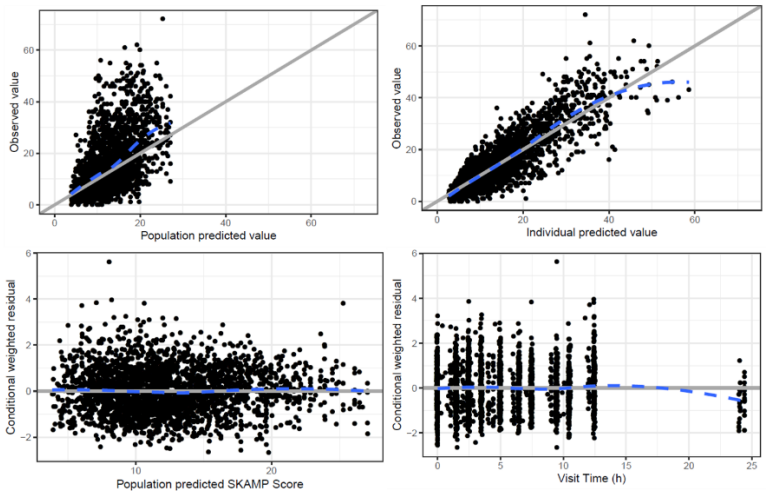
The population PK/Efficacy analysis data set was developed from the pooled data of Studies N25-004 and N25-006. The dataset included 122 subjects and 2546 observations. The study population consisted of children and adolescents with ADHD, age ranged from 6 to 17 years and weights ranged from 20.1 to 82.0 kg. Subjects were mainly White (84/122) or Black/African American (28/122), approximately two-thirds were male (83/122) and half had combined ADHD while another half had inattentive ADHD.

The SKAMP time course was modeled as the product of a monoexponential increase in SKAMP score under placebo treatment and an Emax model representing the amphetamine drug effect:

$$\mathrm{SKAMP} = \mathrm{R} \times \left(1 - \frac{\mathrm{E_{max}} \times \mathrm{CP}}{\mathrm{EC_{50}} + \mathrm{CP}}\right)$$

where R is the monoexponentially increasing placebo effect, EC50 is the concentration producing half of maximal effect (Emax), and CP is the simulated amphetamine concentration using individual-specific PK parameters derived from the established PopPK model for d-ATS. The full covariate model started with the base model and added estimated covariate effects for age, sex, non-White race, study, and ADHD subtype on the baseline SKAMP score (BASE), ADHD subtype on EC50, and study-specific Emax parameterized as a proportional shift in Emax for Study N25-004 relative to Study N25-006. The final model parameters were estimated using the base model equations with the additional covariate effects (i.e., age, weight, race, and combined ADHD subtype) on BASE, $EC_{50}$, and Emax. Goodness of fit plots showed that the data were generally well described by the model (Figure 23). The final model parameters were generally well estimated, but with some reduced precisions compared to the base model. The estimated d-AMP EC50 in the final covariate model was 22.7 ng/mL and the estimated d-AMP EMAX was 0.582. Parameter estimates from the final population PK/Efficacy model of d-ATS are shown in Table 38 and Table 39.

Figure 23: Diagnostic Plots for the SKAMP Final Model




Solid black circles represent the individual residual values associated with each observation record. The dashed blue line represents a LOESS smooth through the data.

*Source: Applicant's PopPK report NVN0601 Addendum, Page 90 and Page 95, Figure S17 and S22*

Table 38: SKAMP Final Model: Summary of Fixed Effect Parameter Estimates

| | | | Estimate | 95% CI |
|---|---|---|---|---|
| **Structural model parameters** | | | | |
| BASE | $\exp(\theta_1)$ | Baseline SKAMP, N25-006 data | 12.3 | 10.9, 13.9 |
| KOUT (1/hr) | $\exp(\theta_2)$ | Placebo KOUT | 0.116 | 0.0335, 0.404 |
| AA | $\exp(\theta_3)$ | Placebo response amplitude | 0.496 | 0.308, 0.799 |
| EC50 (ng/mL) | $\exp(\theta_4)$ | d-amphetamine concentration producing 50% maximal effect | 22.7 | 7.36, 70.1 |
| EMAX | $\exp(\theta_5)$ | Maximum effect [proportional], N25-006 data | 0.582 | 0.411, 0.824 |
| **Covariate effect parameters** | | | | |
| BASE ~ 004 | $\exp(\theta_7)$ | Shift in BASE in N25-004 data | 0.633 | 0.524, 0.765 |
| EMAX ~ 004 | $\exp(\theta_8)$ | Shift in EMAX in N25-004 data | 1.43 | 1.11, 1.83 |
| BASE ~ FEMALE | $\exp(\theta_9)$ | Shift in BASE for female SEX | 0.890 | 0.780, 1.02 |
| BASE ~ RACE | $\exp(\theta_{10})$ | Shift in BASE for non-white RACE | 0.987 | 0.957, 1.02 |
| BASE ~ ADHD Type | $\exp(\theta_{11})$ | Shift in BASE for combined ADHD type | 1.15 | 1.01, 1.30 |
| BASE ~ (AGE/10) | $\theta_{12}$ | Power effect of AGE on BASE | -0.651 | -0.876, -0.426 |
| EC50 ~ ADHD Type | $\exp(\theta_{14})$ | Shift for combined ADHD type on EC50 | 0.903 | 0.635, 1.28 |

Estimates presented here were back-transformed from the log-domain for clarity

*Source: Applicant's PopPK report NVN0601 Addendum, Page 53, Table S10*

Table 39: SKAMP Final Model: Summary of Random Effect Parameter Estimates

| | | Estimate | 95% CI | Shrinkage (%) |
|---|---|---|---|---|
| **Interindividual variance parameters** | | | | |
| IIV-BASE | $\Omega_{(1,1)}$ | 0.0967 [CV%=31.9] | 0.0582, 0.135 | 15.1 |
| IIV-AA | $\Omega_{(2,2)}$ | 0.692 [CV%=99.9] | 0.282, 1.10 | 28.5 |
| **Interoccasion variance parameters** | | | | |
| IOV-BASE | $\Omega_{(3,3)}$ | 0.0471 [CV%=22.0] | 0.0313, 0.0630 | 35.4 |
| **Residual variance** | | | | |
| Additive, N25-006 | $\Sigma_{(1,1)}$ | 5.20 [SD=2.28] | 3.21, 7.19 | 5.66 |
| Proportional, N25-006 | $\Sigma_{(2,2)}$ | 0.0975 [CV%=31.2] | 0.0796, 0.115 | 5.66 |
| Additive, N25-004 | $\Sigma_{(3,3)}$ | 1.99 [SD=1.41] | 0.525, 3.45 | 5.26 |
| Proportional, N25-004 | $\Sigma_{(4,4)}$ | 0.174 [CV%=41.8] | 0.100, 0.249 | 5.26 |

*Source: Applicant's PopPK report NVN0601 Addendum, Page 54, Table S11*

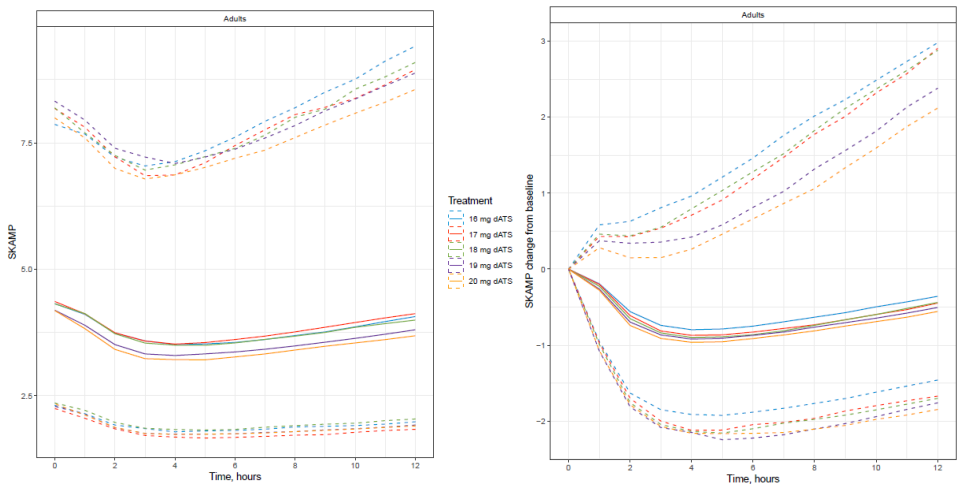
*Reviewer's comment:*

*The applicant's PK/Efficacy model is acceptable. The reviewer was able to run the applicant's final PK/Efficacy model and obtained similar results as reported by the applicant.*

Impact of Product Shelf-life on Efficacy

The impact of decreasing total d-Amphetamine available for delivery due to degradation during storage on the SKAMP score time course was also evaluated. The SKAMP score and SKAMP score change from baseline time course after five sequential d-ATS doses are shown in Figure 24. Briefly, the predicted SKAMP response for the five sequential doses of d-ATS was comparable, with a generally higher response for higher doses, but overlap in the median and 90% PI was present across the dose groups.

Figure 24: Simulated SKAMP Responses (Left) and SKAMP Change from Baseline (Right) over Time following Administration of d-ATS (16 mg, 17 mg, 18 mg, 19 mg or 20 mg)




Solid and dashed lines indicate the median and 90% prediction intervals, respectively, from 1000 Monte Carlo simulations.

*Source: Applicant's response to OCP IR2, Page 26 and 27, Figure 14 and 15*

## Reviewer's Analysis

### Methods

#### Data Sets

Data sets used are summarized in Table 40.

Table 40: Analysis Data Sets

| Study | Name | Link to EDR |
|---|---|---|
| N25-002 N25-004 N25-005 N25-010 | tran_dATS_allStudies.xpt | \\CDSESUB1\evsprod\nda215401\0022\m5\datasets\nvn0601\analysis\legacy\datasets\tran_dats_allstudies.xpt |

| | | |
|---|---|---|
| N25-012 N25-015 | | |
| N25-004<br>N25-006 | transk12.xpt | \\CDSESUB1\evsprod\nda215401\0001\m5\datasets\nvn0601-add\analysis\legacy\datasets\transk12.xpt |

Software

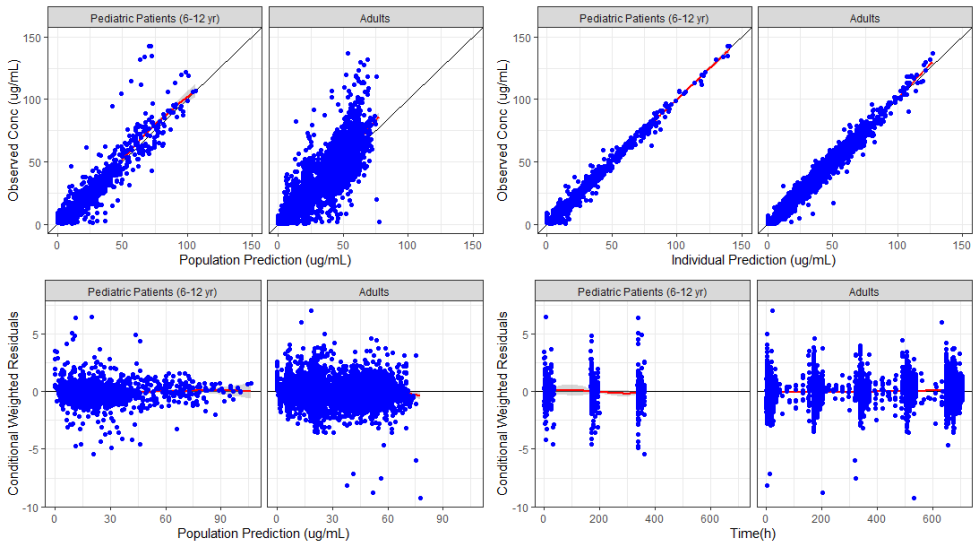
Population PK model fitting was performed in NONMEM 7.4.3 and Pirana 2.9.9. Primary analysis and plotting were performed in R 4.0.2.

## Results

### Evaluation of PopPK model

The reviewer was able to reproduce the model and obtain similar model diagnostics for PopPK models. The applicant's PopPK analysis appears adequate for describing the PK of d-ATS in both adult and pediatric patient population as evidenced by the diagnostic plot (Figure 25).

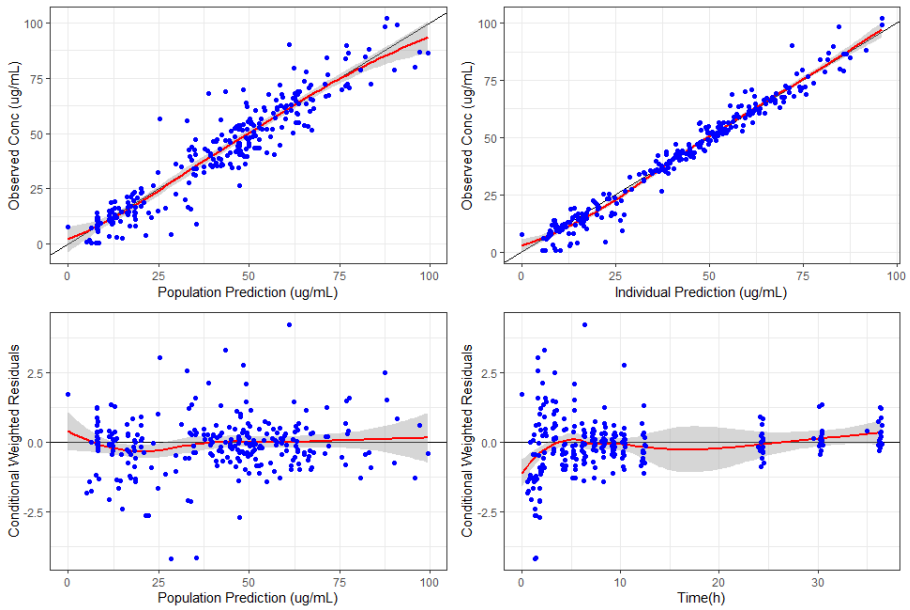
Figure 25: Goodness-of-fit plots for Final PopPK Model of d-amphetamine in Pediatric and Adult Subjects




*Source: Reviewer's analysis*

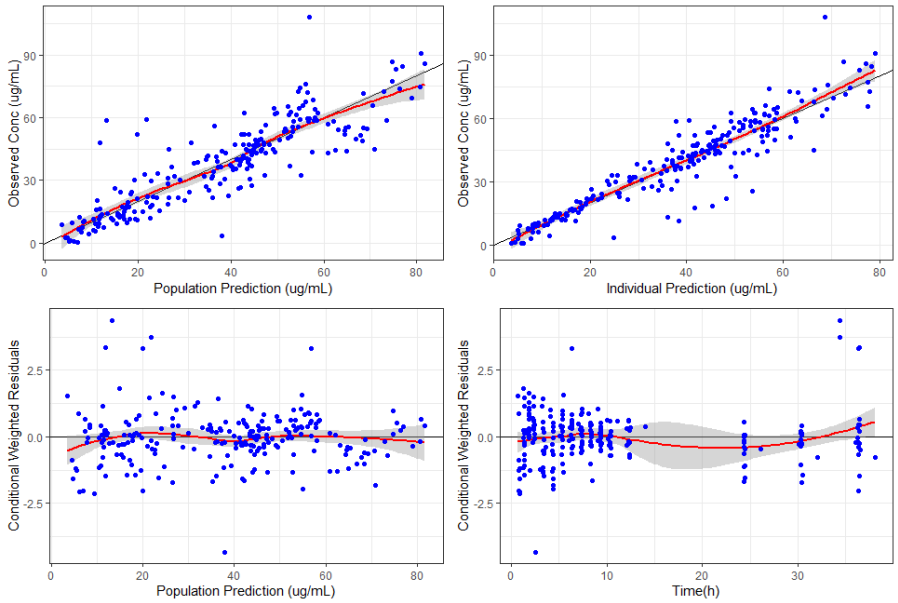
The reviewer conducted PopPK analysis to characterize the PK for Vyvanse and Adderall XR (d-amphetamine only) using data from Study N25-012. The diagnostic plots as shown in Figure 26 and Figure 27 indicate that the PopPK model describes the data adequately.

Figure 26 : Goodness-of-fit Plots for Vyvanse Final PopPK Model




*Source: Reviewer's analysis*

Figure 27: Goodness-of-Fit Plots for Adderall XR Final PopPK Model Using Only d-Amphetamine




*Source: Reviewer's analysis*

Comparison of $C_{max}$ and $AUC_{0\text{-}24h}$ in pediatric and adult subjects based on proposed dosing regimen

To compare adult $C_{max}$, $AUC_{0\text{-}24h}$ to those in children and adolescents at the effective doses (4.5 mg/9 hours,9 mg/9 hours,13.5 mg/9 hours or 18 mg/9 hours QID), for each age group, 1000 subjects were sampled with replacement from the 156 subjects from applicant's clinical studies including Study N25-002, N25-004, N25-005, N25-010, N25-012, and N25-015. Figure 3 (Please

refer to Section 6.3.2 of Clinical Pharmacology Review for more detail) and Table 41 presents the simulated exposure metrics for the three age groups at doses 4.5 mg/9 hours, 9 mg/9 hours, 13.5 mg/9 hours,18 mg/9 hours.

The findings suggest that an initial dose of 4.5 mg/9 hours in pediatric patients would result in 26% lower $C_{max}$ and 30% lower in $AUC_{0-24h}$ when compared 4.5 mg/9 hours adult patients (Figure 3). At the highest recommended dose of 18 mg/9 hours, pediatric patients would show 44% increase in $C_{max}$ and 39% increase in $AUC_{0-24h}$ compared to adults at the same dose level (Table 41).

Table 41: Summary of d-ATS $C_{max}$ & $AUC_{0-24h}$ by Age and Dose Group

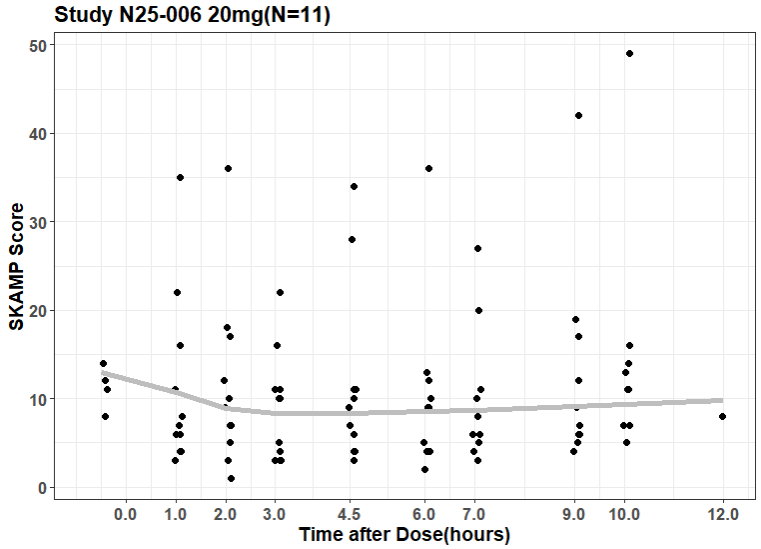
| Age Group | Dose | $C_{max}$(ng/mL) | $AUC_{0-24h}$(ng*hr/mL) |
|---|---|---|---|
| Children and Adolescents | d-ATS 4.5 mg/9 hours | 21[14.9, 27.1] | 291[202, 380] |
| | d-ATS 9 mg/9 hours | 39.8[27.7, 51.8] | 574[398, 750] |
| | d-ATS 13.5 mg/9 hours | 58.7[40.3, 77.2] | 861[597, 1124] |
| | d-ATS 18 mg/9 hours | 77[52.4, 101.6] | 1135[786, 1484] |
| Adults | d-ATS 4.5mg/9 hours | 15.7[12.2, 19.2] | 214[158, 271] |
| | d-ATS 9 mg/9 hours | 28.2[21.2, 35.2] | 417[308, 526] |
| | d-ATS 13.5 mg/9 hours | 40.7[30.1, 51.2] | 620[455, 784] |
| | d-ATS 18 mg/9 hours | 53.3[40.4, 66.2] | 815[618, 1011] |

*Source: Reviewer's analysis*

Evaluation of PopPK/Efficacy model

The reviewer was able to reproduce applicant's analysis. The applicant's PopPK/Efficacy analysis appears adequate for characterizing the time course of SKAMP scores in Study N25-006. The reviewer was able to generate similar diagnostic plots (Figure 28).

Figure 28: SKAMP Total Scores across Laboratory Classroom Visits during the First Double-Blind Treatment Period after Administration of 20mg d-ATS (Study N25-006)



Observed values are indicated by solid black circles. The solid grey line represents the median of the population predictions.

*Source: Reviewer's analysis*

The PK/Efficacy analysis suggested that 70 mg Vyvanse (eq.20.8 mg) is predicted to have the largest decrease in the SKAMP score over time, followed by d-ATS 18 mg/9 hours and 30 mg Adderall XR (eq. 22.7 mg). All three products would show a maximum change in SKAMP score at 2-3 hours post dose. The maximum change in SKAMP score after administration of 18 mg/9 hours d-ATS is 80.2% of 70 mg Vyvanse and 102.0% of 30 mg Adderall XR (Figure 1)( Please refer to Section 6.3.2 of Clinical Pharmacology Review for more detail). The efficacy of d-ATS is likely to be lower than 70 mg Vyvanse but similar to 30 mg Adderall XR.

Evaluation of impact of d-amphetamine degradation during storage

Simulations were conducted using the PK/Efficacy model to evaluate the impact of d-amphetamine degradation in d-ATS during storge on clinical efficacy (SKAMP score). Simulations suggest that no more than 10.1% difference in SKAMP score (change from baseline) would be observed over the range of d-ATS dose levels from 16-20 mg. Overall, a loss of up to 20% d-amphetamine, due to degradation, in d-ATS during storage is not expected to impact clinical efficacy (Figure 9 and Figure 10) (Please refer to Section 6.3.2 of Clinical Pharmacology Review for more detail).

Listing of Analyses Codes and Output Files

| File Name | Description | Location |
|---|---|---|
| pk_analysis_d-ATS.R | PK and PopPK analysis file | M:\Review\NDA_215401_Xelstrym\ Reviewer\PopPK\Rscript |

## 15.5. Additional Clinical Outcome Assessment Analyses

Not applicable to this application

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/s/

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