NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	217645
Priority or Standard	Standard
Submit Date(s)	7/24/23
Received Date(s)	7/24/23
PDUFA Goal Date	5/24/24
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	5/24/24
Established/Proper Name	Clonidine hydrochloride extended-release oral suspension
(Proposed) Trade Name	Onyda XR
Pharmacologic Class	Alpha-2 adrenergic agonist
Code name	N/A
Applicant	Tris Pharma, Inc.
Dosage form	Extended-release suspension
Applicant proposed Dosing Regimen	Starting dosage: 0.1 mg once daily at bedtime Maximum recommended dosage: 0.4 mg once daily at bedtime
Applicant Proposed Indication(s)/Population(s)	For the treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	387121001 |Clonidine hydrochloride (substance)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to central nervous system (CNS) stimulant medications in pediatric patients 6 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	406506008 |Attention-deficit/hyperactivity disorder
Recommended Dosing Regimen	Starting dosage: 0.1 mg once daily at bedtime Maximum recommended dosage: 0.4 mg once daily at bedtime

Table of Contents

Table of Tables

Table of Figures

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Glossary

AC	advisory committee
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
AR	adverse reaction
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
DP	Division of Psychiatry
DPMH	Division of Pediatrics and Maternal Health
ECG	electrocardiogram
ER	extended release
FDA	Food and Drug Administration
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISS	integrated summary of safety
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
[redacted]	(b) (4)
OPQ	Office of Pharmaceutical Quality
OS	oral solution
OSE	Office of Surveillance and Epidemiology
OSIS	Office of Study Integrity and Surveillance
PI	prescribing information
PK	pharmacokinetics
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SGE	special government employee
SOC	system organ class
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Clonidine hydrochloride is a centrally acting alpha2-adrenergic receptor agonist. Tris Pharma, Inc. (the Applicant) is seeking approval of clonidine hydrochloride extended-release oral suspension (clonidine ER OS; proposed trade name: Onyda XR) for the treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to central nervous system (CNS) stimulant medications in pediatric patients 6 years of age and older. Clonidine ER OS contains 0.1 mg clonidine hydrochloride per mL and is supplied in 120 mL bottles with a child-resistant closure.

The proposed starting dosage of clonidine ER OS is 0.1 mg (1 mL) once daily at bedtime. The dose of clonidine ER OS is titrated in increments of 0.1 mg (1mL) per day at weekly intervals depending on clinical response up to the maximum recommended dosage of 0.4 mg (4 mL) once daily at bedtime. Clonidine ER OS formulation is intended to offer additional flexibility for the dose titration.

This 505(b)(2) application relies on FDA's previous findings of safety and effectiveness of clonidine for the treatment of ADHD in pediatric patients 6 years of age and older. The listed drug (LD) is clonidine ER tablets (Kapvay, NDA 022331). The clonidine ER tablet was approved on September 28, 2010, for the treatment of ADHD.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the treatment of ADHD in pediatric patients 6 years of age and older is provided by the Agency's previous findings of effectiveness for the LD and the establishment of a scientifically acceptable pharmacokinetic (PK) bridge between the LD and clonidine ER OS.

The pivotal relative bioavailability studies (2021-5094 and 2021-5095) after single- and multiple-dose administration demonstrated that scientific bridge between clonidine ER OS formulation and the LD is adequate (see Section 6); therefore, substantial evidence of effectiveness is established for product approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This NDA relies on the Agency's previous findings of safety and effectiveness for the listed drug (LD, Kapvay; NDA 022331) and the PK bridge that was established between the LD and clonidine ER OS. Therefore, the effectiveness of clonidine ER OS for treatment of attention-deficit/hyperactivity disorder (ADHD) is expected to be similar to the LD. No new safety issues were identified from the Applicant's pharmacokinetic studies. The benefit-risk profile of clonidine ER OS does not differ from the LD. This assessment supports the marketing approval of clonidine ER OS for the treatment of ADHD in pediatric patients 6 years of age and older. The approval of clonidine ER OS ODT allows additional flexibility of dose titration and offers additional options for treatment based on patients' needs and preferences.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ADHD is a chronic neurodevelopmental condition marked by a persistent pattern of inattention or hyperactivity/impulsivity or by a combination of symptoms from these two domains. • ADHD is the most common neurodevelopmental disorder of childhood. • ADHD has been associated with depression, suicidal behavior, substance abuse, and poor educational and occupational outcomes.	Effective treatment of ADHD reduces functional impairment in the short-term, and may result in long-term benefits, such as a reduced risk of substance abuse and reduced risk of injuries/accidents.
Current Treatment Options	• Stimulant and nonstimulant treatment options are available for ADHD. Kapvay, the LD, is an alpha-2 adrenergic agonist approved for the treatment of ADHD (as monotherapy and as adjunctive therapy to stimulant medications). Approved labeling for the LD recommends twice-daily dosing. Clonidine hydrochloride extended-release oral suspension is intended for once-daily dosing.	Pediatric patients with ADHD may benefit from additional nonstimulant therapy options. Nonstimulant medications are frequently used when patients are unable to tolerate adverse reactions associated with stimulants or when patients prefer a nonstimulant treatment. Once-daily dosing may be preferred by some patients and could improve adherence.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant submitted two pivotal relative bioavailability studies (single-dose Study 2021-5094 and multiple-dose Study 2021-5095) to establish a pharmacokinetic (PK) bridge between clonidine ER OS formulation and the LD. The effect of food on clonidine ER OS was also evaluated as part of the single-dose relative bioavailability study. In addition, the Applicant included a modeling and simulation report to establish that the PK difference (i.e., slightly lower Ctrough at steady-state for the proposed clonidine ER OS formulation compared to the LD) would not affect the efficacy in pediatric patients. • The Office of Clinical Pharmacology (OCP) review found that the exposures (peak plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC)) from equal total doses of clonidine ER OS were comparable to that of the LD (Kapvay tablets) after both single- and multiple-dose administration. However, Ctrough at steady-state (Ctrough,ss) was about 26% lower than that of the LD. This difference is not expected to be clinically meaningful. • A high-fat meal did not significantly affect the PK of clonidine after administration of clonidine ER OS under fed compared to fasting conditions.	Clonidine ER OS can rely on safety and effectiveness of the LD as described in approved labeling. However, patients stabilized on other immediate-release (IR) or ER clonidine formulations cannot be switched on a mg-per-mg basis to clonidine ER OS due to potential differences in the PK shape between the formulations and lower Ctrough at steady state for clonidine ER OS.
Risk and Risk Management	• The most common adverse reactions (incidence at least 5% and twice the rate of placebo) with the LD administered as monotherapy in ADHD include somnolence, fatigue, irritability, nightmare, insomnia, constipation, and dry mouth. The most common adverse reactions (incidence at least 5% and twice the rate of placebo) with the LD administered as adjunct therapy to psychostimulant in ADHD include somnolence, fatigue, decreased appetite, and dizziness. Other adverse	The safety of this product is expected to be similar to that of the LD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	events more common than placebo include aggression, affect lability, emotional disorder, insomnia, upper abdominal pain, and dizziness. Warnings and precautions include hypotension/bradycardia/syncope, somnolence/sedation, cardiac conduction abnormalities. Contraindications include a history of hypersensitivity reaction to clonidine (e.g., generalized rash, urticaria, angioedema).	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		N/A
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		N/A
	☐	Patient-focused drug development or other stakeholder meeting summary reports		N/A
	☐	Observational survey studies designed to capture patient experience data		N/A
	☐	Natural history studies		N/A
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		N/A
	☐	Other: (Please specify):		N/A
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		N/A
	☐	Patient-focused drug development or other stakeholder meeting summary reports		N/A
	☐	Observational survey studies designed to capture patient experience data		N/A
	☐	Other: (Please specify):		N/A
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

ADHD typically presents in childhood with symptoms of difficulty paying attention, hyperactivity, and/or impulsive behavior. According to a survey conducted from 2017 to 2022, the estimated U.S. ADHD prevalence was approximately 10% among pediatric patients 4 to 17 years of age, a similar prevalence to the 2015 to 2016 report from the National Center for Health Statistics (NCHS).[1] ADHD may persist into adulthood and has an estimated prevalence in adults of 3%.[2] Pediatric patients with ADHD often experience difficulty with school performance, difficulty interacting with peers, and engage in dangerous activities due to impulsivity. Adults with ADHD may experience impairment in their workplace, social relationships, and with completing tasks. Many individuals with ADHD obtain symptom reduction with appropriate medication treatment resulting in significant decreases in impairment in daily tasks and functioning.

2.2. Analysis of Current Treatment Options

There are numerous drugs approved for the treatment of ADHD that are classified as stimulants (e.g., methylphenidate, d-methylphenidate, amphetamine, dextroamphetamine, methamphetamine, lisdexamfetamine, dextroamphetamine) or non-stimulants (e.g., norepinephrine reuptake inhibitors, alpha agonists). Stimulant products are available as IR and ER formulations; a once-a-day administration of an ER tablet can offer ADHD symptom reduction for an entire day, whereas an IR tablet requires dosing at least twice daily. The once-daily dose administration often increases medication adherence and can alleviate the stress associated with pediatric patients requiring dosing during school hours (e.g., avoiding interruptions in their school day to have drug administration by the school nurse). This NDA proposes a once-daily administration of clonidine, which is expected to offer similar convenience advantages to other once-daily treatments.

Both guanfacine ER tablets (marketed under trade name Intuniv) and clonidine ER tablets (marketed under trade name Kapvay) are α2-adrenergic receptor agonists approved as monotherapy and as adjunctive therapy to stimulant medications for the treatment of ADHD. Clonidine stimulates α2-adrenergic receptors in the brain stem, reduces sympathetic outflow from the central nervous system, and decreases peripheral and renal vascular resistance, heart rate, and blood pressure. The most common adverse events (AEs) reported with clonidine ER

[1] Yanmei L, Xiaofang Y, Qishan L, Qian L, Guifeng X, Jinhua L, WenhanY. Prevalence and trends in diagnosed ADHD among US children and adolescents, 2017-2022. JAMA Network Open. 2023;6(10):e2336872. doi:10.1001/jamanetworkopen.2023.36872

[2] Getinet A, Tsegay L, Gizachew Y, Necho M, Yohannes K, Abraha M, Demelash S, Anbesaw T, Alati R., Prevalence of attention deficit hyperactivity disorder in adults: Umbrella review of evidence generated across the globe. Psychiatry Research. 2023;328:115449DOI of original article: https://doi.org/10.1016/j.psychres.2023.115449.

are somnolence, fatigue, irritability, insomnia, nightmare, constipation, dry mouth, decreased appetite, and dizziness. Warnings and Precautions in the clonidine ER label include hypotension/bradycardia/syncope, somnolence/sedation, and cardiac conduction abnormalities (e.g., may worsen sinus node dysfunction and atrioventricular (AV) block—especially in patients taking other sympatholytic drugs). The label for clonidine ER indicates that no studies evaluating abrupt discontinuation of clonidine have been conducted; however, there are instructions to gradually reduce the dose to minimize the risk of rebound hypertension, which has been observed with abrupt discontinuation of clonidine ER in adult patients.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Kapvay, the LD, was approved on September 28, 2010, for the treatment of ADHD as monotherapy or adjunctive therapy to stimulant medication. On December 6, 2023, the sponsor of Kapvay informed the Agency about their plan to discontinue Kapvay 0.1 mg ER tablets. The Sponsor of Kapvay indicated that this discontinuation is not related to product quality, safety, or efficacy.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 238004

November 20, 2015: The Division of Psychiatric Products (DP) sent a Written Response to the Applicant (under pre-IND 128004) to offer feedback regarding their drug development plan for the proposed ER formulation of clonidine. The Written Response addressed the Applicant's questions regarding their plan to conduct two bioavailability studies, NDA requirements for nonclinical studies, chemistry data, and timing of their initial Pediatric Study Plan (iPSP). The Applicant was informed that sponsors for a clonidine product for ADHD would be required to provide data in pediatric subjects ages 4 to <6 years old with ADHD to support labeling and that safety and efficacy studies in this younger population may be a post-marketing requirement.

March 17, 2023: The Applicant submitted their agreed iPSP for the treatment of ADHD as monotherapy or as adjunctive therapy to simulant medications.

April 14, 2023: DP issued an Agreed Initial Pediatric Study Plan (iPSP)-No Agreement letter to the Applicant. DP informed the Applicant that their plan to request a partial waiver in patients younger than 4 years of age due to impracticability of conducting studies and to establish an assessment to patients older than 6 years of age with ADHD by establishing a bridge to the LD was acceptable. However, the Applicant would be required to do clinical studies in pediatric subjects 4 to <6 years of age with ADHD. The required studies could be deferred until after NDA approval.

June 5, 2023: The Sponsor submitted a revised agreed iPSP.

June 30, 2023: DP issued an Agreed iPSP-Agreement to the Sponsor's June 5, 2023, submission of their agreed iPSP for the treatment ADHD as monotherapy or as adjunctive therapy to stimulant medications.

January 31, 2024: The Sponsor submitted two protocols (b) (4)

(b) (4)

February 5, 2024: DP sent correspondence regarding the pediatric protocols stating that, because the NDA was under review, these (b) (4) protocols would be on hold until the NDA review was completed and approved for safety and efficacy.

February 7, 2024: In response to the DP communication of February 5, 2024, the Applicant withdrew the protocols from January 31, 2024.

NDA 217645

July 24, 2023: The Applicant submitted their NDA for clonidine hydrochloride ER OS via the 505(b)(2) pathway with Kapvay as the LD. The Applicant included two bioavailability studies to support their application. The Applicant also made a request for the proprietary name of Onyda XR.

October 21, 2023: FDA sent the Sponsor a Proprietary Name Request Conditionally Acceptable letter stating that the proprietary name, Onyda XR, was conditionally acceptable.

November 27, 2023: A memorandum was sent to DP from the Office of Study Integrity and Surveillance (OSIS) stating that on-site inspections for this NDA were not needed. OSIS offered the rationale that two sites from this NDA had been inspected under previous NDA/ANDAs submitted by this Applicant and it was concluded that both sites had reliable data.

Other Pertinent Regulatory History

December 6, 2023: Concordia, the Sponsor of Kapvay (NDA 022331), the LD, issued a letter to FDA, proposing the discontinuation of Kapvay 0.1 mg ER tablets as per

21 CFR 314.150(c), noting that this product discontinuation is not related to product quality, safety, or efficacy. Kapvay 0.1 mg ER tablets was the only marketed formulation of Kapvay. The Sponsor of Kapvay confirmed that they were requesting withdrawal of Kapvay's application in addition to discontinuing the product.

FDA's Office of Regulatory Policy (ORP) was asked to consider if there were implications for the Applicant's 505(b)(2) NDA if the LD requested to be withdrawn from the market during the review period. ORP concluded that if approval of Kapvay is withdrawn under 314.150(c), the 505(b)(2) applicant may continue to rely on Kapvay, even after the notice of withdrawal of Kapvay's approval is announced in the Federal Register. However, if approval of Kapvay is withdrawn/announced prior to approval of the 505(b)(2) application (NDA 217645), ORP suggests that it be documented in one of the clinical reviews for NDA 217645 that approval of Kapvay, the LD relied upon, was not withdrawn for reasons of safety and/or effectiveness.

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

4.1. Office of Study Integrity and Surveillance (OSIS)

OSIS was consulted for an inspection of the clinical site, Pharma Medica, Toronto (Ontario, Canada) and bioanalytical site, (b) (4) However, OSIS determined that an inspection of the clinical and bioanalytical sites was not needed due to the recent inspection of the same clinical and bioanalytical sites for Non-responsive and Non-responsive, respectively.

During the inspection of the clinical site in December 2022, the following items were discussed with the site:

- Lack of a standardized time period for conducting adverse event follow up
- Confusion about eligibility criteria for subjects with blood loss or donation ≥500 mL within 56 days prior to study drug administration (Specifically, one subject was identified as being ineligible for the study due to a record noting blood loss of >500 mL, but the calculation was later determined to be incorrect.)

After review of the inspection findings, OSIS determined that data from the reviewed study were reliable with the exception of data for one subject. OSIS recommended that the review division consider the eligibility of the subject due to OSIS's inability to verify the subject's eligibility. The review division found the results were acceptable.

The remote regulatory assessment of the bioanalytical site in (b) (4) found the following objectionable condition:

(b) (4)

After review of the objectionable condition and the site's response, OSIS concluded that the data were reliable.

4.2. Product Quality

The Office of Product Quality (OPQ) recommends approval for this application based on drug substance, drug product, process/facilities, biopharmaceutics, and microbiology reviews.

Drug Substance: Clonidine hydrochloride drug substance is a white to almost-white crystalline powder which is soluble in water, ethanol, and slightly soluble in chloroform with a melting point of 312 °C. The characterization of physicochemical properties, manufacturing, and control of critical and intermediate steps of drug substance and its specifications are adequate. Clonidine hydrochloride drug substance was stable when stored at long-term (b) (4)

[redacted] months and accelerated conditions [redacted] months. The drug master file (DMF) holder [redacted] currently has a retest period of [redacted] months for the drug substance while stored at [redacted]. The DMF Holder has shown that no [redacted] impurities are present in the active pharmaceutical ingredient (API), clonidine hydrochloride.

Drug Product: Clonidine hydrochloride is manufactured in strength of 0.1 mg per mL, which is equivalent to 0.09 mg of clonidine base per mL. The finished product contains a combination of the immediate-release uncoated clonidine [redacted] and extended-release coated clonidine [redacted] components. It is light beige to tan viscous suspension packaged into [redacted] white high-density polyethylene (HDPE) and [redacted] bottle. All excipients except [redacted], are of compendial grade (USP/NF). The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substance. For each packaging configuration, the Applicant has provided 18 months of long-term stability data (25 ± 2°C/60% ± 5% RH) for three batches, along with corresponding 6 months of accelerated stability data (40 ± 2°C and 75 ± 5% RH), and weight loss study results performed under lower humidity conditions. The Applicant has also provided adequate information for [redacted] risk in the proposed drug product. Additionally, the Applicant has provided adequate freeze-thaw study data to support temperature excursion. In-use stability data are provided to support the storage of the product [redacted]. All the stability data met the proposed specifications. The overall stability data provided by the Applicant, support the proposed shelf-life (without frequent opening and closing of the bottle) of 24 months. The Applicant has provided adequate data/justification for not including, leachable, [redacted] and elemental impurity testing in the proposed drug product specification.

Manufacturing: Both drug substance and drug product manufacturing facilities and associated testing facilities listed in this NDA are currently acceptable based on the firm's previous inspection history and current good manufacturing practices (cGMP) compliant status. The proposed commercial batch size is the same as that of registration batches, except that the scale-up factor for [redacted] pack size and [redacted] pack size, respectively. [redacted] The process parameters proposed for commercial manufacturing are supported by the process development and process scale up to the registration batch scale. Appropriate in-process controls are proposed.

Biopharmaceutics: The selection of 0.6M KH_2PO_4 dissolution media, 900 mL volume, and 50 rpm paddle speed for the dissolution method is acceptable. The proposed dissolution method is considered discriminating against [redacted] as indicated by dissimilar dissolution profiles (similarity factor f2 <50). Based on the provided dissolution profile of the pivotal bio-batch, the registration batches, and the stability batches, the dissolution acceptance criteria (0.5 hr no more than (NMT) [redacted]%, 4 hr [redacted]%, and 18 hr no less than (NLT) [redacted]% are considered permitted. Based on the in vitro dissolution profiles and multiple dose relative bioavailability

study to establish the pharmacokinetic bridge between clonidine ER OS and the LD, the ER claim can be granted. Based on the in vitro alcohol induced dose dumping study, 20% alcohol but not 5% and 10% alcohol showed faster drug release compared to 0% alcohol. The Applicant's proposed recommendation regarding do not drink alcohol with clonidine ER OS is acceptable.

Microbiology: The submission batches met the microbial limits acceptance criteria. Antimicrobial effectiveness testing (AET) and Burkholderia cepacian Complex (BCC) testing met the acceptance criteria. The stability data is adequate.

See the integrated quality assessment review from OPQ for additional information.

4.3. Clinical Microbiology

No clinical microbiology-related information was submitted with this NDA.

4.4. Devices and Companion Diagnostic Issues

Not relevant to this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No nonclinical studies were conducted or submitted with this application. The Applicant is relying on the Agency's previous findings of safety and efficacy for the LD to support this application.

During the review, the CMC review team identified the potential presence of (b) (4), in the drug substance and drug product and requested pharmacology/toxicology evaluation to establish an acceptable intake (AI) limit for (b) (4).

Because (b) (4) belongs to the (b) (4) category, it is considered out-of-scope of the (b) (4) and requires the use of alternative methods for establishing an AI limit. The FDA/CDER Computational Toxicology Consulting Services (CTCS)/Division of Applied Regulatory Science (DARS) conducted (Q)SAR analysis and read-across to identify a surrogate molecule for (b) (4). Based on the (Q)SAR analysis, it is concluded that (b) (4) is the appropriate surrogate for (b) (4) with an AI limit of (b) (4) ng/day.

For the drug substance, the Applicant cross-referenced DMF (b) (4), which proposed an AI limit of (b) (4) ng/day for (b) (4). In addition, analytical testing from three batches showed that the level of (b) (4) was below the level of detection (LoD, (b) (4) ppm). For the drug product, based on the Applicant's testing results from three (b) (4) manufacture lots, (b) (4) was below the LoD of (b) (4) ppm.[4] Therefore, from a nonclinical safety perspective, the level of (b) (4) in both the drug substance and drug product is within the AI limit. For more information regarding the analytical evaluation of (b) (4), see the CMC review.

There are no other excipients, impurities, or degradation products that are of safety concern or need additional nonclinical safety evaluation. Based on the available information, there are no safety concerns for the proposed drug product and this NDA is approvable from a Pharmacology and Toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA 022331, DMF (b) (4)

(b) (4)

[4] Based on the maximum daily dose of 0.4 mg, at the LoD of (b) (4) ppm, the amount is equal to (b) (4) ng.

6 Clinical Pharmacology

6.1. Executive Summary

The LD was approved for the treatment of ADHD as monotherapy or as adjunctive therapy to stimulant medications in pediatric patients 6 to 17 years of age under NDA 022331. The Applicant is seeking approval of clonidine ER OS via the 505(b)(2) route for the same indication as the LD. The Applicant stated that this ER OS formulation of clonidine is intended to offer additional flexibility for the dose titration. Clonidine ER OS will be administered once-daily while the LD is given twice-daily. This application relies on the Agency's previous findings of safety and effectiveness of the LD.

The clinical pharmacology program in this current submission consists of a pilot relative bioavailability (BA) study to select the optimal formulation (this study was not reviewed) and two pivotal relative BA studies (2021-5094 and 2021-5095) after single- and multiple-dose administration to establish an acceptable PK bridge between clonidine ER OS formulation and the LD. The effect of food on clonidine ER OS was also evaluated as part of the single-dose relative BA study. In addition, the Applicant included a modeling and simulation report to support the PK difference (i.e., slightly lower Ctrough at steady-state for the proposed clonidine ER OS formulation compared to the LD) would not affect the efficacy in pediatric patients.

OCP reviewed the pivotal relative bioavailability studies and the modeling and simulation report submitted in this application and finds that the exposures (peak plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC)) from equal total doses of clonidine ER OS were comparable to that of the LD after both single- and multiple-dose administration. However, Ctrough at steady-state (Ctrough,ss) was approximately 26% lower than that of the LD. This difference is not expected to be clinically meaningful in treatment naïve patients who are initially being treated with Clonidine ER OS. Therefore, the proposed product, clonidine ER OS can rely on safety and effectiveness of the LD. Patients stabilized on other IR or ER clonidine formulations cannot be switched on a mg-per-mg basis to clonidine ER OS due to potential differences in the PK shape between the formulations and lower Ctrough,ss at steady state. A high-fat meal did not significantly affect the PK of clonidine after administration of clonidine ER OS under fed conditions compared to fasting conditions.

Per recommendation from OSIS, the clinical and bioanalytical sites for the pivotal relative BA studies (2021-5094 and 2021-5095) are acceptable. OCP recommends the approval of clonidine ER OS for the treatment of ADHD.

6.2. Summary of Clinical Pharmacology Assessment

In a single-dose relative BA study in healthy subjects under fasting conditions, the PK of clonidine was compared between clonidine ER OS and the LD. The effect of food on clonidine ER OS was also evaluated. In this open-label, randomized, three-period, three-treatment,

crossover study, 0.2 mg of clonidine ER OS was administered after a high-fat meal under fasting conditions and the LD was given in divided doses (0.1 mg at 0 and 12 hours) under fasting conditions. The three periods were separated by a washout period of at least 7 days. The results indicated that Cmax and AUCinf were comparable to those of the LD. The 90% confidence intervals (CIs) for the geometric mean ratio of Cmax and AUCinf were contained within the acceptable range (80% to 125%) to conclude that the products are comparable.

Compared to fasted conditions, a high-fat meal did not significantly affect the exposures of clonidine. The median time to reach Cmax (Tmax) was slightly reduced from 7.5 hours to 7 hours. Because clonidine ER OS is intended for chronic administration, a shorter reduction in Tmax was deemed clinically not meaningful. Therefore, clonidine ER OS can be given with or without food.

In a multiple-dose (steady state) relative BA study in healthy subjects, the PK at steady state was compared between clonidine ER OS and the LD. In this open-label, multiple-dose, randomized, two-period, two-treatment, crossover study, subjects were administered clonidine ER OS or the LD under fasting conditions according to the randomization schedule. Clonidine ER OS 0.2 mg was administered once daily for 5 days, or 0.2 mg of LD was administered (given as 0.1 mg twice daily) for 5 days. The washout period between the drug administration from the first dose of period 1 to the first dose of period 2 was at least 14 days. The results indicated that Cmax and AUC at steady state were comparable. The 90% CI of the geometric mean ratios of plasma clonidine for AUCt,ss and Cmax,ss for Clonidine ER OS and LD were within 80% to 125%. However, the 90% CI of C24h,ss (Ctrough, ss) of clonidine ER OS was not within 80% to 125% of the LD. The geometric mean Ctrough, ss after drug administration at steady state for clonidine ER OS was 26% (90% CI: 21-31%) lower than that of the LD. Given that clonidine ER OS is administered as a titration-based regimen, the efficacy of the LD was similar between 0.2 mg/day and 0.4 mg/day dosing regimens following 5 weeks of treatment and 0.1 mg/day regimen showed significant efficacy following 1 week of treatment, the slightly lower C24hr, ss with clonidine ER OS is considered to be clinically not meaningful for the treatment naïve patients. The difference in shape of the plasma concentration time profile between Clonidine ER OS and the LD is also not expected to clinically meaningful in treatment naïve patients.

Because the PK profiles of other IR or ER formulations of clonidine could be different from that of clonidine ER OS formulation and efficacy is expected to be lower in patients who switch from other clonidine ER products to clonidine ER OS, it is not recommended to substitute with clonidine ER OS on a mg-per-mg basis in patients who are stabilized with other clonidine formulations.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The pharmacology and clinical PK information are based on the approved label for the LD.

Absorption

Following a single 0.2-mg dose of Onyda XR in 20 healthy adult subjects under fasting conditions in a crossover study, the median (range) time to peak plasma concentrations (Tmax) for clonidine was 7.50 (4 to 17) hours after dosing. Peak concentration (Cmax) was 95.6% of the Cmax of Clonidine ER tablet 0.1 mg administered at 0 and 12 hours under fasting conditions. The relative BA of ONYDA XR compared with an equal dose of Clonidine ER tablet was 96.1%. After oral administration of 0.2 mg of Onyda XR once-daily over 5 days under fasted conditions in healthy adult subjects, the peak steady state plasma concentration (Cmax.ss) was 107.9%, and steady state relative BA (AUCt, ss) was 97.7% compared with 0.1 mg of clonidine extended-release tablet administered twice-daily under fasting conditions. The minimum concentration at steady state (Cmin,ss) of ONYDA XR was about 26% lower than that of the equal dose of clonidine extended-release tablet.

Following oral administration of an IR formulation, plasma clonidine concentration peaks in approximately 3 to 5 hours.

A comparison across studies suggests that the Cmax is 50% lower for ER clonidine hydrochloride compared to IR clonidine hydrochloride.

Food Effect

High-fat meal (900 Kcal) did not affect the PK of clonidine ER OS.

Distribution

The volume of distribution (V/F) is approximately 330 L/h.

Elimination

Metabolism

About 50% of the absorbed dose of clonidine is metabolized in the liver.

Excretion

Following oral administration, approximately 40 to 60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. The mean (± SD) plasma half-life of clonidine ER OS after single-dose administration under fasting conditions was about 13.54 (± 3.40) hours. Although studies of the effect of renal impairment and studies of clonidine excretion have not been performed with clonidine ER OS, results are expected to be similar to those of the IR formulation.

6.2.2. General Dosing and Therapeutic Individualization

Because the exposures (Cmax and AUC) of clonidine after administration of clonidine ER OS compared to the LD tablets are contained within the 80 to 125% bioequivalence limits of the LD under fasted conditions, the information relevant to dosing and therapeutic individualization of clonidine ER OS can rely on the LD. However, patients cannot switch on a mg-per-mg basis

from other clonidine ER products to clonidine ER OS due to potential differences in the PK profiles between the formulations.

6.2.3. Clinical Pharmacology Questions

Are the exposures to clonidine after clonidine ER OS 0.2 mg similar to the LD, Kapvay 0.2 mg, after single-dose administration?

Yes, the exposures to clonidine after clonidine ER OS are similar to the LD after single-dose administration.

An open-label, single-dose, randomized, three-period, three-treatment, three-sequence, crossover, relative bioavailability study in adult healthy subjects was conducted under fasting and fed conditions to compare the exposures after administration of clonidine ER OS and the LD. The three treatments used in the study were:

- Treatment A (Test product): 0.2 mg (2 mL of clonidine ER OS, 0.1 mg/mL) administered 30 minutes after the start of a high fat meal (about 900 Kcal). Subjects fasted for at least 10 hours prior to and 4 hours after drug administration.

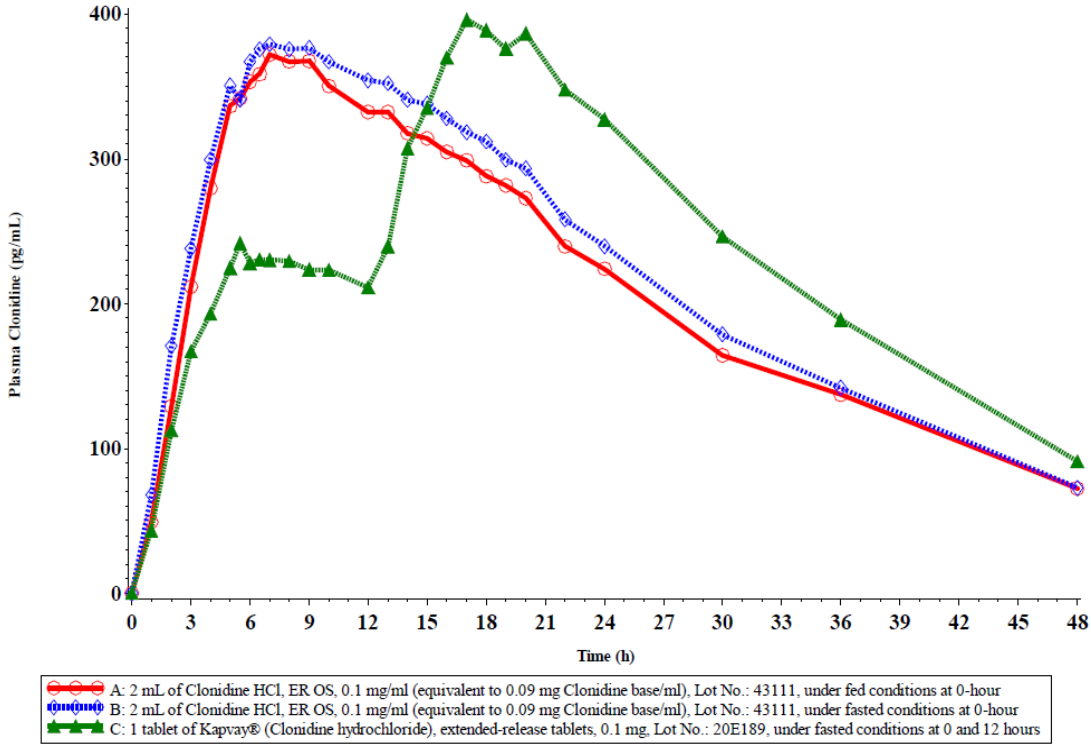
- Treatment B (Test product): 0.2 mg (2 mL of clonidine ER OS 0.1 mg/mL) administered under fasted conditions. Subjects fasted for at least 10 hours prior to and until 4 hours after drug administration.

- Reference product (Treatment C, LD) 0.1 mg (1 ER tablet of LD) administered once at 0 and 12 hours under fasted conditions. Subjects fasted for at least 10 hours prior to and until 4 hours after drug administration. Subjects fasted for at least 2 hours prior to and 2 hours after the 12-hour administration.

The three study periods were separated by a washout period of 7 days.

The results are shown in Figure 1 and Table 1.

Figure 1. Mean Plasma Clonidine Concentration-Time Profile following a Single Oral 0.2 mg Clonidine ER OS (Treatment A—Fed (red line) and Treatment B—Fasting (blue line)) and 0.1 mg Kapvay ER Tablet (Treatment C) Administered at 0 hour and 12 hours under Fasting Conditions (green line)



Source: Study 2021-5094 p. 41

Table 1. Summary Statistics of Clonidine Pharmacokinetic Parameters for Treatment B versus Treatment C

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**B**	20	10556.3 (27)	10198.9	**B vs C**	97.17	91.61 - 103.07	11
*(hr*pg/mL)*	**C**	20	10876.5 (28)	10495.8				
AUC_{inf}	**B**	20	12107.2 (31)	11597.0	**B vs C**	96.13	89.38 - 103.39	13
*(hr*pg/mL)*	**C**	20	12624.2 (32)	12064.0				
C_{max}	**B**	20	404.2 (22)	394.8	**B vs C**	95.62	89.81 - 101.80	11
(pg/mL)	**C**	20	424.5 (23)	412.9				

Treatment B (Test)	2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fasted conditions at 0-hour
Treatment C (Reference)	1 tablet of Kapvay® (Clonidine hydrochloride), extended-release tablets, 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet), Lot No.: 20E189 (Concordia Pharmaceuticals, USA), under fasted conditions at 0 and 12 hours

Source: Study 2021-5094 p. 39

The PK parameters (Cmax and AUCinf) are comparable after administration of clonidine ER OS and the LD. The 90% CI for the geometric mean ratio of Cmax and AUC are contained within the

acceptable regulatory interval of 80 to 125%. The results suggest that clonidine ER OS can rely on the Agency's previous findings of safety and efficacy of the LD.

What is the effect of food on the exposures of clonidine ER OS? Does this product require specific dosing instruction regarding food?

There is no clinically meaningful difference in exposures when clonidine ER OS is administered under fed or fasting conditions. Clonidine ER OS can be administered with or without food.

Table 2. Summary of Clonidine Pharmacokinetic Parameters for Treatment A vs Treatment B

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	19	9956.4 (26)	9716.8	**A vs B**	95.27	91.08 - 99.66	8
*(hr*pg/mL)*	**B**	20	10556.3 (27)	10198.9				
AUC_{inf}	**A**	19	11639.0 (29)	11236.5	**A vs B**	96.89	91.80 - 102.26	9
*(hr*pg/mL)*	**B**	20	12107.2 (31)	11597.0				
C_{max}	**A**	19	392.7 (24)	382.4	**A vs B**	96.87	93.26 - 100.61	7
(pg/mL)	**B**	20	404.2 (22)	394.8				

Treatment A (Test): 2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fed conditions at 0-hour

Treatment B (Test): 2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fasted conditions at 0-hour

Source: Study 2021-5094 p. 39

The exposures (Cmax and AUCinf) are comparable when clonidine ER OS is administered under both fed and fasting conditions (Table 2). The 90% CI for the geometric mean ratio of Cmax and AUC are contained within 80 to 125%, the acceptable regulatory limit indicating that Cmax and AUC are comparable. Tmax is reduced from 7.5 hours to 7 hours when administered under fed conditions compared to fasting conditions. Given that clonidine ER OS is intended for chronic administration, slightly lower Tmax is not expected to be clinically meaningful.

Are the exposures to clonidine after clonidine ER OS 0.2 mg daily similar to the LD, Kapvay 0.1 mg, twice-daily after multiple dose administration?

Yes, the exposures (Cmax and AUC) after multiple-dose administration of 0.2 mg clonidine ER OS once-daily and Kapvay (LD) 0.1 mg twice-daily are comparable. However, the geometric mean Ctrough, ss was approximately 26% lower as compared to the LD. In a randomized, double-blind, placebo-controlled phase 3 efficacy and safety study in pediatric patients with ADHD 6 to 17 years of age (CLON-301), the LD showed similar efficacy at 0.2 mg/day and 0.4 mg/day dosing regimens following 5 weeks treatment and lower (but statistically significant) efficacy was observed at 0.1 mg/day at Week 1. As the efficacy of 0.1 mg/day regimen at Week 5 was not studied, the efficacy of 0.1 mg/day at Week 5 is not known. Given that clonidine ER OS is administered as a titration based regimen, the efficacy of the LD was similar between 0.2 mg/day and 0.4 mg/day dosing regimens and 0.1 mg/day regimen showed significant efficacy at

Week 1, slightly lower Ctrough,ss with clonidine ER OS is deemed to be clinically not meaningful for treatment naïve patients.

An open-label, multiple-dose, randomized, two-period, two-treatment, two-sequence, crossover, relative bioavailability study was conducted in healthy subjects. In each period, subjects either self-administered the test product or were administered the reference product, in accordance with the randomization scheme. The treatments were as follows:

- Treatment A (Test): Clonidine HCl, ER OS, 0.1 mg/ml. Dose: 0.2 mg daily for 5 days (2 mL of 0.1 mg/mL self-administered at 0, 24, 48, 72, and 96 hours). Subjects fasted for at least 10 hours prior to, and at least 4 hours after, the 96-hour drug administration.

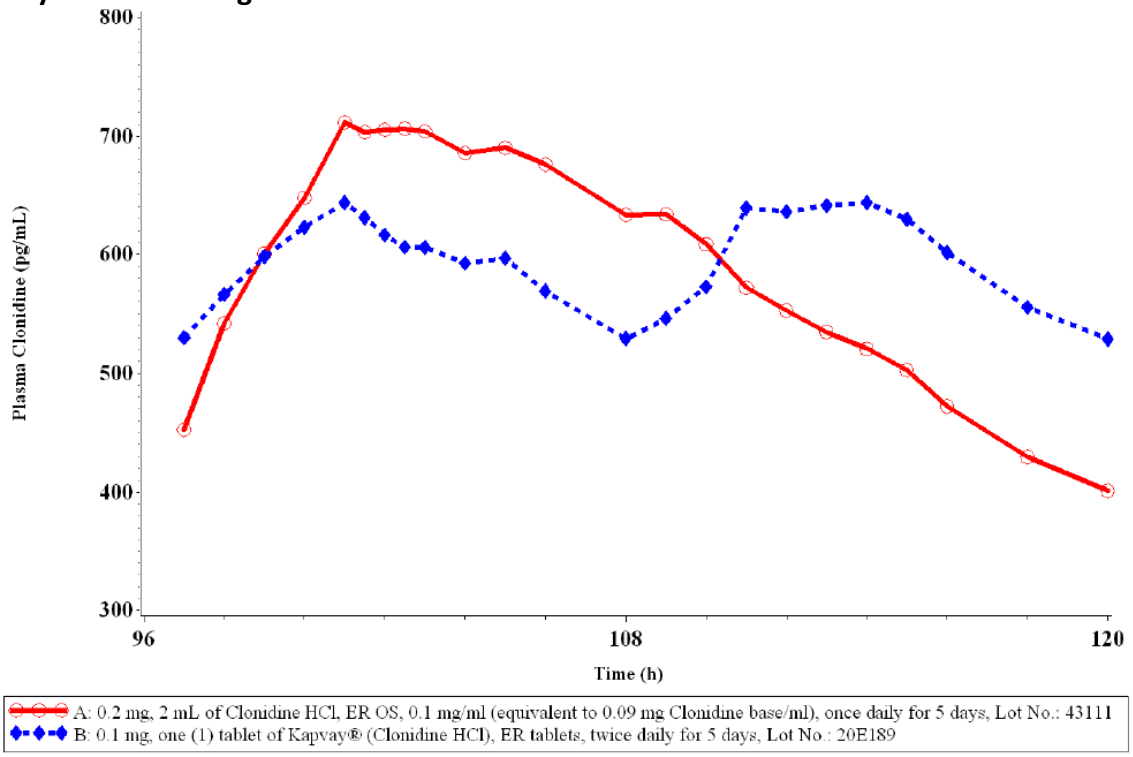
- Treatment B (Reference, LD): Kapvay (Clonidine hydrochloride), ER Tablets, 0.1 mg. Dose: 0.2 mg daily for 5 days (0.1 mg administered at 0, 12, 24, 36, 48, 60,72, 84, 96 and 108 hours).

Subjects fasted for at least 10 hours prior to and at least 4 hours after the 96-hour drug administration. Subjects fasted for at least 2 hours prior to and at least 2 hours after the 108-hour drug administration.

The washout period between the drug administration from the first dose of period 1 to the first dose of period 2 was at least 14 days.

The results are shown in Figure 2 and Table 3.

Figure 2. Mean Plasma Clonidine Concentrations Time Profile at Steady State following Once-daily Administration of 0.2 mg Clonidine ER OS (Treatment A—Red Solid Line) for 5 Days and Twice-daily Administration of 0.1 mg Kapvay ER Tablet (Treatment B—Blue Dashed Line) for 5 Days under Fasting Conditions



Source: Study 2021-5095 p. 42

Table 3. Summary Statistics of Clonidine Pharmacokinetic Parameters for Treatment A versus Treatment B

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
$AUC_{t,ss}$	**A**	19	13791.0 (26)	13353.1	**A vs B**	97.68	93.41 - 102.14	8
*(hr*pg/mL)*	**B**	19	14120.9 (26)	13670.6				
$C_{max,ss}$	**A**	19	740.2 (25)	719.7	**A vs B**	107.90	103.80 - 112.17	7
(pg/mL)	**B**	19	682.7 (23)	667.0				
$C_{24,ss}$	**A**	19	401.1 (35)	378.2	**A vs B**	74.01	69.33 - 79.00	12
(pg/mL)	**B**	19	528.9 (27)	511.0				

CV, Coefficient of Variation; n, number of subjects in statistical dataset; Sbj, Subject; Trt, Treatment.

Treatment A (Test): 0.2 mg (2 mL of Clonidine hydrochloride (HCl), extended release (ER) oral suspension (OS), 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111, (Tris Pharma, Inc., USA) under fasted conditions at 0, 24, 48, 72, and 96 hours

Treatment B (Reference): One (1) tablet of Kapvay® (Clonidine hydrochloride), extended-release tablets, 0.1 mg,(equivalent to 0.087 mg of the free base in 0.1 mg tablet) Lot No.: 20E189, (Concordia Pharmaceuticals, USA) under fasted conditions at 0, 12, 24, 36, 48, 60, 72, 84, 96, and 108 hours

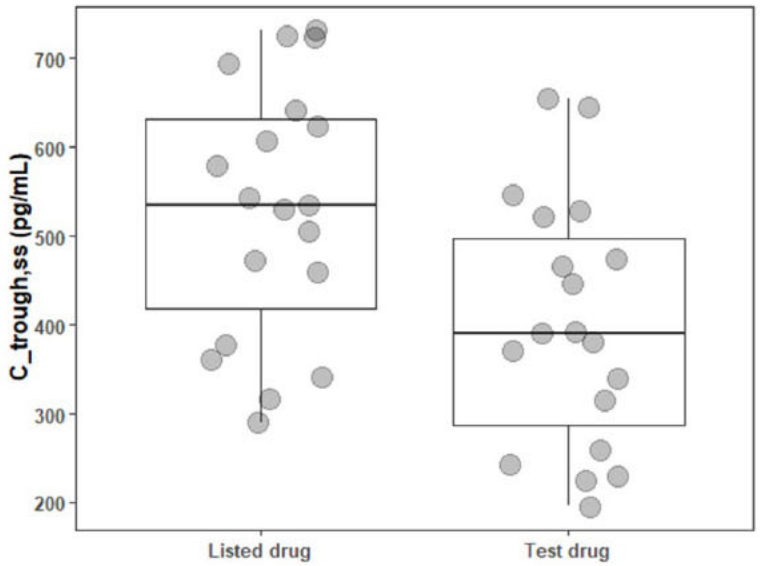
Source: Study 2021-5095 p. 41

Is the proposed (b) (4) acceptable?

No, it is not acceptable.

The Applicant proposed that (b) (4) The results from Study 2021-5905 showed that the clonidine ER OS has 26% (95% CI: 21 to 31%) lower Ctrough at steady state compared to the LD. (b) (4), we recommend that subjects do not substitute other clonidine ER formulations with clonidine ER OS. The following figure compares the trough concentrations for clonidine ER OS and the LD.

Figure 3. Boxplot Comparison of Observed Ctrough,ss from the Test Drug (Clonidine ER OS 0.2 mg Once-daily) and the Listed Drug (Kapvay 0.1 mg Twice-daily) Using Data from Study 2021-5905

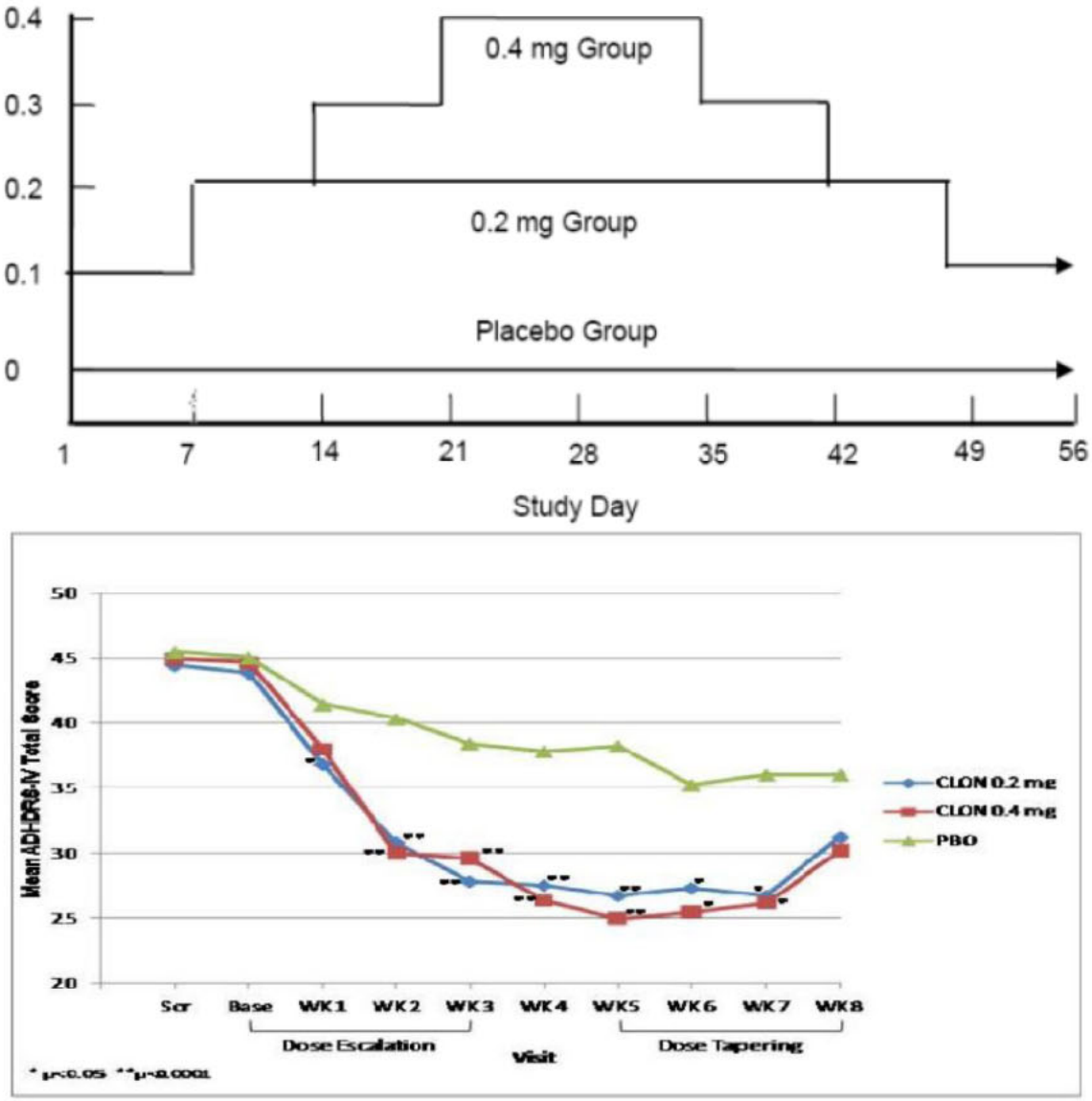


Source: FDA Pharmacometric analysis

(b) (4).

Briefly, CLON-301 was a phase 3, 5-week, parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of two dosing regimens (0.2 mg/day and 0.4 mg/day, given as oral tablets) in pediatric subjects 6 to 17 years of age who met DSM-IV criteria for ADHD. Dosing for the treatment group started at 0.1 mg/day and increased every week by 0.1 mg/day until the target dose of 0.2 mg/day or 0.4 mg/day. Subjects were maintained at their dose level for a minimum period of 2 weeks before being gradually tapered to 0.1 mg/day for the last week of treatment. The study design and efficacy findings are presented in Figure 4.

Figure 4. Study Design of CLON-301 (Top); and Mean of the ADHDRS-IV Score by Treatment and Visit (Bottom)

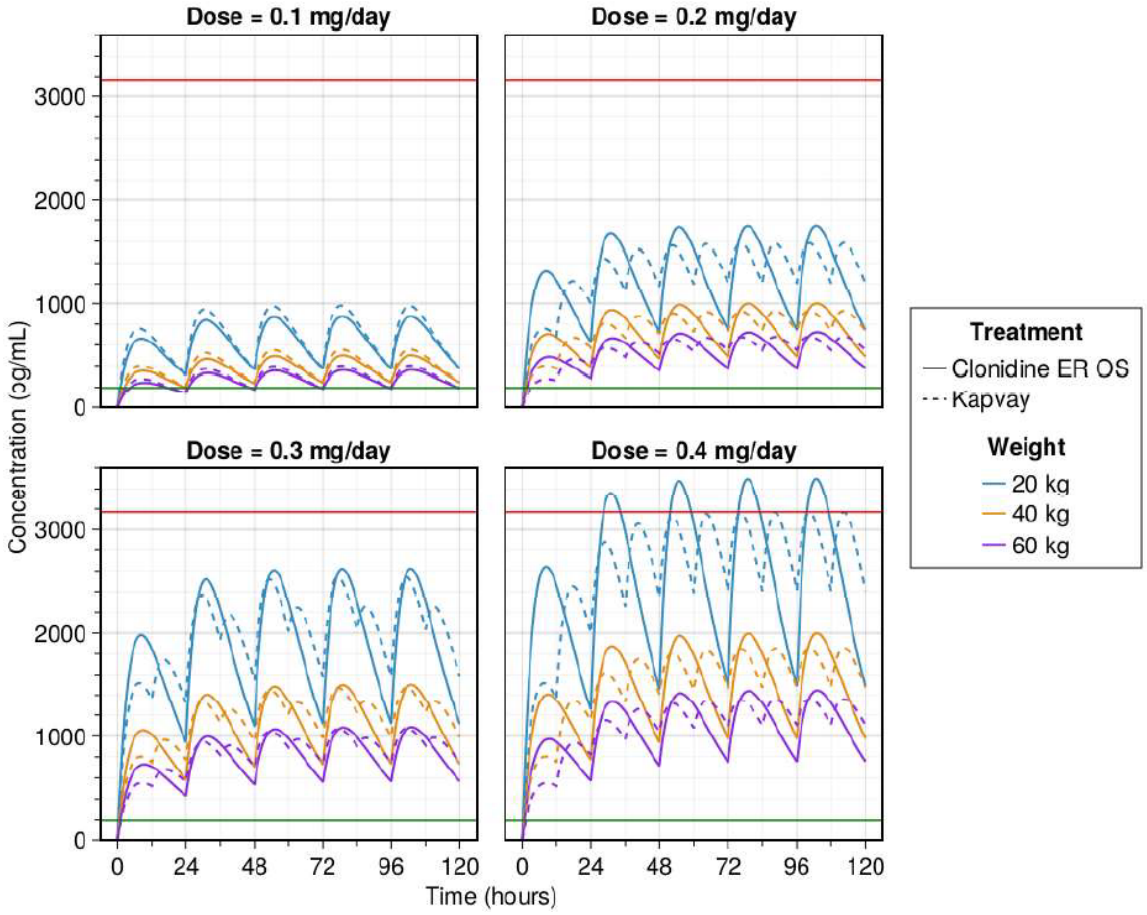


Source: Clinical Overview, p. 24, Figure 7

There was a statistically significant ($p<0.05$) difference between the treatment and placebo achieved as early as Week 1 at the 0.1 mg dose. For this reason, the Applicant considers steady-state plasma concentrations derived from dose 0.1 mg as an efficacy threshold for their PK simulations. Although the Applicant asserts that 0.1 mg is efficacious dose due to statistically significant ($p<0.05$) difference from placebo at Week 1, the efficacy data until Week 5 for 0.1 mg/day is not available, and thus it is unclear if the 0.1 mg/day dosing regimen is clinically significantly different from placebo at Week 5. Therefore, there is insufficient evidence to consider the dose of 0.1 mg/day as an efficacious dose.

Focusing on the Applicant's PK simulations, weight-based PK modeling was performed using data from single-dose study (2021-5094) and multi-dose study (2021-5095) in adults. The developed PK model was then used to simulate typical PK profiles of pediatric subjects between 6 to <18 years of age. Figure 5 shows the PK profile of clonidine for typical subjects with weights of 20 kg, 40 kg, or 60 kg, corresponding to the median weight of pediatric patients 6 years, 12 years, and 17 years old, respectively. At steady state, all PK profiles of the clonidine ER OS have Ctrough concentrations between 189 pg/mL to 1490 pg/mL, which are similar or higher than those of the applicant proposed efficacy threshold of 195 pg/mL (Table 4). (b) (4)

Figure 5. Simulated Clonidine ER OS PK Profiles in Pediatric Patients



Green horizontal line: minimum typical Ctrough,ss value with 0.1 mg/day KAPVAY dosing (efficacy threshold); Red horizontal line: maximum typical Cmax,ss value with 0.4 mg/day KAPVAY dosing (safety threshold).
Source: PK modeling report, p. 22, Figure 3

Table 4. Comparison of Simulated Ctrough,ss For the Test Drug (Onyda XR) and the Listed Drug (Kapvay) in Subjects with Varying Bodyweights

	Test drug: Onyda XR			Listed Drug: Kapvay			Difference		
Dose	20 kg	40 kg	60 kg	20 kg	40 kg	60 kg	20 kg	40 kg	60 kg
0.1 mg/day	372	244	189	377	250	195	1%	2%	3%
0.2 mg/day	744	488	378	1200	737	552	38%	34%	32%
0.3 mg/day	1120	732	567	1580	988	747	29%	26%	24%
0.4 mg/day	1490	975	756	2410	1470	1100	38%	34%	31%

Source: PK modeling report, p. 26, Adapted from Table 10

For treatment-naïve subjects, the proposed label recommends a starting dose of 0.1 mg/day and to allow titration of the dose according to the therapeutic needs and response of the patient until the maximum target dose of 0.4 mg/day. Findings from Study CLON-301 showed similar efficacy between 0.2 mg/day and 0.4 mg/day dosing regimens. Therefore, 26% reduced Ctrough,ss observed in the clonidine ER OS is not anticipated to impact the efficacy in the treatment-naïve subjects.

(b) (4), the proposed label (b) (4) the PK simulations have shown that the clonidine ER OS can decrease Ctrough,ss up to 38% reduction when compared to the LD. As per efficacy results of the LD from CLON-301, during the dose-tapering phase, the efficacy was reduced when the dose was reduced from 0.2 mg/day to 0.1 mg/day on Week 8 (placebo corrected change from baseline in ADHRS-IV total score from Week 7 to Week 8: -6.5 to -2.8 for 0.2 mg/day group and -7.9 to -4.6 for 0.4 mg/day group). Given the PK profiles of other clonidine ER products could be different from clonidine ER OS formulation and efficacy is expected to be lower in patients who switch from other clonidine ER products to clonidine ER OS, it is not recommended to substitute other clonidine ER products with clonidine ER OS formulation on a mg-per-mg basis.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Sources of clinical data included the pivotal bioavailability studies 2021-5094 and 2021-5095. See Table 5 for a description of each study.

Table 5. Listing of Clinical Trials Relevant to this NDA217645

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. patients enrolled	Study Population	No. Centers and Countries
2021-5094	Single-center, open-label, single dose, randomized, three periods, three-treatment, three sequence, crossover	Test: Clonidine Hydrochloride (HCl) Extended-Release (ER) Oral Suspension (OS) 0.1 mg/mL (equivalent to 0.09 mg Clonidine base per mL); a single dose of 2 mL (0.2 mg) (0.1 mg/ ml) under both fed and fasting conditions Reference: 0.1 mg (one extended -release tablet of Kapvay (clonidine hydrochloride)) administered at 0- and 12-hours under fasted conditions (total dose = 0.2 mg (two extended-release tablets)).	Pharmacokinetic (PK) Parameters Cmax AUCt AUCinf	Single Dose	23 (19 completed)	Healthy Subjects	One Canada
2021-5095	Open-label, multiple-dose, randomized, two periods, twp-treatment, two-sequence, crossover	Test Product: 0.2 mg (2 mL clonidine hydrochloride extended -release oral suspension, 0.1 mg/mL) self-administered at 0, 24, 48, 72, and 96 hours. Subjects fasted for at least 10 hours prior to, and at least 4 hours after, the 96-hour drug administration.	PK Parameters Cmax,ss AUCt,ss Cmin,ss	5 days	20 (19 completed)	Healthy Subjects	One Canada

		Reference Product: 0.1 mg (one ER tablet of Kapvay (clonidine hydrochloride), 0.1 mg) administered at 0, 12, 24, 36, 48, 60, 72, 84, 96, and 108 hours Subjects fasted for at least 10 hours prior to and at least 4 hours after the 96-hour drug administration. Subjects fasted for at least 2 hours prior to, and at least 2 hours after, the 108-hour drug administration.					

Source: Clinical Reviewer generated

7.2. Review Strategy

Because this NDA was submitted under the 505(b)(2) pathway, much of the understanding of the safety and effectiveness of clonidine hydrochloride extended-release oral suspension relies on the Agency's previous findings for the LD, Kapvay (NDA 022331). The clinical review for this application focused on whether the safety data from the submitted pharmacokinetic studies were consistent with the available safety information for the LD. Given that this is a 505(b)(2) application, many sections of the clinical review will be abbreviated or not applicable.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

There were no clinical efficacy studies in this submission. See Section 6 for the clinical pharmacology evaluation of the PK studies submitted by the Applicant to provide a scientific bridge between this product and the LD.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant proposes to rely on the Agency's prior findings of safety for the LD by establishing an acceptable scientific bridge to clonidine ER OS, 0.1 mg/mL. The safety review is based on the Applicant's integrated summary of safety (ISS), which presents an analysis of safety data across the completed three PK studies: Study 20-VIN-0304, a pilot, open-label, single-dose study with a prototype formulation and Studies 2021-5094 (single-dose) and 2021-5095 (multiple-dose), which were conducted with the proposed commercial formulation. All three studies were conducted in healthy adult subjects.

Post-treatment safety assessments conducted in at least one of the three PK studies include adverse events (AEs), vital signs, clinical laboratory tests (hematology, chemistry, urinalysis), and electrocardiograms.

8.2.2. Review of the Safety Database

Overall Exposure

Of the 59 subjects enrolled in the three studies, 57 subjects were exposed to at least one dose of clonidine ER OS 0.1 mg/mL. One subject discontinued after eight doses of the LD, and one subject was withdrawn for noncompliance (positive urine THC). Of the 57 subjects exposed to the test drug, 16 subjects were administered a prototype formulation (Study 20-VN-034) and the remaining 41 subjects were administered the formulation planned for commercial use (Studies 2021-5094 and 2021-5095). Table 1, below, summarizes the exposure of clonidine hydrochloride extended-release, oral suspension, 0.1mg/mL (clonidine HCl ER OS).

Table 6. Exposure to Clonidine HCl ER OS

Study Number	Study Design	Test Product Dose and Formulation	Number of Healthy Adult Subjects Exposed
20-VN-034	Open-label, single-dose, randomized, two-period, two treatment, two-sequence, crossover, comparative bioavailability study	Single 2 mL (0.2mg) dose of clonidine HCl ER OS 0.1 mg/ml (prototype formulation)	16 Males
2021-5094	Open-label, single-dose, randomized, three-period, three-treatment, three-sequence, crossover, relative bioavailability and food-effect study	Single 2 mL (0.2mg) dose of clonidine HCCL ER OS 0.1 mg/ml (final formulation) in fed and fasting condition	23 subjects enrolled; 19 completed the study. 22 subjects were exposed to at least one dose of study drug Four subjects withdrew (due to positive urine THC; emesis; kidney stones and renal colic; and personal reasons).
2021-5095	Open-label, 5-day, multiple-dose, randomized, two-period, two-treatment, two-sequence, crossover, relative bioavailability study	2 mL (0.2mg) dose of clonidine HCL ER OS, 0.1 mg/ml at times 0, 24, 48, 72, and 96 hours (final formulation)	20 subjects enrolled; 19 completed the study. One subject withdrew after administration of reference product due to fever.
		Total number of subjects	**59**

Source: Adapted from ISS Table 5, p.15
Test Product=clonidine HCL ER OS; Reference Product=LD (Kapvay)

Adequacy of the safety database:

The safety population includes all subjects who received a dose of study medication. See

Table 2, Table 3, and Table 4 for subject demographic and baseline characteristics from Studies 20-VIN-0304 2021, 2021-5094, and 2021-5095, respectively.

> *Clinical Reviewer Comment: Study 20-VIN-0304 was conducted in India with all Asian male subjects. This study had a younger mean age than the other two PK studies (approximately 28 years of age). Studies 2021-5094 and 2021-5095 were both conducted in Canada, had similar mean ages (approximately 44 years of age). Approximately 2/3 of subjects across treatment arms were White males. The original clinical review for the LD indicates that both the Sponsor for the LD and the FDA statistical reviewer conducted subgroup analyses on treatment effect by gender and race and concluded that there were no significant treatment interactions of gender and race (July 20, 2010, Cross-Discipline Team Leader Review Memo, DARRTS).*

Table 7. Demographic Profile of Subjects Who Completed Study 20-VIN-0304

		Treatment Group N = 16
Age (years)	**Mean ± SD**	28.4 ± 5.5
	Range	20 – 41
Age Groups	**< 18**	0
	18 – 40	15 (94%)
	41 – 64	1 (6%)
	65 – 75	0
	> 75	0
Sex	**Male**	16 (100%)
	Female	0
Race	**Asian**	16 (100%)
	Black	0
	Caucasian	0
	Hispanic	0
	Other	0
BMI (Kg/m^2)	**Mean ± SD**	22.8 ± 2.5
	Range	18.6 – 26.6
Height (cm)	**Mean ± SD**	167.0 ± 6.3
	Range	158.7 – 179
Weight (Kg)	**Mean ± SD**	63.7 ± 7.7
	Range	50.1 – 75.6

Source: Module 5.2.5.2 ISS Table 8, p. 17

Table 8 Demographic Profile of Subjects Who Completed Single-dose Study 2021-5094

		Treatment Groups		
		Trt A Test Fed N = 21	**Trt B Test Fasted N = 22**	**Trt C Reference Fasted N = 21**
Age (years)	**Mean ± SD**	44 ± 11	43 ± 11	43 ± 11
	Range	20 – 54	20 – 54	20 – 54
Age Group	**<18**	0	0	0
	18 – 40	6 (29%)	7 (32%)	7 (33%)
	41 – 64	15 (71%)	15 (68%)	14 (67%)
	65 – 75	0	0	0
	>75	0	0	0
Sex	**Female**	8 (38%)	8 (36%)	7 (33%)
	Male	13 (62%)	14 (64%)	14 (67%)
Race	**White**	13 (62%)	13 (59%)	13 (62%)
	Black or African American	5 (24%)	6 (27%)	5 (24%)
	Asian	2 (10%)	2 (9%)	2 (10%)
	Other	1 (5%)	1 (5%)	1 (5%)
Ethnicity, n (%)	**Hispanic or Latino**	10 (48%)	9 (41%)	9 (43%)
	Not Hispanic or Latino	11 (52%)	13 (59%)	12 (57%)
BMI	**Mean ± SD**	26.4 ± 2.8	26.4 ± 3.0	26.6 ± 2.9
	Range	20.0 - 30.0	20.0 - 30.0	20.0 - 30.0

Source: Module 5.2.5.2 Integrated Summary of Safety Table 9 pp. 17-18

Table 9. Demographic Profile of Subjects Who Completed Multiple Dose Study 2021-5095

		Treatment Groups	
		Trt A Test Fasted N = 19	Trt B Reference Fasted N = 20
Age (years)	Mean ± SD	43 ± 11	43 ± 11
	Range	22 – 55	22 – 55
Age Group	<18	0	0
	18 – 40	7 (37%)	7 (35%)
	41 – 64	12 (63%)	13 (65%)
	65 – 75	0	0
	>75	0	0
Sex	Female	8 (42%)	8 (40%)
	Male	11 (58%)	12 (60%)
Race	White	5 (26%)	6 (30%)
	Black or African American	5 (26%)	5 (25%)
	Asian	9 (47%)	9 (45%)
	Other	0	0
Ethnicity, n(%)	Hispanic or Latino	0	1 (5%)
	Not Hispanic or Latino	19 (100%)	19 (95%)
BMI	Mean ± SD	25.3 ± 2.5	25.1 ± 2.7
	Range	20.0 - 30.0	20.0 - 30.0

Source: Module 5.2.5.2 ISS Table 10, p. 18

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data quality was acceptable for review.

Categorization of Adverse Events

The Applicant categorized AEs using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. AEs were sorted alphabetically by both system organ class (SOC) and preferred term (PT). Assessments were based primarily on frequency and severity of AEs and clinically significant values for laboratory tests and vital signs.

> *Clinical Reviewer's Comment: The Applicant's AE definitions, monitoring, and severity determinations appear reasonable.*

Routine Clinical Tests

The following blood and urine samples for clinical safety laboratory tests were collected at baseline and end-of-study: serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase, total bilirubin, albumin, cholesterol, total protein, creatinine, direct and indirect bilirubin, urea, uric acid, lactate dehydrogenase, hemoglobin, total leukocyte count, neutrophils, lymphocytes, white blood count, platelet, HIV and Hepatitis C antibody, and Hepatitis B surface antigen. Pre-dose vitals (respiratory rate, pulse rate, temperature, and blood pressure) and post-dose vitals were measured in each

study.

Electrocardiograms were recorded prior to drug administration and at 6-, 11-, and 24-hours post-dose (relative to 0-hour dose) in Study 2021-5094 only.

> *Clinical Reviewer's Comment: The Applicant's routine clinical tests appear generally reasonable for these comparative bioavailability studies with an approved LD.*

8.2.4. Safety Results

Deaths

No deaths occurred in the three studies.

Serious Adverse Events

No serious adverse events occurred in the three studies.

Dropouts and/or Discontinuations Due to Adverse Effects

- Study 20-VIN-0304: There were no discontinuations reported in this study.
- Study 2021-5094:
  - Subject (b) (6) was withdrawn due to noncompliance (positive urine THC) prior to Period 2 (did test-fed only)
  - Subject (b) (6) withdrew due to emesis in Period 3 (Treatment B: test or clonidine HCl ER OS) fasted
  - Subject (b) (6) withdrew due to kidney stones and renal colic in Period 3 (reference or LD under fasted condition)
  - Subject (b) (6) withdrew prior to period 2; the reason listed in the ISS was personal reasons, but according to the case report form (CRF), this subject had hypotension that occurred after the last dose administered of test drug (clonidine HCl ER OS under the fed condition).
- Study 2021-5095:
  - Subject (b) (6) withdrew due to fever prior to the 96-hour (Day 4) drug administration and only received eight administrations of the reference product (Treatment B) in Period 1.

    Clinical Reviewer's Comment: These AEs do not appear to indicate a new or worsened

safety signal for clonidine hydrochloride ER OS. Per the LD label, hypotension is listed as a Warning and Precaution occurring with clonidine use, and nausea is a common adverse reaction. Emesis, fever, kidney stones, and renal colic are not listed as adverse reactions in the LD label; however, the sample size is small and there are too few subjects reporting these events to conclude that any change to labeling for the LD is warranted. Of note, the Applicant listed Subject (b) (6) (Study 2021-5094) as withdrawing due to personal reasons, yet the CRF revealed that this subject experienced episodes of hypotension just prior to withdrawal, suggesting that this subject could have withdrawn due to an AE.

Significant Adverse Events

No AEs were considered severe in any of the three studies.

There were no dose reductions possible in these studies. The only concomitant medications reported were morphine sulfate and paracetamol (one subject each; morphine for the subject with kidney stones), which were both administered after the last PK sample was collected. Therefore, these concomitant medications would not affect the pharmacokinetic samples.

Treatment Emergent Adverse Events and Adverse Reactions

Study 20-VIN-0304

There were no adverse events, serious adverse events, or clinically significant adverse events reported.

Study 2021-5094

There was a total of 71 treatment emergent adverse events (TEAEs) during the study; all except one (kidney stones) resolved by the end of the study. There were 37 events of hypotension occurring in 17 subjects, of which 14 subjects had the event after Treatment A (clonidine HCl ER OS in the fed state), 14 subjects after Treatment B (clonidine HCl ER OS in fasted state), and nine subjects after Treatment C (LD in fasted state).

There were 11 events of bradycardia reported in eight subjects (four subjects after Treatment A, four subjects after Treatment B, and three subjects following Treatment C). Vomiting occurred in both the Test and Reference Group but is not an adverse event listed in the label for the LD. Constipation, dry mouth, headache, dizziness, and QT prolongation are labeled adverse reactions in the prescribing information for the LD. See Electrocardiogram section below for discussion of the QTc prolongation event.

Table 10. Incidence of Adverse Events in Study 2021-5094

MedDRA System Organ Class/ Preferred Term	Trt A (Test Fed) N=21	Trt B (Test Fasted) N=22	Trt C (Ref Fasted) N=21
Subjects reporting adverse events	15 (71%)	16 (73%)	13 (62%)
Cardiac disorders	**4 (19%)**	**4 (18%)**	**3 (14%)**
Bradycardia	4 (19%)	4 (18%)	3 (14%)
Gastrointestinal disorders	**1 (5%)**	**3 (14%)**	**2 (10%)**
Constipation	1 (5%)	0	1 (5%)
Dry mouth	1 (5%)	1 (5%)	1 (5%)
Vomiting	0	1 (5%)	1 (5%)
Investigations	**0**	**1 (5%)**	**0**
Electrocardiogram QT Prolonged	0	1 (5%)	0
Nervous system disorders	**0**	**4 (18%)**	**2 (10%)**
Dizziness	0	2 (9%)	1 (5%)
Headache	0	3 (14%)	1 (5%)
Renal and urinary disorders	**0**	**0**	**1 (5%)**
Nephrolithiasis	0	0	1 (5%)
Renal colic	0	0	1 (5%)
Vascular disorders	**14 (64%)**	**14 (64%)**	**9 (43%)**
Hypotension	14 (64%)	14 (64%)	9 (43%)

Test: clonidine hydrochloride extended-release oral suspension
Ref=Reference: LD
Source: Adapted from ISS Section 3.1.2.1.1 p. 20, Table 11

> *Clinical Reviewer's Comment: These AEs do not appear to indicate a new or worsened safety signal of clonidine ER OS. The most common events of bradycardia and hypotension are listed in the LD label and not unexpected in this safety data base.*

Study 2021-5095

There were five events of hypotension occurring in three subjects: three events affecting three subjects following Treatment A (clonidine HCl ER OS fasted state), and three events affecting one subject following Treatment B (LD fasted state). See section of Laboratory Findings for discussion of anemia and increased creatinine.

Table 11 Incidence of Significant Adverse Events in Study 2021-5095

MedDRA System Organ Class/Preferred Term	A (Test Fed) N=19	B (Reference Fasted) N=20	Total N=20
Subject reporting adverse events	**6(32%)**	**4(20%)**	**9 (45%)**
Blood and lymphatic system disorders	**1 (5%)**	**0**	**1 (5%)**
Anemia	1 (5%)	0	1 (5%)
Investigations	**1 (5.3%)**	**0**	**1 (5%)**
Blood creatinine increased	1 (5%)	0	1 (5%)
Vascular disorders	**3 (15%)**	**1 (5%)**	**3 (15%)**
Hypotension	3 (15%)	1 (5%)	3 (15%)

Test: clonidine hydrochloride extended-release oral suspension
Reference: LD (Kapvay)
Subjects having two or more adverse events under the same treatment are counted only once within a category.
The same subject may appear in different categories and treatments.
Source: Adapted from ISS Section 3.1.2.1.1 p. 24, Table 15

Laboratory Findings

In Study 2021-5095, Subject (b) (6), a 53-year-old female, had elevated creatinine levels that occurred 5 days (119.98 hours) after dosing of clonidine HCl ER OS and resolved within 2 weeks (330.32 hours). This subject had creatinine levels slightly elevated at baseline.

Also in Study 2021-5095, Subject (b) (6), a 40-year-old female, reported adverse events of anemia, hypotension, and menstrual cramping. Her hemoglobin was slightly below normal limits at baseline (109 g/L; reference range: 115-155) and decreased to 93 g/L; the study report stated that her anemia resolved within 2 weeks post-dosing.

Otherwise, there were no other laboratory abnormalities identified in this safety data base.

> *Clinical Reviewer's Comment: Elevated creatinine and anemia are not listed in the LD label as known adverse reactions. However, it is difficult to attribute these events to drug exposure based on these single cases. Furthermore, Subject (b) (6) had elevated creatinine at baseline and Subject (b) (6) had another plausible underlying reason for transient anemia (menstruation).*

Vital Signs

There were no significant findings related to vital signs observed in Study VIN-0304.

In Study 2021-5094, eight (35%) subjects experienced bradycardia (11 episodes) and 17 (73.9%) subjects reported hypotension (37 episodes).

In Study 2021-5095, five subjects (25%) had adverse events related to vital signs (hypotension, tachycardia, and pyrexia). There were three subjects reporting hypotension after treatment A (clonidine HCl ER OS, in fasted state) and one subject (5%) receiving Treatment B (LD, in fasted state).

> *Clinical Reviewer's Comment: It is not surprising that the adverse event of hypotension occurred at a relatively high incidence in this database, because hypotension is a well-recognized adverse event of the LD and listed in the Warnings and Precaution section. Increased and decreased heart rate is listed as a common adverse reaction in the LD label. The label also indicates that rebound tachycardia may also occur in the context of sudden drug cessation. Although pyrexia is not listed in the LD label, it is difficult to attribute causality to drug given that this is a nonspecific symptom that could have many etiologies.*

Electrocardiograms (ECGs) and QT

In Study 2021-5094, Subject (b) (6), a 48-year-old female, had a normal electrocardiogram (ECG) at baseline, but 11 hours after dosing in Period 3 (clonidine HCl ER OS in fasted state), her ECG showed a QTc prolongation during Period 3. Her QTc interval reverted to a normal value as shown in the ECG reading at 24 hours post-dosing. See Table 7, below, for further details.

Table 12 Electrocardiogram of Subject (b) (6) after Clonidine HCL ER OS in the Fasted State

	Period 3 Check-In	Period 3 6 hours post-dosing	Period 3 11 hours post-dosing	Period 3 24 hours post-dosing
QTcB Interval (msec)	411	439	518	402
QT Interval (msec)	378	360	440	378
QRS Interval (msec)	76	74	188	72
PR Interval (msec)	194	180	98	192
RR Interval (msec)	854	685	732	895
Heart Rate (bpm)	70	88	82	67

Bpm=beats per minute
Source: CRF of Subject (b) (6)

Clinical Reviewer's comment: It is difficult to establish causality of the QTc prolongation event because this database is small and the incidence is low. However, it is noted that QTc prolongation is listed in the LD label in Section 6.2 Postmarketing Experience as an adverse reaction that has been identified during post-approval use of the LD.

Immunogenicity

There were no potentially immunogenicity-related AEs reported in any of the three studies.

8.2.5. Analysis of Submission-Specific Safety Issues

There were no specific safety issues explored in this application.

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

There were no clinical outcome assessment analyses informing safety and tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

The demographic groups relevant to age, gender, race, and ethnicity in Studies 2021-5094 and 2021-5096 were too small for useful subgroup analysis.

8.2.8. Specific Safety Studies/Clinical Trials

There were no specific safety studies requested by the Division.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No data on human carcinogenicity or tumor development were submitted. **Human Reproduction and Pregnancy**

No data on human reproduction and pregnancy were submitted. The Applicant is relying on the information in approved labeling for the LD.

Pediatrics and Assessment of Effects on Growth

There were no pediatric subjects in the submitted studies.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience with clonidine hydrochloride ER OS. If approved, the study drug labeling will include the following postmarketing experience of adverse reactions for the LD (as described in Section 6.2 of labeling):

- Psychiatric: hallucinations
- Cardiovascular: QT prolongation

Expectations on Safety in the Postmarket Setting

The Applicant has demonstrated that PK profiles of clonidine hydrochloride ER OS are comparable to the LD. The safety of this product in the postmarket setting is expected to be similar to that of the LD. Per the LD label, in premarketing studies, the most common adverse reactions (incidence at least 5% and twice the rate of placebo) with the LD administered as monotherapy in ADHD include somnolence, fatigue, irritability, nightmare, insomnia, constipation, and dry mouth. The most common adverse reactions (incidence at least 5% and twice the rate of placebo) with the LD administered as adjunct therapy to psychostimulant in ADHD include somnolence, fatigue, decreased appetite, and dizziness. Other adverse events more common than placebo include aggression, affect lability, emotional disorder, insomnia, upper abdominal pain, and dizziness. Warnings and precautions include hypotension/bradycardia/syncope, somnolence/sedation, cardiac conduction abnormalities. Contraindications include a history of hypersensitivity reaction to clonidine (e.g., generalized rash, urticaria, angioedema).

8.2.11. Integrated Assessment of Safety

The Applicant proposes to rely on the Agency's previous safety findings for the LD with an adequate scientific PK bridge. No new or more severe/serious safety signals are apparent from the PK trials of clonidine ER OS data. Clonidine ER OS is expected to have a similar safety profile as the LD.

The Sponsor of the LD proposed to discontinue the LD (Kapvay 0.1 mg extended-release tablets) during the review cycle of this NDA. Based on a review of recent annual reports and available safety data for the LD, it does not appear that the LD was withdrawn for any reasons related to safety or efficacy.

8.3. Statistical Issues

Not applicable.

8.4. Conclusions and Recommendations

Based on the PK profiles of clonidine hydrochloride ER OS and the LD, the product is adequately bridged to the LD and clonidine hydrochloride ER OS can rely on the Agency's previous findings of safety and efficacy of the LD. No new or more severe/serious safety signals are apparent from the PK trials of clonidine hydrochloride ER OS.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not convened for this submission. This 505(b)(2) application relies on the findings of safety and efficacy of the LD. There were no questions for an Advisory Committee.

10 Pediatrics

This submission did not include any pediatric studies. DP sent the Applicant an Agreed Initial Pediatric Study Plan (iPSP) letter dated July 4, 2023. The following pediatric studies in subjects 4 to <6 years of age will be postmarketing requirements under the Pediatric Research Equity Act (PREA):

1. An adequately powered, double-blind, placebo-controlled efficacy and safety study of clonidine hydrochloride extended-release oral suspension in subjects ages 4 to < 6 years with attention deficit hyperactivity disorder.

2. A long-term, open-label study to evaluate the safety and tolerability of clonidine hydrochloride extended-release oral suspension in pediatric subjects ages 4 to < 6 years with attention deficit hyperactivity disorder.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The prescribing information (PI) for clonidine hydrochloride extended-release oral suspension is generally consistent with that of the LD. Throughout the PI, where appropriate, the LD is referred to as either "clonidine hydrochloride extended-release tablets" or clonidine hydrochloride extended-release." Proposed revisions to the PI (specific to the oral suspension) are listed below, but the PI was not finalized at the time of this review.

Prescribing Information
The following sections in the proposed label for clonidine hydrochloride ER OS are generally aligned with the LD: Section 1 (Indications and Usage); Section 4 (Contraindications), Section 5 (Warnings and Precautions), Section 6 (Adverse Reactions), Section 7 (Drug Interactions); Section 8.1 (Pregnancy); Section 8.2 (Lactation); Section 8.3 (Females and Males of Reproductive Potential); Section 8.4 (Pediatric Use); Section 8.6 (Renal Impairment); Section 10 (Overdosage); Section 13 (Nonclinical Toxicology); and Section 14 (Clinical Studies).

Section 2 Dosage and Administration

- Dosage recommendations specific to clonidine hydrochloride extended-release oral suspension were added to Section 2.

- A new subsection, Section 2.2 Administration Instructions, was added to relay important administration details to the reader.

    - The following text was added as Section 2.2:

      2.2 Administration Instructions

      Instruct patients to read the "Instructions for Use" for complete administration instructions.

      - Use the oral dosing dispenser and bottle adapter provided with ONYDA XR.
      - Ensure that the bottle adapter is firmly inserted into the bottle before first use and keep the adapter in place for the duration of the usage of the bottle.
      - Gently shake ONYDA XR with a smooth up and down motion (to avoid foaming) for at least 10 seconds before each administration.
      - Discard any unused ONYDA XR remaining in the bottle after 60 days of first opening the bottle.

- A new subsection, Section 2.3 Switching from Other Clonidine Products, was added to relay that clonidine hydrochloride extended-release oral suspension cannot be switched with other clonidine products.

- The following text was added as Section 2.3:

2.3 Switching from Other Clonidine Products

For patients switching from another clonidine product, discontinue that treatment, and titrate with ONYDA XR using the titration schedule *[see Dosage and Administration (2.1)]*. Do not substitute for other clonidine products on a milligram-per-milligram basis because of differing pharmacokinetic profiles *[see Clinical Pharmacology (12.3)].*

Section 3 Dosage Forms and Strengths

- Information about the strength or potency and identifying characteristics of clonidine hydrochloride extended-release oral suspension was added.

(b) (4)

Section 11 Description

- Qualitative and quantitative information about clonidine hydrochloride extended-release oral suspension was included.

Section 12 Clinical Pharmacology

- Section 12.3 Pharmacokinetics was revised to include relevant PK measures and parameters that are important for the safe and effective use of clonidine ER OS, as per current labeling guidance.

Section 16 How Supplied/Storage and Handling

- Information about the strength or potency, identifying characteristics, NDC number, and storage of clonidine ER OS was added.

- Expiration:

  - Based on information submitted by the Applicant, (b) (4) The expiration date was discussed with the Division of Medical Error Prevention and Analysis (DMEPA) and the Office of Pharmaceutical Quality (OPQ). (b) (4)

(b) (4) To mitigate this risk, the team determined that the product should be dispensed to the patient in the original bottle with an expiry date of 60 days, which was best supported by the available stability data. See the DMEPA and OPQ reviews for additional information.

- The following text was added "Discard any unused ONYDA XR remaining in the bottle after 60 days of first opening the bottle."

- Per DMEPA recommendation the expiration for the bottle was indicated to be 60 days after first opening.

  - DMEPA's review provides the following comment to Applicant: "Based on the review of your submitted data, 60 days will be the use by date for your product. Add the following statement (or similar verbiage) to the container labels and carton labeling: "Discard unused Onyda XR 60 days after first opening the bottle. Date bottle first opened: __/__/__."

- Dispensing Information

  - The following dispensing information (or similar) will be added to relay important information for the product:

    - "Store and dispense ONYDA XR in the original bottle. Dispense with bottle adapter and oral dosing dispenser supplied in the carton. Discard any unused ONYDA XR remaining in the bottle after 60 days of first opening the bottle."

Section 17 Patient Counseling Information

- Administration information specific to clonidine ER OS added.

Patient labeling

- Patient Package Insert (PPI)

  - The currently approved labeling for the listed drug includes a PPI. The Division worked with the Division of Medical Policy Programs (DMPP) to develop a PPI that aligns with more current language and updated the formatting.

- Instructions for Use (IFU)

  - An IFU document will be included as part of labeling because clonidine hydrochloride

extended-release oral suspension is intended for administration by the caregiver or patient and there are specific administration instructions for appropriate use.

12 Risk Evaluation and Mitigation Strategies (REMS)

No specific risk evaluation and mitigation strategies are recommended as the safety profile of clonidine hydrochloride ER OS does not require risk mitigation strategies beyond labeling and does not appear to differ from the LD.

13 Postmarketing Requirements and Commitment

See Section 10, Pediatrics.

14 Deputy Division Director (Clinical) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15 Appendices

15.1. References

See footnotes.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 20-VIN-0304, 2021-5094, and 2021-5095

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S 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. Clinical Pharmacology

Clinical Pharmacology Studies

Clinical Study Report	
Study Report #: 2021-5094	Study Period: 9/19/22 – 10/18/22
Study Sites:	Pharma Medica Research Inc, Toronto, Canada
Principal Investigators:	Janice Faulknor, MD, Mark Freedman, MD
Analytical Site:	(b) (4)
Principal Scientist:	(b) (4)
EDR Link:	\\cdsesub1\evsprod\nda217645\0001\m5

Study Title: An Open-Label, Randomized, Three-Way, Pivotal Study to Evaluate the Relative Bioavailability of Clonidine HCl Extended-Release Oral Suspension to an Equivalent Dose of Kapvay Extended-Release Tablets and to Evaluate the Food Effect of Clonidine HCl Extended-Release Oral Suspension.

Objectives:
Primary: To evaluate the relative bioavailability between 2 mL of clonidine hydrochloride (HCl) ER OS 0.1 mg/mL (equivalent to 0.09 mg clonidine base per mL; Tris Pharma, Inc., USA) and 2 Kapvay (clonidine HCl) ER tablets 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet; Concordia Pharmaceuticals, USA) after a single dose in healthy subjects under fasted conditions and to evaluate the effect of food on the bioavailability of clonidine HCl ER OS 0.1 mg/mL (Tris Pharma, Inc., USA).

Secondary: To evaluate the safety and tolerability of the study treatments and to ensure that the plasma concentration versus time profile was established for the ER test product, met the goal of once-a-day dosing, and to demonstrate that there was no dose dumping.

Study Design: This is an open-label, single-dose, randomized, three-period, three-treatment, three-sequence, crossover, relative bioavailability study. In each study period, in accordance with the randomization scheme, subjects were administered one of the following treatments: **Test product (treatment A)**: 0.2 mg (2 mL of clonidine HCl ER OS, 0.1 mg/mL) administered 30 minutes after the start of a high-fat, high-calorie (about 900 Kcal) meal. Subjects fasted for at least 10 hours prior to and 4 hours after 0-hour drug administration. Subjects who did not consume the entire meal in the required time (within 30 minutes of drug administration) would have been dismissed from the study prior to drug administration. **Test product (treatment B)**: 0.2 mg (2 mL of clonidine HCl ER OS, 0.1 mg/mL) administered under fasted conditions. Subjects fasted for at least 10 hours prior to and 4 hours after 0-hour drug administration.

Reference product (treatment C): 0.1 mg (one ER tablet of Kapvay (clonidine HCl)) administered once at 0- and 12-hours under fasted conditions. Subjects fasted for at least 10

hours prior to and 4 hours after 0-hour drug administration. Subjects fasted for at least 2 hours prior to and 2 hours after 12-hour drug administration.

Investigational Products:

Test Product (Administered in Treatment A and B):	2 mL of Clonidine HCl, ER OS , 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA) Dose: 0.2 mg (2 mL of 0.1 mg/mL ER OS) administered at 0-hour Mode of Administration for Treatment A: Oral under fed conditions. Mode of Administration for Treatment B: Oral under fasted conditions.
Reference Product (Administered in Treatment C):	1 Tablet of Kapvay® (Clonidine HCl), ER Tablets, 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet) Lot No.: 20E189 (Concordia Pharmaceuticals, USA.) Dose: One (1) ER tablet administered once at 0-hour and 12-hour Mode of Administration: Oral under fasted conditions.

Source: Study 2021-5094 p. 24

The three study periods were separated by a washout period of 7 days, corresponding to at least five half-lives.

Bioanalysis:

Method: Liquid chromatographic tandem mass spectrometry detection (LC-MS-MS).

Calibration range: 10 to 800 pg/mL.

Incurred Sample Reanalysis (ISR): Met the acceptance criteria. ISR acceptance criteria required two thirds (two out of three) of the repeat samples within ± 20% of the mean value. The method is considered reliable and reproducible since 98.6% of the repeated results are within the acceptance criteria of 20%.

Information Requested	Data
Bioanalytical method validation report location	Section: 5.3.1.4, Document Name: 2021-5094-analytical-method-validation.pdf, Pages 2 - 1655
Analyte	Clonidine
Internal standard (IS)	Clonidine-d_4
Method description	Liquid-liquid extraction; liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method
Limit of quantitation	10.0 pg/mL
Average recovery of drug (%)	89.6% to 96.1%
Average recovery of IS (%)	98.7% to 101.4%
Standard curve concentrations (pg/mL)	10.0, 20.0, 40.0, 80.0, 150, 300, 600 and 800
QC concentrations (pg/mL)	LLOQ QC (10.0), QC A (30.0), QC B (400), QC C (650) and QC E (125)
QC Intraday precision range (%)	LLOQ QC: 4.6 to 8.3 QC A, QC B, QC C and QC E: 1.3 to 6.2
QC Intraday accuracy range (%)	LLOQ QC: 80.4 to 103.0 QC A, QC B, QC C and QC E: 93.3 to 103.4
QC Interday precision range (%)	LLOQ QC: 11.0 QC A, QC B and QC C: 2.0 to 5.2
QC Interday accuracy range (%)	LLOQ QC: 94.0 QC A, QC B and QC C: 98.0 to 100.3
Bench-top stability (hrs)	20.75 hours @ room temperature; 21.25 hours @ room temperature
Stock stability (days)	62 days @ 5 ± 3 °C
Processed stability (hrs)	2.00 hours @ room temperature; 84.00 hours @ 5°C (autosampler stability), 199.75 hours @ 5°C(autosampler stability), 115.25 hours @ 5°C (reinjection stability)
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	62 days @ -25 ± 10 °C
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Source: Summary of Biopharmaceutics and Associated Analytical Methods pp. 16-17

PK Sampling: PK blood samples were collected prior to dosing (0-hour) and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 30, 36, and 48 hours after drug administration.

The analytical method and its validation are acceptable.

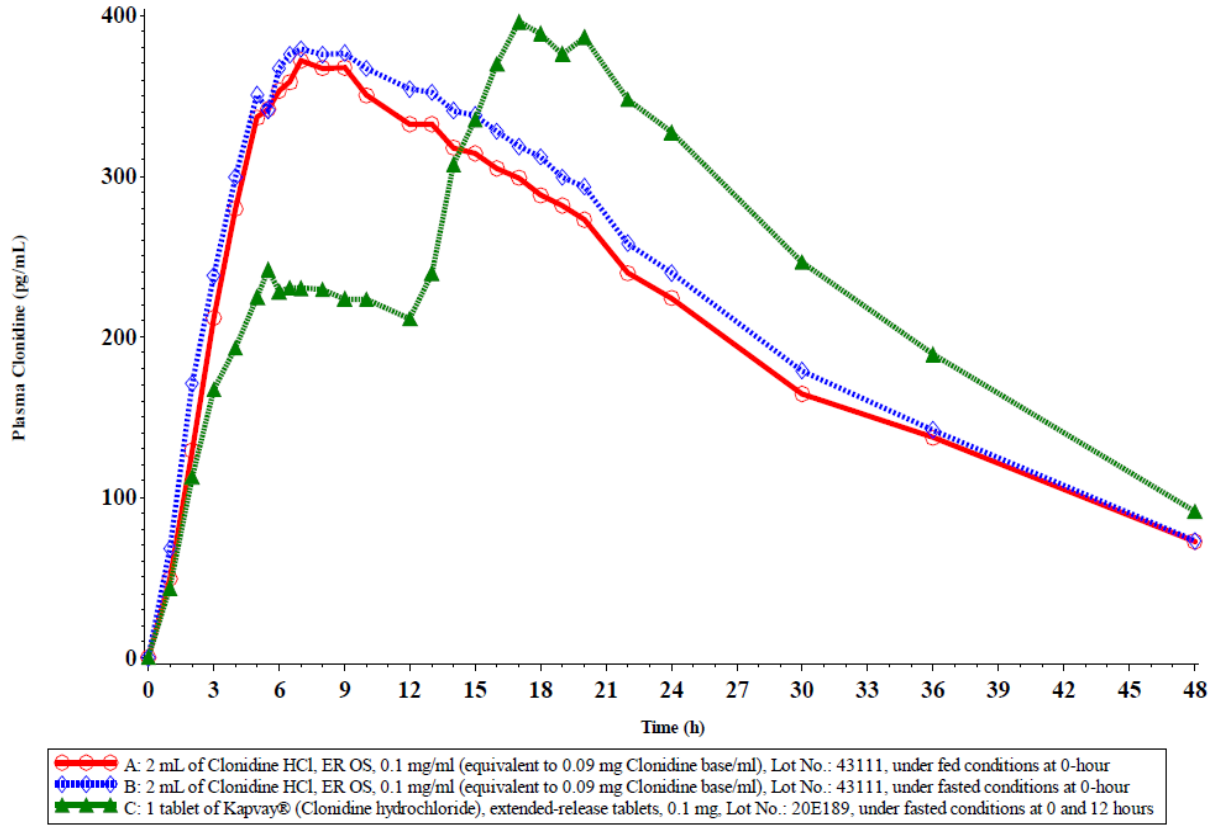
Results

Table 13. Subject Disposition

Randomized/Completed/Discontinued due to AE	23/19/2
Mean (± SD) Overall Age (Median (range)) years	43 ± 11 (47 (20 – 54))
Male/Female	14/9
Race (Caucasian/Black/Other)	14/6/3
Overall Weight (± SD), lbs	76.1 ± 12.6

Source: FDA Reviewer-generated

Figure 6. Mean Plasma Clonidine Concentration-Time Profile of Clonidine following a Single Oral 0.2 mg Clonidine ER OS (Treatment A—Fed (red line) and Treatment B—Fasting (blue line)) and 0.1 mg Kapvay ER Tablet (Treatment C) Administered at 0 Hours and 12 Hours under Fasting Conditions (green line)



Source: Study 2021-5094 p. 40

Table 14. Descriptive Statistics for Plasma Clonidine Pharmacokinetic Parameters

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	A	9626.1	9956.4	2541.7	25.53	9772.4	5306.4	15067.4	19
*(hr*pg/mL)*	B	10155.4	10556.3	2868.6	27.17	11074.9	6037.4	15171.4	20
	C	10455.0	10876.5	3013.9	27.71	10832.7	5909.8	17389.1	20
AUC_{inf}	A	11138.4	11639.0	3429.6	29.47	11175.0	5612.8	18661.9	19
*(hr*pg/mL)*	B	11529.6	12107.2	3800.0	31.39	12401.4	6837.5	21348.2	20
	C	12004.4	12624.2	3977.1	31.50	12867.6	6425.1	21425.3	20
AUC_t/AUC_{inf}	A	86.42	86.58	5.32	6.14	87.62	72.30	94.54	19
(%)	B	88.08	88.26	5.50	6.23	89.51	71.07	97.54	20
	C	87.09	87.25	5.28	6.05	88.04	71.92	94.72	20
C_{max}	A	382.2	392.7	92.6	23.58	380.0	232.0	602.0	19
(pg/mL)	B	394.2	404.2	88.1	21.81	410.0	232.0	532.0	20
	C	413.5	424.5	97.4	22.94	418.5	243.0	655.0	20
T_{max}	A	7.19	7.42	2.06	27.76	7.00	5.00	14.00	19
(hr)	B	7.76	8.32	3.42	41.05	7.50	4.00	17.00	20
	C	17.37	17.89	3.46	19.33	18.02	5.53	24.00	20
T_{half}	A	14.78	15.05	3.12	20.72	14.50	11.00	23.57	19
(hr)	B	13.19	13.54	3.40	25.08	12.76	7.88	24.19	20
	C	12.05	12.31	2.77	22.47	11.61	8.24	19.50	20
K_{el}	A	0.0469	0.0477	0.0085	17.91	0.0478	0.0294	0.0630	19
(1/hr)	B	0.0526	0.0538	0.0118	22.00	0.0543	0.0287	0.0879	20
	C	0.0575	0.0586	0.0114	19.50	0.0597	0.0356	0.0841	20
TLIN	A	17.34	18.54	6.70	36.15	17.00	7.00	30.00	19
(hr)	B	20.65	21.40	5.75	26.86	21.00	11.92	30.05	20
	C	25.49	25.81	4.10	15.87	24.00	20.00	30.03	20
R^2	A	0.9873	0.9874	0.0138	1.39	0.9905	0.9469	0.9990	19
	B	0.9891	0.9892	0.0140	1.42	0.9953	0.9417	1.0000	20
	C	0.9885	0.9886	0.0142	1.44	0.9927	0.9483	1.0000	20
Ct	A	65.2	72.4	32.7	45.10	70.6	19.3	152.0	19
(pg/mL)	B	64.4	72.6	35.6	48.95	69.0	15.7	177.0	20

Treatment A: 2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fed conditions at 0-hour

Treatment B: 2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fasted conditions at 0-hour

Treatment C: 1 tablet of Kapvay® (Clonidine hydrochloride), extended-release tablets, 0.1 mg, (equivalent to 0.087 mg of the free base in 0.1 mg tablet) Lot No.: 20E189 (Concordia Pharmaceuticals, USA), under fasted conditions at 0 and 12 hours

Source: Study 2021-5094 p. 63

Table 15. Summary of Clonidine Pharmacokinetic Parameters for Treatment B vs Treatment C

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**B**	20	10556.3 (27)	10198.9	**B vs C**	97.17	91.61 - 103.07	11
*(hr*pg/mL)*	**C**	20	10876.5 (28)	10495.8				
AUC_{inf}	**B**	20	12107.2 (31)	11597.0	**B vs C**	96.13	89.38 - 103.39	13
*(hr*pg/mL)*	**C**	20	12624.2 (32)	12064.0				
C_{max}	**B**	20	404.2 (22)	394.8	**B vs C**	95.62	89.81 - 101.80	11
(pg/mL)	**C**	20	424.5 (23)	412.9				

Treatment B (Test)	2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fasted conditions at 0-hour
Treatment C (Reference)	1 tablet of Kapvay® (Clonidine hydrochloride), extended-release tablets, 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet), Lot No.: 20E189 (Concordia Pharmaceuticals, USA), under fasted conditions at 0 and 12 hours

Source: Study 2021-5094 p. 39

Table 16. Summary of Clonidine Pharmacokinetic Parameters for Treatment B vs Treatment C

Parameter	Treatment	Geometric LSMean	Contrast	Ratio (%)	90% CI
AUCt (hr.pg/mL)	B	10207.48	B vs C	97.32	92.72 – 102.10
	C	10488.50			
AUCinf (hr.pg/mL)	B	11600.31	B vs C	96.20	90.72 – 102.01
	C	12059.10			
Cmax (pg/mL)	B	394.21	B vs C	95.44	90.08 – 101.12
	C	413.03			

Source: Reviewer's Analysis

Table 17. Summary of Clonidine Pharmacokinetic Parameters for Treatment A vs Treatment B

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	19	9956.4 (26)	9716.8	**A vs B**	95.27	91.08 - 99.66	8
*(hr*pg/mL)*	**B**	20	10556.3 (27)	10198.9				
AUC_{inf}	**A**	19	11639.0 (29)	11236.5	**A vs B**	96.89	91.80 - 102.26	9
*(hr*pg/mL)*	**B**	20	12107.2 (31)	11597.0				
C_{max}	**A**	19	392.7 (24)	382.4	**A vs B**	96.87	93.26 - 100.61	7
(pg/mL)	**B**	20	404.2 (22)	394.8				

Treatment A (Test): 2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fed conditions at 0-hour

Treatment B (Test): 2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fasted conditions at 0-hour

Source: Study 2021-5094 p. 39

Table 18. Summary of Clonidine Pharmacokinetic Parameters for Treatment A vs Treatment B

Parameter	Treatment	Geometric LSMean	Contrast	Ratio (%)	90% CI
AUCt (hr.pg/mL)	A	10207.48	A vs B	95.92	91.33 – 100.74
	B	9791.01			
AUCinf (hr.pg/mL)	A	11330.96	A vs B	97.68	91.99 – 103.72
	B	11600.31			
Cmax (pg/mL)	A	386.50	A vs B	98.05	92.42 – 104.02
	B	394.21			

Source: Reviewer's Analysis

Pharmacokinetic Summary

The reviewer's BE analysis is consistent with the Sponsor's analysis. The PK parameters (Cmax, AUCinf) of clonidine HCl ER OS are within the bioequivalence (BE) limit 80 to 125% of the LD under fasting conditions. Furthermore, the exposures (Cmax and AUC) are equivalent when clonidine ER OS is administered under both fed and fasting conditions. Median Tmax was about 10.5 hours shorter after administration of clonidine ER OS compared to the LD.

> *<u>OCP Reviewer's Comments:</u> The reviewer agrees with the Sponsor's evaluation that after single-dose administration, the PK parameters of 0.2 mg of clonidine ER OS are equivalent to those of 0.2 mg of clonidine ER oral tablet (Kapvay) administered as 0.1 mg twice daily. Therefore, clonidine ER OS can rely on the Agency's previous findings of safety and efficacy of the LD, Kapvay.*

Clinical Study Report

Study Report #: 2021-5095	Study Period: 11/28/2022 – 1/12/2023
Study Site	Pharma Medica Research Inc. Toronto, Canada
Principal Investigator:	Mark Freedman, MD, Janice Faulknor, MD
Analytical Site:	(b) (4)
Principal Scientist:	(b) (4)
EDR Link:	\\cdsesub1\evsprod\NDA217645\0001\m5

Study Title: A Multiple-Dose, Open-Label, Randomized, Two-Way, Pivotal Study to Evaluate the Relative Bioavailability at Steady-State of Clonidine HCl Extended-Release Oral Suspension to an Equivalent Daily Dose of Kapvay Extended-Release Tablets under Fasting Conditions

Objectives:
Primary: To evaluate the relative bioavailability between clonidine HCl ER OS (OS) 0.1 mg/mL (equivalent to 0.09 mg clonidine base per mL) (Tris Pharma, Inc., USA) and Kapvay® (clonidine HCl) ER tablets 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet) (Concordia Pharmaceuticals Inc., USA) at steady state in healthy subjects under fasting conditions.

Secondary: To evaluate the safety and tolerability of the study treatments and to evaluate the human factor assessment regarding the ease of self-dosing after receiving each dose of Test Product.

Study Design: Open-label, multiple-dose, randomized, two-period, two-treatment, two-sequence, crossover, relative bioavailability study in non-smoking male and female subjects aged 10 to 55 years. In each period, subjects either self-administered the test product or were administered the reference product, in accordance with the randomization scheme. Subjects self-administered a single, oral dose of the test product at 0, 24, 48, 72, and 96 hours, and subjects were administered a single, oral dose of the reference product at 0, 12, 24, 36, 48, 60, 72, 84, 96, and 108 hours. Subjects fasted for at least 10 hours prior to and at least 4 hours after the 96-hour drug administration for both products, and for at least 2 hours prior to and at least 2 hours after the 108-hour drug administration for the reference product Concentrations of clonidine were measured in plasma from pre-dose samples collected prior to dosing at 0, 24, 72, 84, and 96 hours (Cpd24, Cpd48, Cpd72, Cpd84, Cpd96) in each period for the assessment of steady state pharmacokinetic (PK) characteristics.

Treatments: Test formulation of clonidine HCl ER OS 0.1 mg/mL and a reference product (Kapvay ER tablets. 0.1 mg) in healthy male and female subjects at steady state under fasting conditions.

Treatment A (Test): Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg clonidine base/ml) (Tris Pharma, Inc., USA)

Dose: 0.2 mg daily for 5 days (2 mL of 0.1 mg/mL self-administered at 0, 24, 48, 72, and 96 hours).

Subjects fasted for at least 10 hours prior to, and at least 4 hours after, the 96-hour drug administration.

Treatment B (Reference): Kapvay (Clonidine HCl), ER Tablets, 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet; Concordia Pharmaceuticals, USA)

Dose: 0.2 mg daily for 5 days (0.1 mg administered at 0, 12, 24, 36, 48, 60,72, 84, 96 and 108 hours

Subjects fasted for at least 10 hours prior to and at least 4 hours after the 96-hour drug administration. Subjects fasted for at least 2 hours prior to and at least 2 hours after, the 108-hour drug administration.
The washout period between the drug administration from the first dose of period 1 to the first dose of period 2 was at least 14 days corresponding to more than 5 half-lives.

PK Sampling: PK blood samples for the determination of plasma clonidine PK parameters were collected prior to Treatment A dosing at 0, 24, 48, 72, 96 hours, and at 97, 98, 99, 100, 101, 101.5, 102, 102.5, 103, 104, 105, 106, 109, 110, 111, 112, 113, 114, 115, 116, 118, and 120 hours after Treatment A dosing; and prior to Treatment B dosing at 0, 24, 48, 72 , 84, 96, and 108 hours, and at 97, 98, 99, 100, 101, 101.5, 102, 102.5, 103, 104, 105, 106, 109, 110, 111, 112, 113, 114, 115, 116, 118, and 120 hours after Treatment B dosing. The PK parameters, AUCt,ss, Cmin,ss, Cmax,ss, C24,ss, Cavg, Tmax,ss, %Swing and %Fluctuation were estimated using a non-compartmental approach.

Bioanalytical Analysis: Plasma concentrations of clonidine in subject samples were measured utilizing liquid chromatographic tandem mass spectrometric detection (LC-MS/MS) method. The standard calibration range was from 10.0 to 800 pg/mL using a plasma sample volume of 0.300 mL.

Bioanalytical Method Validation:

Information Requested	Data
Bioanalytical method validation report location	Section: 5.3.1.4, Document Name: 2021-5095-analytical-method-validation.pdf, Pages 2 - 1655
Analyte	Clonidine
Internal standard (IS)	Clonidine-d4
Method description	Liquid-liquid extraction; liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method
Limit of quantitation	10.0 pg/mL
Average recovery of drug (%)	89.6% to 96.1%
Average recovery of IS (%)	98.7% to 101.4%
Standard curve concentrations (pg/mL)	10.0, 20.0, 40.0, 80.0, 150, 300, 600 and 800
QC concentrations (pg/mL)	LLOQ QC (10.0), QC A (30.0), QC B (400), QC C (650) and QC E (125)
QC Intraday precision range (%)	LLOQ QC: 4.6 to 8.3 QC A, QC B, QC C and QC E: 1.3 to 6.2
QC Intraday accuracy range (%)	LLOQ QC: 80.4 to 103.0 QC A, QC B, QC C and QC E: 93.3 to 103.4
QC Interday precision range (%)	LLOQ QC: 11.0 QC A, QC B and QC C: 2.0 to 5.2
QC Interday accuracy range (%)	LLOQ QC: 94.0 QC A, QC B and QC C: 98.0 to 100.3
Bench-top stability (hrs)	20.75 hours @ room temperature; 21.25 hours @ room temperature
Stock stability (days)	62 days @ 5 ± 3 °C
Processed stability (hrs)	2.00 hours @ room temperature; 84.00 hours @ 5°C (autosampler stability), 199.75 hours @ 5°C(autosampler stability), 115.25 hours @ 5°C (reinjection stability)
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	62 days @ -25 ± 10 °C
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Incurred Sample Reanalysis (ISR): One hundred and eleven study samples corresponding to 10.1% of the analyzed 1102 study samples were re-assayed as ISR. ISR acceptance criteria require two thirds (2 out of 3) of the repeat samples within ± 20% of the mean value. Hundred percent (100%) of the repeated results are within the acceptance criteria of 20%.

The analytical method and its validation are acceptable.

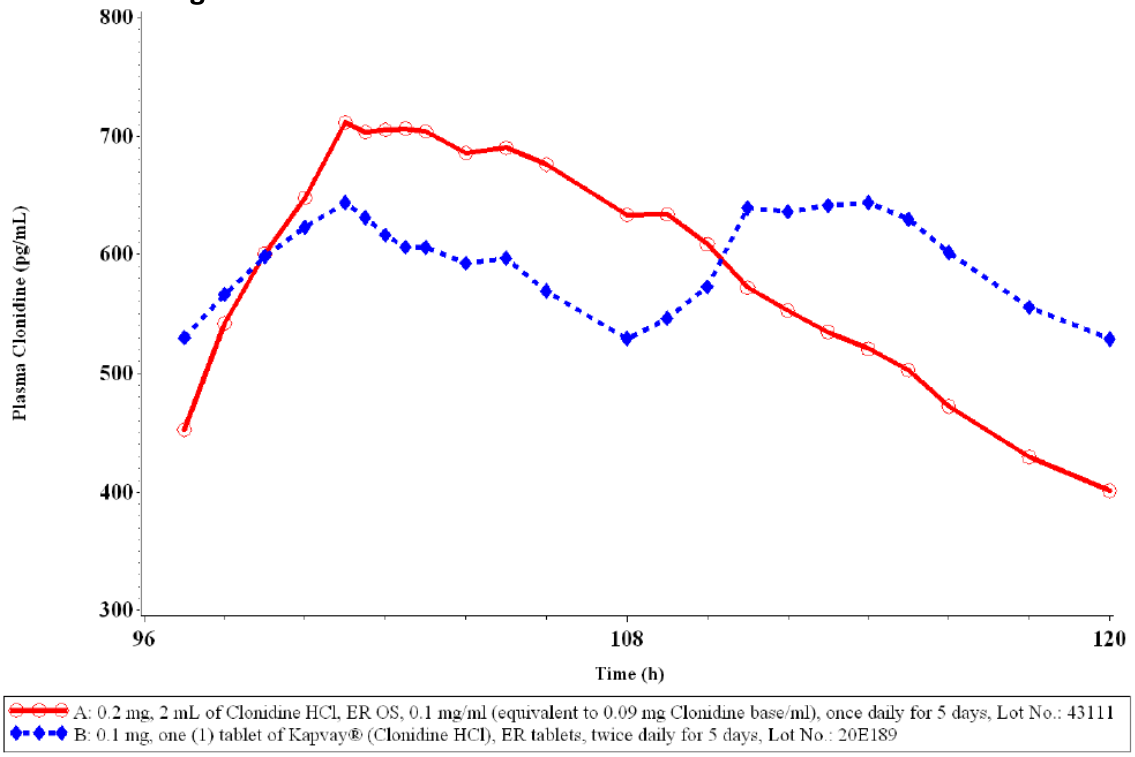
Results

Table 19. Subject Disposition

Randomized/Completed/Discontinued due to AE	20/19/1
Male/Female	12/8
Race (Caucasian/Black/Other)	6/5/9
Overall Weight (±SD), lbs	70.9 ± 11.6

Source: Reviewer generated

Figure 7. Mean Plasma Clonidine Concentrations-Time Profile at Steady-State following Once Daily Administration of 0.2 mg Clonidine ER OS (Treatment A—Red Solid Line) for 5 Days and Twice-daily Administration of 0.1 mg Kapvay ER Tablet (Treatment B—Blue Dashed Line) for 5 Days under Fasting Conditions



Source: Study 5095 p. 42

Table 20. Descriptive Statistics for Plasma Clonidine Pharmacokinetic Parameters

Parameter	Trt	GeoMean	ArithMean	SD	CV%	Median	Minimum	Maximum	N
AUC_{tss}	A	13309.2	13791.0	3586.1	26.00	14300.9	7663.0	19767.9	19
*(hr*pg/mL)*	B	13609.8	14120.9	3703.1	26.22	14598.8	8086.4	19383.8	19
C_{maxss}	A	716.6	740.2	182.7	24.68	783.0	404.0	983.0	19
(pg/mL)	B	664.2	682.7	157.5	23.07	697.0	423.0	936.0	19
T_{maxss}	A	102.89	102.91	1.99	1.94	102.50	101.00	106.07	19
(hr)	B	107.52	107.66	5.61	5.21	111.00	100.00	115.00	19
C_{minss}	A	374.7	396.8	132.9	33.50	391.0	196.0	642.0	19
(pg/mL)	B	472.1	495.8	148.1	29.87	529.0	258.0	723.0	19
C_{24ss}	A	377.5	401.1	139.0	34.66	391.0	196.0	655.0	19
(pg/mL)	B	508.9	528.9	143.6	27.15	534.0	291.0	731.0	19
C_{pd24}	A	257.9	275.7	99.9	36.23	291.0	125.0	516.0	19
(pg/mL)	B	366.6	382.9	116.3	30.39	367.0	220.0	638.0	19
C_{pd48}	A	347.3	372.5	134.7	36.17	382.0	165.0	626.0	19
(pg/mL)	B	474.3	488.7	117.8	24.12	509.0	275.0	691.0	19
C_{pd72}	A	373.4	401.1	145.2	36.20	438.0	162.0	660.0	19
(pg/mL)	B	501.7	520.7	138.9	26.67	547.0	272.0	776.0	19
C_{pd84}	A	597.0	622.2	172.3	27.70	636.0	344.0	874.0	19
(pg/mL)	B	515.2	534.7	144.9	27.10	546.0	298.0	765.0	19
C_{pd96}	A	374.4	395.5	127.4	32.21	422.0	204.0	614.0	19
(pg/mL)	B	488.6	517.6	161.6	31.22	545.0	230.0	740.0	19
C_{avg}	A	554.6	574.6	149.4	26.00	595.9	319.3	823.7	19
(pg/mL)	B	566.9	588.2	154.3	26.23	608.3	336.9	807.7	19

Source: Applicant

Table 21. Summary of Clonidine Pharmacokinetic Parameters for Treatment A vs Treatment B

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
$AUC_{t,ss}$	A	19	13791.0 (26)	13353.1	A vs B	97.68	93.41 - 102.14	8
*(hr*pg/mL)*	B	19	14120.9 (26)	13670.6				
$C_{max,ss}$	A	19	740.2 (25)	719.7	A vs B	107.90	103.80 - 112.17	7
(pg/mL)	B	19	682.7 (23)	667.0				
$C_{24,ss}$	A	19	401.1 (35)	378.2	A vs B	74.01	69.33 - 79.00	12
(pg/mL)	B	19	528.9 (27)	511.0				

CV, Coefficient of Variation; n, number of subjects in statistical dataset; Sbj, Subject; Trt, Treatment.

Treatment A (Test): 0.2 mg (2 mL of Clonidine hydrochloride (HCl), extended release (ER) oral suspension (OS), 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111, (Tris Pharma, Inc., USA) under fasted conditions at 0, 24, 48, 72, and 96 hours

Treatment B (Reference): One (1) tablet of Kapvay® (Clonidine hydrochloride), extended-release tablets, 0.1 mg,(equivalent to 0.087 mg of the free base in 0.1 mg tablet) Lot No.: 20E189, (Concordia Pharmaceuticals, USA) under fasted conditions at 0, 12, 24, 36, 48, 60, 72, 84, 96, and 108 hours

Source: Study 5095 page 41

Table 22. Statistical Analysis of Pre-dose Plasma Clonidine Concentration- Treatment A

Time	*LSMeans (95% CI)*	*Helmert Contrasts*	*Ratio (95% Simultaneous CI)*
48	347.3 (286.5, 421.0)	48 Hr vs. (72 Hr, 96 Hr)	0.9 (0.9, 1.0)
72	373.4 (307.1, 454.0)	72 Hr vs. 96 Hr	1.0 (0.9, 1.1)
96	374.4 (316.2, 443.3)		. (. , .)

Treatment A: 0.2 mg, 2 mL of Clonidine hydrochloride (HCl), extended release (ER) oral suspension (OS), 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), once daily for 5 days (Tris Pharma, Inc., USA)

Source: Study 5095 p. 44

Table 23. Statistical Analysis of Pre-dose Plasma Clonidine Centration- Treatment B

Time	*LSMeans (95% CI)*	*Helmert Contrasts*	*Ratio (95% Simultaneous CI)*
72	501.7 (436.6, 576.5)	72 Hr vs. (84 Hr, 96 Hr)	1.0 (0.9, 1.1)
84	515.2 (449.1, 591.2)	84 Hr vs. 96 Hr	1.1 (1.0, 1.2)
96	488.6 (408.8, 584.1)		. (. , .)

Treatment B: 0.1 mg, one (1) tablet of Kapvay® (Clonidine hydrochloride), extended- release tablets, twice daily for 5 days (Concordia Pharmaceuticals, USA)

Source: Study 5095 p. 44

Pharmacokinetic Summary
The evaluation of the pre-dose concentration appears to suggest steady state was achieved after 48 hours pose dose. The 90% confidence intervals (CIs) of the geometric mean ratios of plasma clonidine PK parameters, AUCt,ss and Cmax,ss of the Test were within 80 to 125% of the LD. However, the 90% CI of C24 h, ss of the Test was not within 80 to 125% of the LD.

The test product, clonidine hydrochloride, ER OS, 0.1 mg/mL (equivalent to 0.09 mg clonidine base/mL; Tris Pharma, Inc., USA), self-administered in 0.2 mg doses once daily for 5 days, exhibited equivalent peak and total exposure compared to the reference product Kapvay (clonidine HCl), ER tablets, 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet; Concordia Pharmaceuticals, USA), administered in 0.1 mg doses twice daily for 5 days at steady state, in healthy subjects. The C24 hr, ss of the oral suspension was 26% lower compared to that of the LD. The difference in C24h is not expected to be clinically meaningful for treatment naïve patients when treated with clonidine ER OS. However, patients stabilized on other formulations should not be switched on a mg-per-mg basis.

> *<u>OCP Reviewer's Comments:</u> The reviewer agrees with the Sponsor's analyses. Following once-daily administration of 0.2 mg clonidine ER OS (clonidine ER OS) at steady state, peak exposures (Cmax) and total exposure (AUC) of clonidine were equivalent to the LD, 0.1 mg clonidine ER tablets (Kapvay) administered twice daily. C24, ss was 26% lower after daily administration of clonidine ER OS compared to twice daily administration of Kapvay tablets and such lower magnitude of decrease in systemic exposures is deemed*

to be clinically not relevant for treatment naïve patients. Given that the PK shape of clonidine ER OS could be different from other clonidine ER formulations and reduction in efficacy is expected with clonidine ER OS formulation when switching from patients who are stabilized with other clonidine ER products based on a mg-per-mg basis, clonidine ER OS should not be substituted with other ER formulations. Overall, the findings suggest that clonidine ER OS can rely on the Agency's previous findings of safety and efficacy of the LD, Kapvay.

15.4. Additional Clinical Outcome Assessment Analyses

No additional Clinical Outcome Assessment Analyses were submitted.

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