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RESEARCH**

APPLICATION NUMBER:

212268Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation NDA 212268 Secuado (asenapine)
transdermal system

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212268
Priority or Standard	Standard
Submit Date(s)	December 13, 2018
Received Date(s)	December 13, 2018
PDUFA Goal Date	October 13, 2019
Division/Office	Division of Psychiatry Products/ODE I
Review Completion Date	
Established/Proper Name	Asenapine Transdermal Delivery System (Asenapine TDS)
(Proposed) Trade Name	Secuado
Pharmacologic Class	Atypical Antipsychotic
Code name	HP-3070
Applicant	Hisamitsu Pharmaceutical Co., Inc.
Dosage form	Transdermal Delivery System (TDS)
Applicant proposed Dosing Regimen	One TDS every 24 hours
Applicant Proposed Indication(s)/Population(s)	Schizophrenia in adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	58214004 Schizophrenia (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of schizophrenia in adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	One TDS every 24 hours

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

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Secuado is a transdermal delivery system (TDS) for the atypical antipsychotic, asenapine. Asenapine is marketed as a sublingual tablet, Saphris (NDA 22117), and is approved for the treatment of adult patients with schizophrenia and patients age 10 years and older with manic or mixed mood episodes associated with bipolar I disorder. Secuado is intended for once daily application to treat adult patients with schizophrenia.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness for the treatment of adults with schizophrenia. This evidence consists of 1) comparable bioavailability to the approved sublingual asenapine product and 2) efficacy data from a 6-week, randomized, double-blind, placebo-controlled, fixed-dose, inpatient study in 614 adult patients who met DSM-5 criteria for schizophrenia and were in acute exacerbation. Both Secuado TDS treatment arms (3.8 mg/24 hours and 7.6 mg/24 hours) were statistically significantly superior to placebo on the primary efficacy endpoint (change from baseline to Week 6 in the Positive and Negative Symptom Symptom Scale (PANSS) total score) and the key secondary endpoint (change from baseline to Week 6 in the Clinical Global Impression-Severity (CGI-S) assessment scale). The Division will not require evidence of long-term efficacy because that has already been demonstrated in a randomized withdrawal study of sublingual asenapine. Also, the Division will not require an efficacy trial in adolescents with schizophrenia because such a trial with sublingual asenapine failed to demonstrate efficacy in that population.

1.3. **Benefit-Risk Assessment**

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Benefit-Risk Summary and Assessment

Schizophrenia and bipolar I disorder are serious psychiatric illnesses that typically continue throughout a patient's lifetime. The estimated prevalence for schizophrenia and bipolar disorder in the U.S. population is roughly 1% and 3%, respectively. These illnesses can have significant and disabling impact on the patient's social functioning. Management generally requires long-term treatment with antipsychotic medication. Early antipsychotic drugs (such as thioridazine) had significant tolerability limitations, leading to non-compliance. Although better tolerated oral agents have been developed in the last decades (e.g., risperidone, aripiprazole, quetiapine, olanzapine, asenapine), the efficacy of these agents is comparable. Thus, clinicians most often switch between these agents to minimize side effects and maximize compliance. Furthermore, many of these agents have been developed into long-acting intramuscular and, most recently, subcutaneous formulations with the goal of increasing medication compliance. However, poor patient adherence to pharmacological treatments continues to be a common problem in this patient population, resulting in increased risk of relapses, hospitalizations, and other poor outcomes.

Asenapine is an atypical antipsychotic currently indicated for the acute and maintenance treatment of schizophrenia and bipolar disorder in adults (Saphris; NDA 22117). Although the exact mechanism of action of asenapine is unknown, it is thought to be mediated through antagonism of D₂ and 5-HT_{2A} receptors. It is available as 5mg and 10mg tablets for twice daily sublingual administration. With this submission, the Applicant is proposing a new transdermal asenapine formulation. The Applicant has established an adequate scientific (PK) bridge to the marketed sublingual asenapine tablets, relying on the Agency's previous findings for safety and effectiveness. The Applicant also conducted an adequate and well-controlled clinical trial, providing additional evidence that the proposed product is effective in the treatment of schizophrenia. In this study, both asenapine transdermal system (TDS) treatment arms (3.8 mg/24 hours and 7.6 mg/24 hours) were statistically superior to placebo on the primary (change from baseline in PANSS) and key secondary (change from baseline in CGI-S) efficacy endpoints after six weeks.

Although the proposed transdermal product introduces new potential risks (e.g., skin irritation, incorrect transdermal system use, detachment), its safety profile is largely consistent with the existing label for asenapine sublingual tablets. Furthermore, these new potential risks can be adequately mitigated with labeling while providing a new, once-a-day alternative route of administration for patients who are unwilling or unable to use the existing asenapine sublingual tablets. Therefore, the benefit:risk assessment for asenapine transdermal system remains favorable and this application is unanimously recommended for approval by the review team.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- Schizophrenia and bipolar I disorder are chronic psychiatric conditions - Treatment frequently requires long-term use of antipsychotic medication - Poor treatment compliance can result in repeated hospitalizations and other poor outcomes	Schizophrenia and bipolar disorder are chronic and serious psychiatric conditions often requiring lifetime antipsychotic use. However, medication noncompliance is a significant problem for many patients, potentially leading to relapses, hospitalizations, and suicide attempts.
<u>Current Treatment Options</u>	- Several medication options are currently available - Tolerability of current treatment options may be limited by adverse reactions - Among the existing options, asenapine tablets are approved for twice-a-day sublingual administration	While several medication options are currently available, tolerability of current medication options may be limited by adverse reactions. These include neuromuscular and metabolic effects. For many patients, adverse reactions may be a contributing factor in poor medication compliance.
<u>Benefit</u>	- The Applicant has established an adequate PK bridge to asenapine sublingual tablets - Asenapine TDS was statistically superior to placebo on the primary and secondary efficacy endpoints in patients with schizophrenia in an adequate and well-controlled clinical trial - Asenapine TDS provides a seemingly convenient, once-a-day alternative for patients who are unwilling or unable to use the approved sublingual tablets; however, the impact of this alternative dosing option on medication compliance is unknown.	The data submitted with this application suggest that we can expect similar efficacy between the proposed product and asenapine sublingual tablets while providing an alternative, potentially convenient dosing option.
<u>Risk and Risk Management</u>	Although there is significant overlap in the safety profile of the existing asenapine sublingual tablets and the proposed asenapine TDS, this new route of administration introduces new risks (e.g., skin irritation, improper patch use, product detachment)	These risks can be mitigated with labeling.

1.4. Patient Experience Data

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

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO) Medication Satisfaction Questionnaire (MSQ)	8.1.2
☐	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.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	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	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Schizophrenia is a severe, chronic psychiatric condition with a variable clinical presentation. The precise cause of schizophrenia is unknown. Typically, the onset of illness occurs in the late teens to early twenties and persists lifelong thereafter. Schizophrenia usually begins earlier and is more common in males than females. The estimated one-year prevalence of schizophrenia in the U.S. is approximately 1%. Schizophrenia is among the top 15 leading causes of disability worldwide.

Patients with schizophrenia experience positive symptoms including delusions, hallucinations, and disorganized speech and behavior. In addition, they experience negative symptoms including flat affect, poverty of speech and thought content, apathy, anhedonia, and social withdrawal. In addition, patients with schizophrenia experience substantial impairment in several areas of cognitive functioning, such as working memory, attention, processing speed, and visual and verbal learning. If untreated, schizophrenia produces significant impairments in social, occupational, and academic functioning.

2.2. Analysis of Current Treatment Options

Several drugs are approved in the U.S. for the treatment of patients with schizophrenia. These drugs are generally classified as typical antipsychotics or atypical antipsychotics based on pharmacologic activity and safety profile.

Typical (or first generation) antipsychotics were first approved in the 1950s and include chlorpromazine, loxapine, thioridazine, thiothixene, fluphenazine, trifluoperazine, molindone, and haloperidol. These drugs block primarily dopamine-2 (D2) receptors and are associated with extrapyramidal symptoms, such as akathisia, dystonic reactions, parkinsonism, and tardive dyskinesia. Other possible effects are hyperprolactinemia, weight gain, sedation, orthostatic hypotension, and anticholinergic adverse reactions, such as constipation, dry mouth, and blurred vision.

Atypical (or second generation) antipsychotics include clozapine, which was approved in the U.S. in 1989 and remains the only drug approved for the treatment of patients with treatment-resistant schizophrenia. Other atypical antipsychotics were approved in the 1990s and later and include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, iloperidone, cariprazine, and brexpiprazole. Atypical antipsychotics vary somewhat in pharmacological activity, which includes D2 and 5-HT1A partial agonism and 5-HT2A

antagonism. These drugs are generally considered to have less risk of extrapyramidal symptoms and tardive dyskinesia but are associated, in varying degrees, with weight gain and metabolic effects such as hyperglycemia and hyperlipidemia. Other adverse reactions associated with some of the atypical antipsychotics include sedation, orthostatic hypotension, akathisia, and QT interval prolongation.

Approved treatments for patients with schizophrenia are effective primarily in improving positive symptoms but there is no cure for this illness and currently no approved treatments that target negative symptoms or cognitive impairment.

Asenapine is approved as a sublingual tablet (Saphris) for the treatment of adult patients with schizophrenia as well as for adult and pediatric patients (ages 10 to 17 years) with manic or mixed mood episodes associated with bipolar I disorder. The asenapine transdermal delivery system (TDS) offers an alternative route of administration of asenapine which avoids mouth and tongue reactions associated with the sublingual tablet.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Asenapine TDS has been developed via the 505(b)(2) pathway as a transdermal formulation of the atypical antipsychotic asenapine for the treatment of schizophrenia. Asenapine is approved and marketed as a sublingual tablet formulation (as Saphris in the US; Sycrest in the European Union) for the treatment of schizophrenia in adults; manic or mixed mood episodes associated with bipolar I disorder in adults and pediatric patients 10 to 17 years of age; adjunctive treatment of bipolar I disorder with lithium or valproate in adults; and maintenance monotherapy treatment in adults with bipolar I disorder.

Hisamitsu is relying on the FDA's nonclinical safety (pharmacokinetic [PK], pharmacology, and toxicology), clinical pharmacology, and clinical safety and efficacy findings and evaluations from the Listed Drug (LD), Saphris (NDA 022117; approved on August 13, 2009).

3.2. Summary of Presubmission/Submission Regulatory Activity

On June 25, 2015, an End of Phase 2 meeting was held with the Division of Psychiatry Products(DPP) to discuss the development program for asenapine transdermal delivery system for the indication of the treatment of schizophrenia.

On November 20, 2015, the Applicant submitted a request for special protocol assessment of a clinical protocol, entitled "HP-3070-GL-04: A Randomized, Double-Blind, Placebo-Controlled,

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Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia”. A Special Assessment Agreement -No Agreement letter was issued by FDA on December 24, 2015. At a February 24, 2016, Type A Clinical SPA Guidance Meeting, the deficiencies were discussed with the Applicant and, subsequently, agreement was reached on the protocol for the pivotal phase 3 Study HP-3070-GL-04.

On November 30, 2015, the Applicant submitted request for Special Protocol Assessment for a carcinogenicity protocol, entitled “ 104-Week Dermal Carcinogenicity Study of Asenapine (b) (4) in Rats”. A Special Protocol - No Agreement was issued by Executive CAC on January 14, 2016, stating that we did not have sufficient information upon which to base dosage selections. A waiver from conducting carcinogenicity studies was granted by the Division on December 19, 2017, indicating that the Applicant has fulfilled the requirements for assessing the potential for systemic and dermal carcinogenicity of asenapine TDS, based on the results of HP-3070 nonclinical toxicology studies as well as on the carcinogenicity studies of asenapine administered subcutaneously for the listed drug (Saphris).

On February 12, 2016, IND 125707 was submitted to DPP to support the initiation of the proposed IND opening phase 3 pivotal efficacy and safety study in schizophrenia patients (HP-3070-GL-04). The proposed study was also intended to support eventual registration of asenapine TDS. The Applicant was notified on March 10, 2016, via a telephone conversation, that the proposed study was placed on clinical hold and may not be initiated due to unreasonable and significant risk of illness or injury to human subjects, specifically due to minimal renal papillary interstitial necrosis observed in the 13-week transdermal asenapine toxicity study conducted in the Sprague-Dawley rat. The Division requested a CFSAN Pathology consultation of the response to the clinical hold. The consultants concluded that the changes described in the 13-week and 26-week rat studies are not test-article (asenapine (b) (4)) related, but likely consistent with artifactual postmortem autolysis. Thus, the proposed IND-opening study was allowed to proceed.

On October 23, 2017, FDA provided written responses in lieu of a Type C meeting on the content and format of the planned NDA submission for asenapine TDS.

On June 19, 2018, a Type B, Pre-NDA meeting was held to discuss the proposed NDA for asenapine TDS for the treatment of schizophrenia and to gain FDA feedback and agreement on the data package and the adequacy of overall submission package to support the NDA filing for HP-3070.

The Applicant submitted the NDA on December 13, 2018, requesting for a priority review. FDA decided to review the application under a Standard review clock because this product would not provide a significant improvement in safety or effectiveness over other products in the class. The application was filed on February 11, 2019.

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

4.1. Office of Scientific Investigations (OSI)

OSI inspected Site #1006 from the pivotal safety and efficacy trial, Study HP-3070-GL-04. Daniel M. Gruener, MD, was the principal investigator at this site, which is located in St. Louis, MO. This site was selected due to high enrollment and good treatment response. The inspection findings were conveyed in a Clinical Inspection Summary written by Jenn Sellers, MD, Medical Officer in the Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation, dated August 19, 2019. The primary and key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. Overall, the study appears to have been conducted adequately and the data generated by this site appear to be acceptable to support this application.

4.2. Product Quality

Hisamitsu Pharmaceutical Co., Inc. has developed Secuado (asenapine) transdermal system, intended to deliver asenapine over a 24-hour period (3.8 mg/24 hours, 5.7 mg/24 hours or 7.6 mg/24 hours). Each transdermal system has a corresponding surface area of 20 cm², 30 cm² or 40 cm², respectively. It contains the drug substance, asenapine base, and the following inactive ingredients: styrene-isoprene-styrene block copolymer, polyisobutylene, alicyclic saturated hydrocarbon resin, mineral oil, sodium acetate anhydrous, isopropyl palmitate, butylated hydroxytoluene, polyester film backing and silicone-treated polyester release liner. The transdermal system is a translucent rounded square with a printed backing on one side and a release liner on the other. The printing includes the strength of the transdermal system. The drug product is supplied in an individual pouch. Thirty pouches are placed in a carton for a one-month supply. The proposed room temperature 24-month expiry has been found to be adequate.

Sufficient data has been provided in the submission to ensure the identity, strength, quality, and purity of the drug product.

4.3. Clinical Microbiology

No clinical microbiology data were submitted with this application.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this application.

4.5. Division of Medication Error Prevention and Analysis

The Applicant submitted results of a Human Factors (HF) validation study as part of the application. The study results indicate there were critical task use errors. The Applicant made a number of revisions and formatting changes to the Instructions for Use (IFU) in order to address the root causes of some of the use errors. These revisions were made after the completion of the HF validation study and the Applicant does not have any data to support that the proposed revisions are effective and do not introduce new use-related risks.

We considered the known use risks with currently marketed transdermal systems and input from the clinical review team. We acknowledge that the errors seen in the HF validation study represent known risks with transdermal systems and we have determined that these risks are not new and unique in the context of the use of the proposed product. We realize this product may offer a benefit to those patients who are unable to tolerate the currently marketed asenapine sublingual dosage form. In addition to the Applicant's revisions, we have identified other labeling strategies that may help to reduce the residual risk associated with the use of this product.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In addition to the findings for Saphris, the Applicant performed nonclinical studies with HP-3070 (the proposed product) to evaluate the safety of the transdermal administration in animals. All safety pharmacology and pivotal toxicology studies were conducted in compliance with Good Laboratory Practices (GLP) guidelines.

The mechanism of action of asenapine, an atypical antipsychotic, is unclear. Based on receptor binding assays, asenapine is a potent multi-receptor antagonist with a high affinity for several dopamine, serotonin, noradrenaline, and histamine receptors. In vitro radioligand-receptor binding studies demonstrated that asenapine exhibits high affinity for dopaminergic, serotonergic, adrenergic, and histaminergic receptors, with inhibitory constant (K_i) values in the range of 0.026 to 5.57 nM. In vivo pharmacodynamics studies with asenapine in rats showed anti-dopaminergic effects in a model of methamphetamine-induced hyperactivity and anti-serotonergic effects in a model of tryptamine-induced convulsions.

Safety pharmacology studies of the central nervous and respiratory systems conducted with HP-3070 in rats and studies of the cardiovascular system conducted with HP-3070 in dogs did not reveal any unexpected toxicological effects of asenapine.

General toxicity studies of up to 39-week duration were conducted in rats, dogs, and minipigs. In the 26-week toxicity study in rats, histopathological changes were observed in the mammary gland, ovary, uterus, and vagina in females; these effects are probably caused by an elevated prolactin level via the pharmacological action of asenapine on dopaminergic neuronal systems. Although prolactin was not measured in this study, these effects are expected as a known class effect for the atypical antipsychotics. In the 13-week toxicity study in dogs, there were no significant test article-related findings, except for the death of one high dose female due to jaundice-like disorder. As no other animals showed jaundice, the relation of this disorder to the test article is unclear. In the 39-week study in minipigs, there were no significant test article-related findings as well. Safety margins based on systemic plasma exposure values (AUC) at the NOAEL are 5.2 to 10.5 times in dogs (13-week study) and 0.8 to 1.1 times in minipigs (39-week study) vs. the AUC of 96.2 ng.h/mL in schizophrenia patients at the maximal dose of (b) (4) /day in the HP-3070 US-02b clinical study.

Local dermal effects at patch application sites were observed in all tested animal species (most pronounced in rats), in all study groups, including groups that received the control patch; however, the effects observed in the control animals were less severe and of lower incidence compared to those in the test article groups. Erythema was observed in the patch application area. Histopathology demonstrated minimal to mild crust formation, ulcer, cell infiltration of the epidermis and dermis, and thickening and/or thinning of the epidermis. These findings were reversible at the end of the recovery period.

No evidence for genotoxic potential was found in the in vitro studies of asenapine or the in vivo studies of HP-3070. In the reproductive and developmental toxicology studies of HP-3070, rat-specific prolactin-related effects were observed, including inhibition of estrous and prolongation of diestrous phase of the cycle, resulting in delayed copulation, low copulation index, and significantly increased number of corpora lutea in the ovary. There were no teratogenic or other noteworthy effects in rats. In rabbits, abortions and fetal growth abnormalities were observed, including decreased fetal body weight, and increased incidence of fetuses with external abnormalities and skeletal variations. These effects have been previously observed with asenapine and there are no new findings with this formulation.

The Applicant was granted a waiver for dermal-, systemic- and photo-carcinogenicity studies for the HP-3070 formulation by the Division, based on the nonclinical safety findings for the LD (Saphris), lack of genotoxic and phototoxicity potential and the systemic and dermal safety profile of HP-3070.

In summary, studies using the HP-3070 transdermal patch provided adequate systemic and local safety margins for the maximum recommended human dose (MRHD) of (b) (4) day asenapine (b) (4) (b) (4) mg/day asenapine) proposed in the label. The transdermal route of administration did not identify any new toxicities of concern relative to the sublingual route. Excipients were tested at higher or similar levels to humans and no new target organs of toxicity were identified and no new toxicities observed. The HP-3070 patch did not elicit any novel systemic safety concerns compared to the listed drug and demonstrated an acceptable dermal safety profile for chronic use in humans.

5.2. Referenced NDAs, BLAs, DMFs

NDA 22117 (Saphris; asenapine (b) (4) sublingual formulation)

5.3. Pharmacology

Pharmacology and safety pharmacology studies were performed with the API (asenapine (b) (4) and with HP-3070 patch to support the change in route of administration of asenapine (b) (4) from sublingual (listed drug Saphris NDA# 022117) to transdermal (HP-3070).

Primary Pharmacology

The pharmacological activity of asenapine (b) (4) was tested in vitro and in vivo (subcutaneous) in animal models of hyperactivity and convulsions.

In vitro receptor binding study of human receptor-expressing cell monolayers (Study # AL-5829-G) demonstrated that asenapine (b) (4) has antagonistic activity with high affinity for a number of the serotonin family receptors: 5HT1A, 5HT1B, 5HT2A (highest), 5HT2B, 5HT2C, 5HT5A, 5HT6, and 5HT7 (Ki mean values of 2.24, 5.57, 0.026, 0.129, 0.057, 5.26, 0.40, and 0.22 nM, respectively); the dopamine receptors: D1, D2 short, D2 long, D3(highest), and D4 (Ki mean

values of 4.92, 2.40, 1.29, 0.39, and 1.03 nM, respectively); adrenaline receptors: α 1A, α 2A, α 2B (highest), and α 2C (Ki mean values of 1.17, 2.06, 0.13, and 2.98 nM, respectively), and histamine H1 (high) and H2 receptors (Ki mean values of 0.50 and 4.66 nM, respectively). Asenapine (b) (4) has weak affinity for muscarinic acetylcholine receptors (M1, M2, M3, and M4) with Ki values in the range of 8.3 to 41.8 μ M.

In vivo, the anti-dopaminergic and anti-serotonergic effects were confirmed in models of hyperactivity and convulsions in rats upon subcutaneous administration of asenapine (b) (4). In a rat model of methamphetamine hydrochloride-induced hyperactivity (Study # P130644) asenapine (b) (4) at subcutaneous doses of 0.1 and 0.3 mg/kg exhibited anti-dopaminergic effect by protecting rats from methamphetamine-induced hyperactivity, as shown by a significant decrease of spontaneous locomotor activity vs. vehicle. The median effective dose (ED50) for protection from hyperactivity was 0.187 mg/kg. In a tryptamine-induced convulsion model in rats (Study # P130645), asenapine (b) (4) demonstrated anti-serotonergic effect by significantly inhibiting tryptamine-induced convulsions at subcutaneous doses from 0.03 to 0.3 mg/kg. The ED50 value for the convulsion inhibitory effect was 0.026 mg/kg.

Safety Pharmacology

Safety pharmacology studies included evaluation of the effects of subcutaneous asenapine (b) (4) on CNS and respiratory functions in rats, and of transdermal HP-3070 administration on cardiovascular function in conscious dogs. Asenapine (b) (4) at subcutaneous doses of up to 0.1 mg/kg did not affect neurological or pulmonary functions in rats. HP-3070 transdermal application in dogs had no effect on heart rate at doses of up to 18 mg, on blood pressure at doses up to 54 mg, nor on QTc up to the highest tested dose of 180 mg. There were no unexpected effects on the CNS, respiratory and cardiovascular systems, which is consistent with those reported with LD Saphris (NDA# 022117). These key findings are discussed in more detail below:

- Central Nervous System (Study # P130550): Asenapine (b) (4) subcutaneous administration to male Crl:CD(SD) rats (n=6/group) at doses of 0.03, 0.1, 0.3, and 1 mg/kg had no effect on the CNS up to 0.1 mg/kg. Hypoactivity occurred at 0.3 and 1 mg/kg in 3 of 6 animals/ group. Additionally, at 1 mg/kg, hyporeflexia, catalepsy, miosis, and half-opened eyes were observed for up to 6 h after administration in 3 of 6 HD animals. These are expected effects, associated with the pharmacological effect of asenapine.
- Cardiovascular System:
 - o hERG assay (Study P130555): Asenapine (b) (4) had no effect on hERG channel current in vitro, at concentrations of up to 100 nM. At 300 and 1000 nM, there was a decrease in relative hERG current vs. vehicle control, with inhibition of 10.7% and 39.9% at 300 and 1000 nM, respectively.
 - o Safety Pharmacology Study of HP-3070 on Cardiovascular System in Dogs (Study # P130554): HP-3070 percutaneous administration to conscious male beagle dogs

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(n=4/group) at doses of 5.4, 18, 54, and 180 mg/dog had no effects on blood pressure, heart rate, and standard ECG at doses of up to 18 mg, and there were no statistically significant differences in QTc at any of the treatment doses vs. control. Significant increases in heart rate were observed after administration of 54 and 180 mg HP-3070 and expected decreases in the systolic blood pressure occurred after the highest dose (statistically significant). There were no statistically significant differences in QTc in any of the treatment groups.

- Respiratory System (Study #P1130551): Asenapine (b) (4) subcutaneous administration to male Crl:CD(SD) rats (n=6/group) at doses of 0.03, 0.1, 0.3, and 1 mg/kg caused increase in respiratory rate at 0.3 and 1 mg/kg; there were no significant changes in respiratory rate at 0.03 and 0.1 mg/kg, nor changes in tidal volume in any of the dose groups.

Pharmtox Reviewer Comments:

The lowest effective dose in the safety pharmacology studies of CNS and respiratory system in rats was 0.3 mg/kg; this dose is 3- to 10-fold higher than the minimal doses effective for ameliorating methamphetamine hydrochloride-induced hyperactivity and tryptamine-induced convulsions in rats (0.1 mg/kg and 0.03 mg/kg, respectively). The lowest effective dose in the safety pharmacology study of HP-3070 on the cardiovascular system in dogs was 54 mg; at this dose, the plasma concentration (C_{max}) of asenapine (10.1 ng/mL) is 2.2-fold higher than the C_{max} for asenapine in humans (4.68 ng/mL) at the highest proposed transdermal dose of HP-3070 in humans ((b) (4) mg/day). These results support the safety of pharmacologically effective doses of asenapine (b) (4) administered subcutaneous and percutaneously.

A comparison between asenapine plasma levels in clinical and safety pharmacology studies is shown in the following Applicant's table.

Table 1: Comparison of Asenapine Levels from Clinical and Safety Pharmacology Studies

Clinical studies					
Study ID	Test System	Method of Administration	Dose	C _{max} (ng/mL)	Ratio ^a
HP-3070-US-02b Noven PK Study ^b	Human	Percutaneous	(b) (4) mg/day	4.68 ^c (0.14) ^d	1
A7501001 Saphris Study Chapel et al 2009	Human	Sublingual	10 mg BID	6.56	1.4
Safety pharmacology studies					
Organ Systems Evaluated	Test System	Method of Administration	Minimum Effective Dose or Concentration	C _{max} or Concentration (ng/mL)	Ratio ^a
Central Nervous System	Rats	Subcutaneous	0.3 mg/kg	14.4 ^e	3.1
Respiratory System	Rats	Subcutaneous	0.3 mg/kg	14.4 ^e	3.1
Cardiovascular System	Dogs	Percutaneous	54 mg/body	10.1 ^h	2.2

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Source: NDA 212268, Section 2.6.2. Pharmacology Written Summary, Table 1, p. 13.

^a Ratio = C_{max} or concentration in safety pharmacology or clinical studies / HP-3070 maximum dose C_{max} in schizophrenia patients (HP-3070-US-02b study). ^b Study was conducted by Noven Pharmaceuticals (Noven), the US subsidiary of Hisamitsu:Chapel S, Hutmacher MM, Haig G, Bockbrader H, et al. Exposure-response analysis in patients with schizophrenia to assess the effect of asenapine on QTc prolongation. J Clin Pharmacol. (2009) 49(11): 1297-308; ^c Mean C_{max,ss} was obtained at the maximum dose of HP-3070, 18 mg/day, in HP-3070-US-02b study. ^d Calculated from the plasma protein binding in human (97.0%; B130837) as the free (unbound) drug. ^e Pharmacokinetics study of asenapine following subcutaneous administration in rats (P130552). ^h Pharmacokinetics study of HP-3070 following percutaneous administration in dogs (P130556). C_{max} data was calculated based on 180 mg/body because the minimum effective dose (54 mg/body) was not evaluated in this study

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Single Dose Studies	
Rat	
PK study of single percutaneous administration of [¹⁴ C] HP-3070 patch to albino and pigmented rats (<i>Study B140529</i>)	Single dose of 3.5 mg/kg for 24 h: T_{max} :24.7 h; C_{max} : 213 and 251 ng eq./mL for albino and pigmented rats, respectively; AUC_{0-inf} : 11700 and 11200 ng eq.·h/mL, respectively. T_{1/2} after patch removal:72h. No PK differences between albino and pigmented rats for normal skin; C _{max} and AUC _{0-inf} . higher upon administration to injured skin vs. normal skin in albino rats.
Dog	
PK study on HP-3070 following percutaneous administration in dogs (<i>Study P130556</i>)	Single doses of 0.5, 1.6, and 15.9 mg/kg for 24 h: T_{max} : 12, 13 and 21 h, respectively C_{max} : 1.4, 4.4, and 33.5 ng eq./mL at LD, MD and HD, respectively; AUC_{0-inf} :29.7, 97.5 and 749 ng eq.·h/mL, respectively. T_{1/2} after patch removal: 5, 7 and 12 h, respectively.
Repeat-dose studies	See below, under TK data from general toxicology studies
Distribution	Tissue distribution of asenapine was evaluated <i>in vivo</i> in rat, and <i>in vitro</i> plasma protein binding in mouse, rat, dog, rabbit, minipig, and human.
PK study of single percutaneous administration of [¹⁴ C] HP-3070 patch to albino and pigmented rats (<i>Study B140529</i>)	After percutaneous administration of [¹⁴ C] asenapine to albino rats, radioactivity was distributed to most of the tissues and was eliminated more slowly from tissues vs. plasma. Radioactivity in all tissues peaked at 24 h post-dose. For brain tissue, the peak was more rapid, with a plateau reached at 4 h after application and radioactivity was maintained until patch removal at 24 h. Metabolite distribution: asenapine and N-desmethyiasenapine present in brain, liver, and kidney; N-desmethyiasenapine-N-carbamoyl glucuronide present in kidney. Metabolite distribution in the brain at 4, 24, and 48 h post-dose showed asenapine largest peak at 4 h post-dose (69.5% as a composition ratio); then it decreased time-dependently (47.4% at 24 h and 7.5% at 48 h). In contrast, the composition ratio of N-desmethyl-asenapine in the brain increased time-dependently (4.6%, 28.6%, and 37.8% at 4, 24 and 48 h., respectively). In pigmented skin, the radioactivity was approximately 6-fold higher at 24 h and 30-fold higher at 48 h. compared to non-pigmented. Radioactivity in the eyeball of pigmented rats was considerably higher than in albino rats.
Protein binding study of [³ H]asenapine ^{(b) (4)} (<i>Study B130837</i>)	The protein binding of [³ H]asenapine was high in rat, dog and human plasma, with dog protein binding similar to human and rat slightly lower. The protein binding ratios of [³ H]asenapine (at concentrations of 5, 50, and 500 ng/mL as [³ H]asenapine) were 93.4%, 93.2%, and 93.7% in rat plasma and 97.2%, 97.1%, and 97.2% in dog plasma, respectively. In human plasma, the protein binding ratios of [³ H]asenapine (at 1, 10, and 100 ng/mL) were 96.7%, 96.7%, and 97.0%, respectively.
Protein binding study of [³ H]asenapine ^{(b) (4)} 2	The protein binding of [³ H]asenapine was high in mouse, rabbit, and minipig plasma, with mouse similar to rabbit plasma protein binding and minipig slightly lower. The

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Type of Study	Major Findings														
<i>(Study B140175)</i>	protein binding ratios of [³ H]asenapine (at concentrations of 5, 50, and 500 ng/mL as [³ H]asenapine) were 96.9%, 96.7%, and 97.2% in mouse, 98.1%, 97.7%, and 98.1% in rabbit, and 92.9%, 93.7%, and 92.6% in minipig plasma, respectively.														
Metabolism	The metabolism of asenapine was evaluated in vivo in rat, and in vitro in mouse, rat, rabbit, dog, minipig, and human hepatocytes, liver and skin microsomes.														
In vitro metabolism study of [¹⁴ C]asenapine (Study B130834)	In liver microsomes, [¹⁴C]asenapine was metabolized most extensively in dogs followed by rats, but it was not metabolized as much in humans. M3 and M5 were detected mainly in rats and dogs, while M3 was detected mainly in humans; M4 was not evident in humans. <u>The metabolites detected in humans were also detected in rats and dogs.</u> In hepatocytes, [¹⁴C]asenapine was metabolized most extensively in dogs followed by rats and humans. M3 was detected mainly in rat and dog hepatocytes, M4 was detected only in dog hepatocytes, and M1 and M2 were detected only in human hepatocytes. M1, M3, and M5 were identified as asenapine N⁺-glucuronide, N-desmethylenapine, and asenapine N-oxide, respectively. M2 and M4 were asenapine monooxide and N-desmethyl-asenapine-N-carbamoyl glucuronide, respectively. The structure of M6 remained unidentified. The identified metabolites are listed in the following Applicant's table: <table border="1" data-bbox="607 852 1464 1045"> <thead> <tr> <th>Metabolite number</th> <th>Identity</th> </tr> </thead> <tbody> <tr> <td>M1</td> <td>Asenapine N⁺-glucuronide</td> </tr> <tr> <td>M2</td> <td>Asenapine+O</td> </tr> <tr> <td>M3</td> <td>N-Desmethylenapine</td> </tr> <tr> <td>M4</td> <td>N-Desmethylenapine-N-carbamoyl glucuronide</td> </tr> <tr> <td>M5</td> <td>Asenapine N- oxide</td> </tr> <tr> <td>M6</td> <td>Unknown</td> </tr> </tbody> </table>	Metabolite number	Identity	M1	Asenapine N ⁺ -glucuronide	M2	Asenapine+O	M3	N-Desmethylenapine	M4	N-Desmethylenapine-N-carbamoyl glucuronide	M5	Asenapine N- oxide	M6	Unknown
Metabolite number	Identity														
M1	Asenapine N ⁺ -glucuronide														
M2	Asenapine+O														
M3	N-Desmethylenapine														
M4	N-Desmethylenapine-N-carbamoyl glucuronide														
M5	Asenapine N- oxide														
M6	Unknown														
In vitro metabolism study of [¹⁴ C] asenapine (b) (4) (no. 2) (Study B140173)	This study examined oxidative metabolism and glucuronidation of [¹⁴ C]asenapine in mouse, rabbit, and minipig liver microsomes and hepatocytes. Oxidative metabolism in liver microsomes was most extensive in minipigs, followed by rabbits and mice. M3 and M5 were the main metabolites detected in mice and rabbits, while M5 was the main metabolite detected in minipigs. Glucuronidation (conjugation of [¹⁴ C]asenapine with glucuronic acid in liver microsomes), resulting in M1 metabolite, was higher in rabbits followed by minipigs; in mice, asenapine was not conjugated with glucuronic acid. In hepatocytes, [¹⁴ C]asenapine was metabolized most extensively in rabbits, followed by minipigs and mice. The main metabolites were M3 in rabbits; M3 and M4 in mice, and M5 in minipigs.														
In vivo PK study of single percutaneous administration of [¹⁴ C] HP-3070 patch to albino and pigmented rats (Study B140529)	The metabolites present in plasma, urine, feces, bile, brain, liver, and kidney were determined. The major metabolites identified were the same as those identified in the in vitro studies. The proportion of these metabolites in urine, feces, and bile suggest that the important metabolic routes were N-oxidation of asenapine for urinary excretion and N-desmethylation of asenapine followed by N-carbamoyl glucuronidation for biliary and fecal excretion. The N-oxide and N-desmethyl form (including the N-carbamoyl glucuronide) were metabolized further to more polar metabolites.														
Identification of enzymes involved in metabolism of [¹⁴ C] asenapine (Study B140411)	This additional in vitro study with recombinant human enzymes and human liver microsomes identified the human enzymes responsible for the metabolism of asenapine. The formation of asenapine monooxide (M2) and of the unidentified metabolite (M6) was mainly by CYP1A2. N-desmethyl asenapine (M3) was also formed mainly by CYP1A2, although other enzymes such as CYP2C19, CYP2D6, and CYP3A4/5 were also involved. M5 formation in human liver microsomes was very low and was not inhibited remarkably by any CYP inhibitors.														

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transdermal system

Type of Study	Major Findings
Excretion	
PK study of single percutaneous administration of [¹⁴ C] HP-3070 patch to albino and pigmented rats (<i>Study B140529</i>)	Following percutaneous administration of [¹⁴ C] HP-3070 patch in rats, the absorbed radioactivity was excreted mainly via bile into the gastrointestinal tract with some excretion in urine. The cumulative radioactivity excretion in urine and feces by 168 h. post-dose was 13.8% and 49.3% of the dosed radioactivity, respectively, and the total recovery was 99.3% of the dosed radioactivity (with no remarkable sex differences, or differences between albino and pigmented rats).
TK data from general toxicology studies	
Rat	
A 2-week repeated dose percutaneous toxicity study of HP-3070 patch in rats (<i>Study B-7471</i>)	Doses: 2.8, 8.4, and 25.2 mg/kg/day for 2 wks. Tmax : 2 to 8 h. Cmax and AUC _{0-24h} increased dose-proportionally. No accumulation with repeat administration. Cmax : Day 1: 21, 53, 208 ng/mL; Day 14: 21, 63, 180 ng/mL; AUC_{0-24h} : Day 1: 284, 856, 3360 ng·h/mL; Day 14: 283, 899, 2550 ng·h/mL, at LD, MD and HD respectively.
A 13-week repeated dose percutaneous toxicity study of HP-3070 patch in rats (<i>Study B-7552</i>)	Doses: 2, 4, and 6 mg/kg/day for 13 wks. Tmax : 4 to 7 h. Cmax and AUC _{0-24h} increased dose-proportionally. No accumulation with repeat administration. Cmax : Day 1: 15, 30, 36 ng/mL; Wk. 13: 27, 54, 76 ng/mL; AUC_{0-24h} : Day 1: 201, 404, 498 ng·h/mL; Wk. 13: 374, 727, 1060 ng·h/mL, at LD, MD and HD respectively.
A 26-week repeated dose percutaneous toxicity study of HP-3070 in rats with a recovery period of 6 weeks (<i>Study B-7755</i>)	Doses: 0.72, 1.2, and 2 mg/kg/day for 26 wks. Tmax : 3-8 h for asenapine and 8-12 h for active metabolite N-desmethyl asenapine. Cmax and AUC _{0-24h} dose-proportional. No accumulation with repeat administration; plasma exposure for both asenapine and active metabolite reached a plateau by week 13 with no further increase at week 26. Cmax asenapine: Day 1: 5.7, 11, 17 ng/mL; Wk 13: 9.9, 18, 28 ng/mL; Wk 26: 9, 18.7, 25 ng/mL; AUC_{0-24h} asenapine: Day 1: 74, 150, 231 ng·h/mL; Wk 13: 156, 269, 407 ng·h/mL; Wk 26: 144, 273, 405 ng·h/mL at LD, MD and HD respectively. T1/2 total active moiety: 12, 13 and 9 h, at LD, MD and HD respectively. T1/2 asenapine: 2.6 - 5.8 h; T1/2 N-desmethyl-asenapine: 8.7-13 h.
Dog	
A 2-week repeated dose percutaneous toxicity study of HP-3070 patch in Beagle dogs (<i>Study B-7204</i>)	Doses: 0.8, 3.1, and 12.3 mg/kg/day for 2 wks. Tmax : Day 1: 24 h; Day 7 and Day 14: 4-5 h. Cmax and AUC _{0-24h} on Day 14 dose-proportional. No accumulation with repeat administration. Cmax asenapine: Day 1: 2.2, 8.7, 10.8 ng/mL; Day 7: 9.2; 26.5, 32 ng/mL; Day 14: 8.8, 24.7, 86 ng/mL; AUC_{0-24h} : Day 1: 27.5, 128, 109 ng·h/mL; Day 7: 146, 439, 636 ng·h/mL; Day 14: 147, 442, 1740 ng·h/mL at LD, MD and HD respectively.
A 13-week repeated dose percutaneous toxicity study of HP-3070 patch in Beagle dogs (<i>Study B 7551</i>)	Doses: 0.86, 2.6, and 7.9 mg/kg/day for 13 wks. Tmax : Day 1: 24 h; Days 28 and 91: 4-8 h. Cmax and AUC _{0-24h} generally increased dose-proportionally. No accumulation with repeat administration. Cmax asenapine: Day 1: 2.1, 4.9, 7.5 ng/mL; Day 28: 11.6, 21, 94 ng/mL; Day 91: 9.2, 18, 54 ng/mL; AUC_{0-24h} : Day 1: 29, 70, 91 ng·h/mL; Day 28: 154, 374, 1120 ng·h/mL; Day 91: 107, 503, 1010 ng·h/mL at LD, MD and HD respectively.
Minipig	
A 4-week repeated dose dermal toxicity study of HP-3070 patch in Gottingen Minipigs (<i>Study 967-030</i>)	Doses: 0.6, 1.8 and 5.4 mg/kg/day for 4 wks. Tmax : Day 1: 13- 24 h; Days 14 and 28: 4-11 h. Cmax and AUC _{0-24h} increased less than dose-proportionally. No accumulation with repeat administration. Cmax asenapine: Day 1: 0.6, 0.7, 2.4 ng/mL; Day 14: 4.4, 14.5, 19 ng/mL; Day 28: 3.9, 14, 16 ng/mL; AUC_{0-24h} : Day 1: 7, 7, 23ng·h/mL; Day 14: 84, 264, 363 ng·h/mL; Day 28: 77, 286, 362 ng·h/mL at LD, MD and HD respectively.

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Type of Study	Major Findings
A 39-week repeated dose dermal toxicity study of HP-3070 patch in Gottingen minipigs with a 4-week recovery period (Study 967-029)	Doses: 0.6, 1.8 and 5.4 mg/kg/day for 39 wks. Tmax : Day 1: 8- 24 h; Days 92 and 182: 8-18 h; Day 273: 12 h. Cmax and AUC _{0-24h} increased less than dose-proportionally. No accumulation with repeat administration. Although the doses were the same as in the 4-wk study, the plasma exposure values in the 39-wk are much lower than those in 4 wk study (potential induction with longer dosing duration). Cmax asenapine: Day 1: 0.1, 0.1, 0.17 ng/mL; Day 92: 1.9, 3.4, 4.4 ng/mL; Day 182: 0.9, 1.2, 4.4 ng/mL; Day 273: 0.9, 1.2, 4.5 ng/mL; AUC_{0-24h} : Day 1: 6, 3.5, 5.2 ng·h/mL; Day 92: 52, 61, 76 ng·h/mL; Day 182: 19, 21, 85 ng·h/mL; Day 273: 16, 22, 79 ng·h/mL at LD, MD and HD respectively. T1/2 asenapine: 21 - 29 h
TK data from reproductive toxicology studies	
Rat	
Preliminary study for effects of percutaneous administration of HP-3070 patch on embryo-fetal development in rats (Study C-R175)	Doses: 1.8, 3.6, and 7.2 mg/kg to pregnant rats, from GD 7 to GD 17. Cmax : GD7: 15, 17, 55 ng/mL; GD 17: 12, 24, 47 ng/mL; AUC_{0-24h} : GD 7: 204, 292, 892 ng·h/mL; GD 17: 170, 342, 683 ng·h/mL, at LD, MD and HD respectively. Cmax and AUC _{0-24h} increased with dose. No accumulation with repeat administration.
Study for effects of percutaneous administration of HP-3070 patch on embryo-fetal development in rats (Study R-1141)	Doses: 0.9, 1.8 and 3.6 mg/kg to pregnant rats, from GD 7 to GD 17. Cmax : GD7: 8, 14, 28 ng/mL; GD 17: 6, 12, 30 ng/mL; AUC_{0-24h} : GD 7: 123, 207, 434 ng·h/mL; GD 17: 90, 199, 450 ng·h/mL, at LD, MD and HD respectively. Cmax and AUC _{0-24h} increased dose-proportionally. No accumulation with repeat administration.
Study for effects of percutaneous administration of HP-3070 patch on fertility and early embryonic development to implantation in rats (Study R-1147)	Doses: 0.72, 1.2, and 2 mg/kg to male and female rats for 2 weeks before mating and throughout the mating period (4 weeks in total) for M, and up to GD 7 for F. TK evaluation on Day 1 and Day 14 (the first and last days of the pre-mating period). Tmax : 5-9 h. for asenapine; 9-24 h for N-desmethyiasenapine, in M and F, on both Days 1 and 14. Cmax and AUC _{0-24h} generally increased with dose, no sex differences. No accumulation with repeat administration. Cmax asenapine: Day 1: 8.4, 8.7, 16.3; Day 14: 6.5, 9.8, 16.6 ng/mL; Cmax N-desmethyiasenapine: Day 1: 11, 10, 36; Day 14: 14, 16, 40 ng/mL AUC_{0-24h} : asenapine: Day 1: 133, 150, 280; Day 14: 110, 173, 265 ng·h/mL; AUC _{0-24h} N-desmethyiasenapine: Day 1: 197, 149, 550 ng·h/mL; Day 14: 268, 309, 746 ng·h/mL at LD, MD and HD respectively.
Rabbit	
Study for effects of percutaneous administration of HP-3070 patch on embryo-fetal development in rabbits (Study R-1142)	Doses: 1.5, 3, and 6 mg/kg to pregnant rabbits, from GD 6 to GD 18. TK evaluation on GDs 6 and 18 (the 1st and last days of dosing) Tmax : asenapine 5-12 h; Tmax N-desmethyiasenapine: 9-20 h. Cmax and AUC _{0-24h} increased dose-proportionally. No accumulation with repeat administration. Cmax asenapine: GD6: 17, 28, 70 ng/mL; GD 18: 13, 34, 82 ng/mL; Cmax N-desmethyiasenapine: GD6: 6, 10, 20; GD18: 7, 19, 33 ng/mL AUC_{0-24h} : asenapine: GD6: 259, 481, 1200; GD18: 227, 604, 1290 ng·h/mL AUC _{0-24h} N-desmethyiasenapine: GD6: 93, 164, 316 ng·h/mL; GD18: 131, 354, 604 ng·h/mL, at LD, MD and HD, respectively.

5.5. Toxicology

5.5.1. General Toxicology

HP-3070 patch was evaluated in a series of pivotal repeat-dose toxicology studies via percutaneous administration, including 13- and 26-week studies in rats, a 13-week study in dogs, and a 39-week repeat-dose toxicity study in minipigs. These studies were reviewed by E. Chalecka-Franaszek, PhD, under IND 125707 (SDN 10, review date June 23, 2016, and SDNs 15-19, review date November 9, 2016); a summary of these studies is presented below. No single-dose toxicity studies were conducted with the HP-3070 patch; the Applicant relied [via the 505(b)(2) regulatory pathway] on the single dose toxicity evaluations of asenapine (b) (4) during the development of the listed drug Saphris (Saphris USPI, 2017).

In the 13-week rat study (Study B-7552) with percutaneous administration of HP-3070 patch containing asenapine (b) (4) at 0, 2, 4, and 6 mg/kg/day, the key findings included: erythema at the application site in both sexes at MD and HD; decreased body weight gain in males at all doses; interstitial necrosis in renal papillary in both sexes at all doses. The incidence of the latter finding, reported by the study pathologist as “kidney, necrosis, papillary, interstitial, minimal” was 0/10, 4/10, 4/10, 5/10 in males and 0/10, 2/10, 1/10, 4/10 in females at dose levels of 0, 2, 4, 6 mg/kg/day, respectively. Because of the decreased body weight in males and the interstitial necrosis in the papillary of the kidney observed in both sexes at all dose levels, a NOAEL was not determined (below the lowest tested dose of 2 mg/kg/day) and there was no safety margin for HP-3070 administration to humans at the proposed clinical dose of (b) (4) asenapine/day. Based on these nonclinical data, a full clinical hold was recommended by the reviewer and imposed by the Division (Clinical hold letter of March 23, 2016).

A similar renal histopathology was later found in both control and test article-treated groups in the subsequent 26-week HP-3070 percutaneous study in rats (Study B-7755). Because of the discrepancies in these findings between the 13- and 26-week studies (i.e., renal histopathology present in both control and treated groups of the 26-week study, while only in treated groups in the 13 week study), and in response to the clinical hold, the Applicant requested a peer review of renal histopathology from the 13- and 26-week studies by Dr. John Seely, a renal pathology expert from Experimental Pathology Laboratories, Incorporated. The independent peer review was performed on the kidney slides from all animals in both the 13- and 26- week rat studies. In addition, the second kidney from each animal was sectioned, stained, and microscopically examined for comparison to the original kidney. The results were submitted with the Final Report Amendments 1 and 2 to Study B-7552 (of June 13 and July 20, 2016, respectively), and were reviewed as follows by E. Chalecka-Franaszek, PhD, under IND 125707 SDN 15-19 (review date November 10, 2016):

The peer review consensus diagnosis for the renal papillary change was different than that originally reported in the 13- and 26-week studies. Dr. Seely concluded that “kidney, rarefaction, papillary: bilateral or unilateral (rarefaction - artifactual change)”

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affecting control as well as treated animals was observed in both studies. The revised incidences of renal papillary rarefaction were as follows: for the 13-week study, males: 1, 4, 4, 4; females: 1, 2, 1, 4, and for the 26-week study, males: 5, 4, 5, 9; females: 2, 0, 2, 1 (in control, LD, MD and HD groups, respectively). Based on this new diagnosis, both study reports were amended to include the revised terminology and the incidence of kidney histopathology. According to the Applicant, "the overall conclusion of the changes, as described by Dr. Seely, represents an error in the original interpretation, which resulted in an incorrect diagnosis of necrosis and edema in the 13- and 26- week rat studies, respectively. The diagnosis of rarefaction was agreed upon by the original study pathologist, and a consensus was reached to correct the pathology diagnosis in the amended study reports."

DPP requested a CFSAN Pathology regulatory review of the information that lead to the peer review consensus diagnosis. Dr. Sabine Francke, D.V.M., Ph.D., FIATP and Dr. Steven Mog, D.V.M., DACVP, Senior Science and Policy Staff, CFSAN, reviewed the Applicant's clinical hold response and concluded that, following their teleconference with Dr. John Seely and in conjunction with the photomicrograph review, they concur overall with the conclusion of the peer review pathologist that "the changes described in the 13-week and 26-week rat studies are not test-article (asenapine (b) (4) related, but likely consistent with artifactual postmortem autolysis."

Based on the conclusions of consultative review conducted by CFSAN expert pathologists and overall review of the Clinical Hold Response submitted by the Applicant, the nonclinical reviewer recommended removal of the clinical hold (E. Chalecka-Franaszek, IND 125707 SDN 15-19, review date November 10, 2016). The Division informed the Applicant that the clinical trial may be initiated (Remove Full Clinical Hold letter of July 26, 2016).

In agreement with the Peer Review conclusions, the NOAEL in the 13-week rat study was determined at 4 mg/kg/day for females (based on anemia at the next higher dose of 6 mg/kg/day), and below the lowest tested dose of 2 mg/kg/day for males (based on significant, dose-dependent decrease in body weight and weight gain in males at all tested doses). At the NOAEL for females (4 mg/kg/day), the AUC_{0-24h} for asenapine (free base) in Week 13 was 501 ng•h/mL in females; for males, the NOAEL was below the lowest tested dose of 2 mg/kg/day with asenapine AUC_{0-24h} of 374 ng•h/mL in males in Week 13.

In the 26-week rat study (Study B-7755), HP-3070 patch administered percutaneously at doses of 0, 0.72, 1.2 and 2 mg/kg/day asenapine (b) (4) caused a significant, dose-dependent decrease in body weight and weight gain in males at all doses and a significant *increase* in body weight gain in females at HD. Histopathology changes in both sexes at all doses were attributable to the pharmacological effects of asenapine. As per the peer histopathology review, the previously found renal papillary histopathology in the control and treated groups was re-assessed as artifactual (see above). At the application site, there were reversible increases in the incidence of ulceration, crust formation, inflammatory cell infiltration, and

thickening or thinning of the epidermis in the control- and all dose groups, with higher incidence in the latter. The NOAEL was 1.2 mg/kg for females (because of body weight and liver clinical chemistry changes at next tested higher dose of 2 mg/kg/day); a NOAEL for males was not determined (below the lowest tested dose of 0.72 mg/kg) because of a significant, dose-dependent decrease in body weight and weight gain in males at all doses. At the NOAEL for females, the AUC_{0-24h} was 162 ng·h/mL, and C_{max} was 11.5 ng/mL; for males, the NOAEL was below the lowest tested dose of 0.72 mg/kg/day with asenapine AUC_{0-24h} of 144 ng·h/mL, and C_{max} of 9 ng/mL in males in Week 26.

In the 13-week dog study (Study B-7551), HP-3070 patch administered percutaneously at doses of 0.85, 2.6 and 7.88 mg/kg/day of asenapine (b) (4), there were no dose-dependent findings in the skin at the application site. One HD female was sacrificed moribund due to jaundice-like disorder; however, the relation to the test article-treatment remained unclear since no other animals showed a similar disorder. The NOAEL was 7.88 mg/kg/day in males and 2.6 mg/kg/day in females. At the NOAEL, asenapine AUC_{0-24h} was 1010 ng·h/mL for males and 503 ng·h/mL for females and C_{max} was 54 ng/mL and 26.9 ng/mL, respectively.

In the 39-week minipig study (Study 967-029) with HP-3070 patch administered percutaneously at doses of 0.6, 1.8, or 5.4 mg/kg/day of asenapine (b) (4) there were no treatment-related systemic effects. The only finding was increased severity of erosion/ulceration of the treated skin (mild to moderate) at HD (1 M and 2F). However, the relationship of this finding to HP-3070 is unclear, because erosion/ulceration was also noted, albeit to a lesser degree (minimal), in the control patch group (1 M and 1 F), as well as at MD (1 F) and LD (1 F). Therefore, the NOAEL for local/dermal and systemic toxicity was 5.4 mg/kg/day. At the NOAEL, asenapine AUC_{0-24h} was 78.7 ng·h/mL for males and 104 ng·h/mL for females, and C_{max} was 4.55 ng/mL for males and 5.51 ng/mL for females.

The pivotal general toxicity studies are described in more detail below.

Study title/ number: A 13-week repeated dose percutaneous toxicity study of HP-3070 patch in rats/ Study B-7552 (as reviewed by E. Chalecka-Franaszek, PhD, under IND 125707, review date June 23, 2016).

Administration of HP-3070 patch to rats at transdermal doses of asenapine (b) (4) of 0, 2, 4, 6 mg/kg/day for 13 weeks resulted in the following key findings:

- Significantly decreased body weight and weight gain in males at all doses during the administration period;
- Hematology changes: Significant decreases in red blood cell count, hemoglobin, and hematocrit and increase in mean corpuscular hemoglobin in females at HD; significant, dose-dependent decreases in WBC, lymphocyte count and ratio, monocyte count and ratio in males at all doses.

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- NOAEL: Males: Not determined (below the lowest tested dose of 2 mg/kg/day) because of significant, dose-related decreases in body weight and in body weight gain at all tested doses. Females: 4 mg/kg/day because of anemia at the next higher dose of 6 mg/kg/day. Asenapine AUC₀₋₂₄ at female NOAEL: 501ng.h/mL.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 4, 6 mg/kg/day asenapine (b) (4), once a day for 13 wks.

Route of administration: Transdermal

Formulation/Vehicle: HP-3070 patch formulation/ HP-3070 placebo patch

Species/Strain: Rat/Sprague-Dawley SPF CrI:CD(SD)

Number/Sex/Group: 10

Age: 6 weeks

Satellite groups/ unique design: TK: 4 animals/group/
Plasma concentrations of asenapine (free base) determined on Day 1 and in Weeks 4 and 13

Deviation from study protocol: No

Observations and Results: changes from control

Mortality	None
Clinical Signs	Erythema at the application site at HD (6 M, 6 F) and MD (2 M, 3 F)
Body Weights	Statistically significant decreases in body weight and weight gain at all doses in males (by -29, -32 and -52% at LD, MD and HD, respectively) and in females (by -9% at HD only).
Ophthalmoscopy	No drug-related findings
Hematology	Statistically significant decreases in red blood cell count (by -14%), hemoglobin (by -10%), and hematocrit (by -11%) and increase in mean corpuscular hemoglobin (by 5%) in females at HD; Statistically significant, dose-dependent decreases in WBC (up to -48%), lymphocyte count and ratio (up to -58%), monocyte count and ratio (up to -50%) in males at all doses.
Clinical Chemistry	Males: Statistically significant increase in ALT by 36% in HDM and decrease in triglycerides by up to -50% in MDM and HDM. Females: Statistically significant decreases in: total cholesterol (by -31%), phospholipids (by -30%), albumin (by -8%), and A/G ratio (by -15%) in MDF and HDF.

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Urinalysis	Males: Statistically significant, dose-dependent decrease in urine volume (by up to -53%), increase in urinary osmotic pressure (by up to 53%) at all doses; HDM only: decrease in water consumption, urinary excretion of sodium, potassium, and chloride by -31, -24 and -29%, respectively. Females: No change
Gross Pathology	Females: Increased incidence of dark red foci in the glandular stomach at HD (this finding was considered stress-related).
Organ Weights	Statistically significant increases in adrenal relative weights at HD (by 50% in M and 21% in F) and at MD (by 21%, males only)
Histopathology Adequate battery: Yes	Findings related to pharmacologic activity of asenapine in both sexes at all doses: in pituitary, mammary gland, ovary, uterus, vagina; Stress-related changes in: adrenals at all doses, both sexes; stomach in females at MD and HD; thymus in males at MD and in both sexes at HD; Extramedullary hematopoiesis in liver and spleen in females at HD (secondary to anemia in HDF); Application site: In both sexes at all doses: increased incidence of cell infiltration of dermis, epidermis and/or subcutaneous; thickening of epidermis, ulcer and/or increased incidence of crust formation. The severity of these changes was minimal to mild.

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

(-): indicates reduction in parameters compared to control.

Study title/ number: A 26-week repeated dose percutaneous toxicity study of HP-3070 patch in rats with a recovery period of 6 weeks. Study B-7755 (as reviewed by E. Chalecka-Franaszek, Ph.D., under IND 125707, review date November 9, 2016)

Administration of HP-3070 patch to rats at transdermal doses of asenapine ^{(b) (4)} of 0.72, 1.2, and 2 mg/kg/day for 26 weeks resulted in the following key findings:

- Significant, dose-related decrease in mean body weight and body weight gain in males at all tested dose levels at the end of the administration period; significant increase in body weight gain and food consumption in females at the high dose (HD, 2 mg/kg/day). Hematology changes in males at HD: significant decrease in WBC, lymphocyte, basophil, and monocyte counts at the end of administration with partial recovery.
- Reversible increase in the incidence of ulceration, crust formation, inflammatory cell infiltration, and thickening or thinning of epidermis at patch application site, all dose levels.
- Reversible histopathology changes in mammary gland, ovary, uterus, and vagina at all doses, related to pharmacologic activity of asenapine (increase in prolactin due to the antagonism of asenapine at the dopamine D2 receptors; these changes are a known class effect for atypical antipsychotics).

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- NOAEL males: not determined (lower than the LD of 0.72 mg/kg) due to suppressed body weight and weight gain at all doses. NOAEL females: 1.2 mg/kg (because of body weight and liver clinical chemistry changes at the next tested higher dose of 2 mg/kg/day). Asenapine AUC₀₋₂₄ at female NOAEL: 162 ng•h/mL.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0.72, 1.2, and 2 mg/kg/day asenapine (b) (4) once a day (exposure for 19-26 h) for 26 weeks

Route of administration: Transdermal

Formulation/Vehicle: HP-3070 patch formulation/ HP-3070 placebo patch

Species/Strain: Rat/Sprague-Dawley strain SPF CrI:CD(SD)

Number/Sex/Group: 14

Age: 6 weeks

Satellite groups/ unique design: TK (5-6 animals/sex/group);
Recovery (6 weeks): 6 additional animals/sex/group in control, MD and HD

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Mortality	One control male and one LD female died on Days 14 and 37, respectively; cause of death not determined, however, these deaths appear to be incidental since they were not dose-related.
Clinical Signs	No
Body Weights	Males: Statistically significant decreases in body weight (- 12, 16, and 26%) and weight gain (- 17, 24, 38%) at LD, MD and HD, respectively. Females: Stat. significant increase in body weight at HD (by 12%)
Ophthalmoscopy	No test article-related findings
Hematology	Males: Decrease in WBC (-35%), lymphocyte (-43%), basophil (-50%), and monocyte (-45%) counts at HD only (WBC and Ly recovered by the end of recovery period)
Clinical Chemistry	Females: Increased ALP (by 37%) at HD; Decreased: total cholesterol (up to -23%), phospholipids (-23%), albumin (-15%) and total protein (-6%), at MD and HD (but without drug-related liver histopathology) Males: Decreased triglycerides (-52%) and blood glucose (-18%) at HD.
Urinalysis <i>[delete the row if not evaluated]</i>	Males: Decreased urine volume (-47%), urinary excretion of K (-24%) and Cl (-19%), and increased incidence of positive protein (4/20 and 5/20) at MD and HD, respectively, vs. 0/20 in control; Females: Increased incidence of positive protein (4/20 and 6/20) and positive ketones (3/20 and 5/20) at MD and HD, respectively, vs. 0/20 in control.

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Gross Pathology
Organ Weights

No test article-related findings
Increased absolute and relative weight of ovary at MD and HD by up to 21 and 32%, respectively; decreased uterine weight at all doses (-22%, 31% and 40%, at LD, MD and HD, respectively).

Histopathology

Adequate battery: Yes

Application site: Increased incidence of cell infiltration in subcutis; ulcer, crust formation and/or cell infiltration in dermis in both sexes at all doses; increased incidence of thickening of epidermis in males at all doses. These changes were also observed in control males and females however, the incidence was higher in dosed groups. They were attributed to skin damage/irritation by application and removal of the patch.
Drug pharmacology-related effects in pituitary, mammary gland, ovary, uterus, vagina, as follows:
Pituitary: focal hyperplasia of pars distalis in one HD male;
Mammary gland: acinar atrophy in males at all doses (i.e., feminization in males); increased incidence of lobular hyperplasia in acinar cells in females at all doses.
Ovary: Enlargement of corpus luteum at all doses;
Uterus: Endometrial atrophy at all doses;
Vagina: Mucification and mucosal atrophy at all doses;
These reversible histopathology changes in the mammary gland, ovary, uterus, and vagina at all doses were related to pharmacologic activity of asenapine (increase in prolactin level due to known antagonism of asenapine at the dopamine D2 receptors); Although prolactin was not measured in this study, this is a known class effect for atypical anti-psychotics, based on prolactin measurement for other D2 atypical antipsychotics.

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

(-): indicates reduction in parameters compared to control.

Study title/ number: A 13-week repeated dose percutaneous toxicity study of HP-3070 patch in Beagle dogs / Study B-7551

(as reviewed by E. Chalecka-Franaszek, PhD under IND 125707, review date June 23, 2016)

- Administration of HP-3070 patch to Beagle dogs at transdermal doses of asenapine ^{(b) (4)} of 0.855, 2.61, and 7.88 mg/kg/day for 13 weeks did not cause significant drug related effects.
- The NOAEL of HP-3070 patch is 7.88 and 2.61 mg asenapine ^{(b) (4)} /kg/day in male and female dogs, respectively. At these NOAELs, asenapine AUC_{0-24h} on Day 91 were 1010 ng•h/mL and 503 ng•h/mL for males and females, respectively

Conducting laboratory and location: ^{(b) (4)}

GLP compliance: Yes

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Methods

Dose and frequency of dosing: 0 (control HP-3070 patch without asenapine), 0.855, 2.61, and 7.88 mg/kg/day (as asenapine (b) (4))/ once a day for 13 weeks
Note: Individual application area size was determined based on animal's most recent body weight

Route of administration: Transdermal
Formulation/Vehicle: HP-3070 patch containing asenapine (b) (4) at (b) (4) HP-3070 placebo patch

Species/Strain: Dog/HRA Beagle
Number/Sex/Group: 3
Age: 7 months

Satellite groups/ unique design: None
Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Mortality One HD female sacrificed moribund on Day 66 due to deteriorating condition caused by jaundice (yellowish discoloration of the conjunctiva, oral mucosa, and brownish yellow urine) on or after Day 56, increased urinary and total bilirubin, increased AST, ALT, LDH, ALP, and CPK, and decreased cholesterol in Weeks 8 and/or 10, ataxic gait on Day 66, decreased body weight and food and water consumption on or after Day 48. Gross pathology: yellow discoloration of organs and subcutaneous tissue and black discoloration of the bile. Histopathology: moderate hepatocyte necrosis, mild focal hemorrhage, mild hyperplasia of bile ducts, bile thrombus, and periductal cell infiltration. The possibility that this is HP-3070-related cannot be excluded.

Clinical Signs Except for the moribund sacrificed animal (see above for detail on clinical signs in this animal), there were no treatment-related abnormal clinical signs.

Body Weights Except for the moribund sacrificed animal, there were no treatment-related abnormal changes in body weights.

Ophthalmoscopy No treatment-related abnormal ophthalmological findings
ECG No treatment-related changes
Hematology No treatment-related changes
Clinical Chemistry Except for the moribund sacrificed animal, there were no treatment-related changes in clinical chemistry.

Urinalysis Except for the moribund sacrificed animal, there were no treatment-related abnormal changes in urine analysis

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Gross Pathology	Except for the moribund sacrificed animal, there were no treatment-related changes in gross pathology
Organ Weights	Except for the moribund sacrificed animal, there were no treatment-related changes in organ weights
Histopathology Adequate battery: Yes	Application site: Minimal or mild thickening of the epidermis in almost all animals of both sexes in the test article-treated groups. However, there were no apparent differences in the severity of changes among the groups and a similar finding was also noted in almost all animals of both sexes in the placebo control group. Therefore, the thickening of the epidermis appears to be patch application-related and not API-related. No other treatment-related changes in histopathology, except for those in the moribund sacrificed animal.

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

(-): indicates reduction in parameters compared to control.

Study title/ number: A 39-week repeated dose dermal toxicity study of HP-3070 patch in Gottingen minipigs® with a 4-week recovery period / Study No. 967-029

(as reviewed by E. Chalecka-Franaszek, Ph.D. IND 125707, review date November 9, 2016)

Administration of HP-3070 patch to minipigs at transdermal doses of asenapine (b) (4) of 0, 0.6, 1.8, and 5.4 mg/kg/day for 39 weeks resulted in the following key findings:

- Increased severity of erosion/ulceration of HP-3070 treated skin in 1 of 6 males and 2 of 6 females at the high dose. This finding was of mild to moderate severity, while in the control patch group, only minimal severity of erosion/ulceration was observed;
- The NOAEL for local/dermal and systemic HP-3070 toxicity in minipigs is the high dose of 5.4 mg/kg/day. No MTD was determined in this study.

Reviewer's note: The AUC values for asenapine achieved in minipigs were generally lower than those in humans; they were comparable to those in humans only at the HD of (b) (4) mg/kg/day (the maximal technically feasible dose in minipigs) at the end of the 39-week administration period (mean AUC_{0-24h} for asenapine (free base): 104 and 78.7 ng•h/mL in M and F, respectively, as compared to AUC_{0-24h} of 96.2 ng•h/mL in schizophrenia patients following administration of (b) (4) mg/40 cm² HP-3070 patch in clinical study HP-3070-US-02b).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

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Methods

Dose and frequency of dosing: 0 (sham control), 0 (control HP-3070 patch without asenapine), 0.6, 1.8, and 5.4 mg/kg/day (as asenapine (b) (4)), once a day for 39 weeks
 Note: Individual application area size determined based on each animal’s most recent body weight.

Route of administration: Transdermal

Formulation/Vehicle: HP-3070 patch containing asenapine (b) (4) at (b) (4) / HP-3070 placebo patch

Species/Strain: Gottingen minipigs

Number/Sex/Group: 4

Age: 4 to 4.5 months

Satellite groups/ unique design: Recovery (4 weeks) group (2 additional animals/sex/group in control, MD and HD groups.

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Mortality None

Clinical Signs Increased severity of skin erosion/ulceration following HP-3070 application in 1/6 M and 2/6 F at HD. Erosion/ulceration of lesser degree (minimal) was also seen in control (1 M and 1 F), LD (1 F), and MD (1 F)

Body Weights No HP-3070 patch-related body weight changes

Ophthalmoscopy No abnormal ophthalmoscopic findings

ECG No test article-related abnormal ECG changes

Hematology No test article-related effects

Clinical Chemistry No test article-related effects

Urinalysis No test article-related effects

Gross Pathology No test article-related macroscopic findings

Organ Weights No test article-related changes

Histopathology No preneoplastic findings. Application site findings (e.g., minimal acanthosis, epidermal exudate, hyperkeratosis, edema, and subacute inflammation) were considered as background findings unrelated to HP-3070 administration.

Adequate battery: Yes

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

Table 2: Summary of safety margins in the General toxicology pivotal studies

Study (number) toxicity	Species sex	NOAEL (mg/kg)	AUC ₀₋₂₄ at NOAEL ng•h/mL	Safety Margin (based on AUC in humans*)
Rat 13-week study (B-7552)	Rat M/F	M: <2 F:4	M: <374 F: 501	< 3.9 x 5.2 x
Rat 26-week study (B-7755)	Rat M/F	M: < 0.72 F:1.2	M: <144 F: 162	< 1.5 x 1.7 x

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Dog 13-week study (B-7551)	Dog M/F	M: 7.88 F: 2.61	M:1010 F:503	10.5 x 5.2 x
Minipig 39-week study (967-029)	Minipig M/F	M/F: 5.4	M:78.7 F:104	0.8 x 1.1 x

*AUC for asenapine in humans: 96.2 ng•h/mL in schizophrenia patients at a dose of (b) (4) mg asenapine (b) (4) 88.6 kg/day (0.20 mg/kg/day) in the HP-3070-US-02b study

Source: Nonclinical reviewer (Partially excerpted from NDA 212268, Section 2.6.6. Toxicology Written Summary, Table 28 p. 92)

General toxicology; additional studies: None

5.5.2. **Genetic Toxicology**

Bacterial reverse mutation test and a mouse lymphoma thymidine kinase assay, both conducted with asenapine (b) (4) as the test article, showed no mutagenic or clastogenic potential. A micronucleus test conducted with the HP-3070 patch as the test article showed no clastogenic potential in the bone marrow of rats. The genetic toxicity studies were reviewed by E. Chalecka-Franaszek, Ph.D. under IND 125707, SDN 10, review date June 23, 2016.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: A bacterial reverse mutation test of asenapine (b) (4) / Study T-1298

Key Study Findings:

- Asenapine (b) (4) had no bacterial reverse mutagenic activity (was negative for genotoxicity) under the conditions of this study

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA100, TA1535, TA98, and TA1537 and
Escherichia coli strain WP2 uvrA

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: A mouse lymphoma TK assay of asenapine (b) (4) / Study T-G093

Key Study Findings:

- Asenapine (b) (4) had neither mutagenic nor clastogenic effects in the mouse lymphoma TK assay under the conditions of this study.

GLP compliance: Yes

Test system: Cultured mouse lymphoma cells (L5178Y *tk*+/- clone 3.7.2C)

Study is valid: Yes

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In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: A micronucleus test of HP-3070 patch in rats / Study M-1507

Key Study Findings:

- HP-3070 patch containing asenapine (b) (4) was not clastogenic in the bone marrow of male rats under the conditions of this study

GLP compliance: Yes

Test system: Rat/Crl:CD(SD)SPF

Study is valid: Yes

Other Genetic Toxicity Studies: No

5.5.3. Carcinogenicity

No carcinogenicity studies were performed with HP-3070. A waiver from conducting carcinogenicity studies was granted by the Division on December 19, 2017, indicating that the Applicant has fulfilled the requirements for assessing the potential for systemic and dermal carcinogenicity of HP-3070, based on the results of HP-3070 nonclinical toxicology studies, showing that HP-3070 has no potential for systemic or dermal carcinogenicity, as well as on the carcinogenicity studies of asenapine administered subcutaneously for the listed drug, (Saphris USPI, 2017) as described in Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of the Saphris USPI, 2017.

5.5.4. Reproductive and Developmental Toxicology

The evaluation of reproductive and developmental toxicity of HP-3070 patch is based on the following pivotal studies: a fertility and early embryonic development study in rats (Study R-1147) and embryo-fetal development studies in two animal species: rats (Study R-1141) and rabbits (Study R-1142). These studies were reviewed by E. Chalecka-Franaszek, Ph.D. under IND 125707 (SDN 10, review date June 23, 2016). In the fertility study, inhibition of estrus and prolongation of diestrus phase, resulting in prolongation of the time until copulation, low copulation index, and significantly increased number of corpora lutea in the ovary, were observed in female rats; these effects were likely prolactin-related, although prolactin was not measured in this study. The NOAEL of HP-3070 patch in the fertility study is lower than 0.72 mg/kg/day for fertility and is 0.72 mg/kg/day for general toxicity in males and females.

In the embryo-fetal development study in rabbits, abortions and fetal growth abnormalities were observed, including decreased fetal body weight and increased incidence of fetuses with external abnormalities and skeletal variations, while in rats there were no teratogenic or other noteworthy developmental effects. The NOAELs for HP-3070 effect on embryo/fetal

development are: 0.9 mg/kg/day for maternal toxicity and 1.8 mg/kg/day for embryo-fetal development in rats, and 1.5 mg/kg/day for both maternal and embryo-fetal toxicity in rabbits. These studies are described in more detail below.

Fertility and Early Embryonic Development

Study title/ number: Study for effects of the percutaneous administration of HP-3070 patch on fertility and early embryonic development to implantation in rats/ Study R-1147

Key Study Findings: HP-3070 percutaneous administration at dose levels of 0, 0.72, 1.2, and 2 mg/kg/day asenapine (b) (4) to male and female rats for 2 weeks before mating, during the mating period for a total of 4 weeks in males, and up to gestation day (GD) 7 in females resulted in the following key findings:

- Decreased body weight, body weight gain, and food consumption in both genders at MD and/or HD. NOAEL for general toxicity: 0.72 mg/kg/day for males and females.
- Inhibition of estrus and prolongation of diestrus phase at all doses, causing prolongation of time until copulation and low copulation index; significantly increased number of corpora lutea in the ovary at HD (prolactin-related effects). NOAEL for fertility not determined (below the LD of 0.72 mg/kg/day).
- No effect on fertility index, number of implantations and embryonic mortality, indicating no test article-related effect on early embryonic development.

The AUC_{0-24h} values for asenapine and N-desmethyl asenapine at 0.72 mg/kg/day on Day 14 (last day of administration in the pre-mating period) are: for males, 110 and 267 ng•h/mL, respectively; for females: 99.4 and 257 ng•h/mL, respectively. Combined values of asenapine and N-desmethyl asenapine AUC_{0-24h} are 377 and 356 for males and females, respectively. These values are 3.5 and 3.3 times, respectively, the combined human steady state AUC_{0-24h} value of 109 ng•h/mL (asenapine: 96.2 ng•h/mL + N-desmethyl asenapine: 12.8 ng•hr/mL) in schizophrenia patients at the MRHD of (b) (4) asenapine (b) (4) / b.w. (b) (4) kg/day (0 (b) (4) mg/kg/day) in study HP- 3070-US-02b.

Conducting laboratory and location
GLP compliance:

(b) (4)
Yes

Methods

Dose and frequency of dosing: 0, 0.72, 1.2, and 2 mg/kg/day asenapine (b) (4), once a day
Route of administration: Transdermal
Formulation/Vehicle: HP-3070 patch containing asenapine (b) (4) at (b) (4) (b) (4) HP-3070 placebo patch
Species/Strain: Rat/Sprague-Dawley strain SPF/Crl:CD(SD)
Number/Sex/Group: 20
Satellite groups: TK animals (3/sex /dose group)

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Study design: HP-3070 was applied to M and F for 2 wks before mating, and during the mating period, for a total of 4 weeks in M, and up to GD 7 in F. The size of individual application area was based on animal's most recent body weight.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Mortality	No
Clinical Signs	No
Body Weights	M: BW gain↓ at MD and HD (-143% and -186%); BW↓ at HD (-10%) F: BW gain↓ at MD and HD (-17%) and -61%
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]	Irregular estrous cycle (inhibition of estrus and prolongation of diestrus phase) in F at LD, MD, and HD (9/20, 10/20 and 12/20, respectively, vs. 0/20 in control); low copulation index (no copulation observed in: 9/20, 11/20 and 11/20 F at LD, MD and HD, vs. 2/20 in control). Increased number of ovarian corpora lutea in HDF. Fertility index after mating similar in all groups. No significant differences in implantations and preimplantation loss at any dose.

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

Embryo-Fetal Development

Study title/ number: Study for effects of the percutaneous administration of HP-3070 patch on embryo-fetal development in rats / Study R-1141

Key Study Findings:

HP-3070 percutaneous administration at dose levels of 0, 0.9, 1.8, and 3.6 mg/kg/day asenapine (b) (4) to pregnant rats from gestation day (GD) 7 to GD 17 (the period from implantation until closure of hard palate) resulted in the following key findings:

- Loss of pregnancy due to post-implantation death of all embryos (total resorptions) in 2/20 dams at HD;
- Decrease in maternal body weight and food consumption at MD and HD;
- No significant differences in embryofetal weight, skeletal ossification and incidence of abnormalities between control and treatment groups.
- NOAEL: 0.9 mg/kg/day for maternal toxicity and 1.8 mg/kg/day for embryo-fetal development. The AUC_{0-24h} for asenapine (b) (4) in dams on GD 17 was 90.7 and 199 ng•h/mL at 0.9 mg/kg and 1.8 mg/kg, respectively. These values are 0.9 and 2.1 times,

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respectively, the human steady state AUC_{0-24h} for asenapine (96.2 ng•h/mL) in schizophrenia patients at the MRHD of (b) (4) asenapine (b) (4) b.w. (b) (4) kg/day (b) (4) mg/kg/day) in study HP-3070-US-02b.

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

Methods

Dose and frequency of dosing: 0, 0.9, 1.8 and 3.6 mg/kg/day asenapine (b) (4) to pregnant rats from gestation day (GD) 7 to GD 17
Route of administration: Transdermal
Formulation/Vehicle: HP-3070 patch containing asenapine (b) (4) at (b) (4) HP-3070 placebo patch
Species/Strain: Rat/Sprague-Dawley strain SPF (CrI:CD(SD))
Number/Sex/Group: 20 pregnant females
Satellite groups: TK animals (3 pregnant females/ group)
Study design: Patches were applied to dams daily for 11 days from GD 7 to 17. The size of individual application area was based on animal's body weight on GD 7. All main groups' dams were sacrificed on GD 20; numbers of corpora lutea, live fetuses and embryo-fetal deaths were determined; all live fetuses were weighed, sexed and examined for external abnormalities. Fetuses in control and HD groups were examined for visceral and skeletal abnormalities
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Mortality	No
Clinical Signs	Erythema at application site in 5/19 MD and 10/20 HD dams from GD 12 to GD 19. Erythema resolved by GD 20.
Body Weights	Maternal body weight gain significantly decreased at MD and HD (by 20% and 28%, respectively, vs. controls) from GD 7 to 18, in correlation with decreased food consumption.
Necropsy findings Cesarean Section Data	Increased post-implantation embryo/fetal lethality at HD: 17.2% vs 9.6% in control (including total resorptions of all embryos in 2 HD dams and 1 control dam); No differences in: number of corpora lutea, implantations, pre-implantation loss and number of live fetuses.
Necropsy findings Offspring	No differences between groups in fetal body weight, ossification, external, visceral and skeletal abnormalities.

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

Study title/ number: Study for effects of the percutaneous administration of HP-3070 patch on embryo-fetal development in rabbits / Study R-1142

Key Study Findings

HP-3070 percutaneous administration at dose levels of 0, 1.5, 3 and 6 mg/kg/day asenapine (b) (4) to pregnant rabbits from gestation day (GD) 6 to GD 18 (the period from implantation until closure of hard palate) resulted in the following key findings:

- Decreased maternal body weight and/or body weight gain and food consumption at MD and HD; Decreased spontaneous movements of dams at MD and HD; Erythema at the application site after removal of patches in all dams in all groups, including control;
- Abortions in one MD and three HD dams;
- Decreased fetal body weight and placental weight at MD and HD; Fetal external malformations at HD (open eyelids in 13 fetuses, cleft palate in four fetuses); Increased incidence of fetuses with skeletal variations at HD.
- NOAEL: 1.5 mg/kg/day for maternal toxicity and embryo-fetal development. At the NOAEL, the maternal AUC_{0-24h} for asenapine (b) (4) and N-desmethyl asenapine on GD 18 was 227 and 131 ng•h/mL, respectively (combined: 358 ng•h/mL). These values are 2.4 times and 3.3 times for asenapine and combined, respectively, the human steady state AUC_{0-24h} for asenapine (96.2 ng•h/mL) and combined AUC_{0-24h} for asenapine and N-desmethyl asenapine (109 ng•h/mL) in schizophrenia patients at the MRHD of (b) (4) asenapine (b) (4) / b.w. (b) (4) kg/day (b) (4) mg/kg/day) in study HP-3070-US-02b.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Dose and frequency of dosing:	0, 1.5, 3 and 6 mg/kg/day to pregnant rabbits from gestation day (GD) 6 to GD 18
Route of administration:	Transdermal
Formulation/Vehicle:	HP-3070 patch containing asenapine (b) (4) at (b) (4) (b) (4) HP-3070 placebo patch
Species/Strain:	Rabbit/(b) (4)
Number/Sex/Group:	19 to 21 pregnant females
Satellite groups:	No
Study design:	HP-3070 patch was applied to dorsal or abdominal skin and changed daily by rotation for 13 days from GDs 6 to 18. The size of individual application area was based on animal's body weight on the days of body weight measurement. TK analysis in three animals/ group on GDs 6 and 18. All animals were sacrificed on GD 28; N corpora

lutea, live fetuses and embryo-fetal deaths were determined; all live fetuses were weighed, sexed and examined for external abnormalities. Visceral and skeletal abnormalities and variations were examined in control and HD groups; since increased incidence of skeletal variations was observed at HD, the skeletal specimens for LD and MD groups were also examined.

Deviation from study protocol: No

Observations and Results

Mortality	No test article-related deaths. One death at MD on GD 18 was due to accident.
Clinical Signs	Erythema at application site in all animals in all groups, incl. control, with trend to reversibility in post-administration period. Decrease in spontaneous movement at MD (6 of 19) and HD (13 of 21).
Body Weights	Maternal body weight gain significantly decreased at HD (by 50% vs. control) from GD 6 to 28, in correlation with decreased food consumption.
Necropsy findings: Cesarean Section	Abortions in 1 MD and in 3 HD dams. Significantly decreased placental weight at MD (-15%) and HD (-18%). No significant differences in the numbers of corpora lutea, implantations, pre-implantation loss, live fetuses, nor gross placental abnormalities.
Table Necropsy findings: Offspring	Decreased fetal body weight at MD (-11 %) and HD (-13%); Increased incidence of external abnormalities at HD (in 17 fetuses, incl. open eyelids in 13 fetuses, cleft palate in 3 fetuses, and 1 fetus with cleft palate and hyper-flexed paw) vs. control (2 fetuses with hyper-flexed paw). Increased incidence of skeletal variations at HD (59% vs.37% in control). No significant differences in visceral abnormalities between control and treatment groups.

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

Prenatal and Postnatal Development: No studies

Table 3: Summary of safety margins in reproductive and developmental toxicology studies with transdermal HP-3070

Study (number) toxicity	Species sex	NOAEL (mg/kg)	AUC ₀₋₂₄ at NOAEL ng•h/mL	Safety Margin (based on AUC in humans*)
Rat Fertility and early embryonic development (Study R-1147)	Rat M/F	0.72 (general toxicity in M and F)	M: 110; F: 99.4	M: 1.1 x F: 1 x

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		<0.72 (ND) (fertility and early embryonic development)	<110 (M) <99.4 (F)	ND
Rat Embryo-fetal development (Study R-1141)	Rat Pregnant F	0.9 (dams) 1.8 (embryo-fetal development)	90.7 (dams)	0.9 x 1.8 x
Rabbit Embryo-fetal development (Study R-1142)	Rabbit Pregnant F	1.5 (dams) 1.5 (embryo-fetal development)	227 (dams)	2.4 x 2.4 x

*Safety margin was calculated with steady state AUC_{0-24h} (asenapine: 96.2 ng-hr/mL) in schizophrenia patients at a dose of (b) (4) asenapine (b) (4) / (b) (4) kg/day (b) (4) mg/kg/day) in the HP-3070-US-02b study; ND: not determined; M: male; F: female
Source: Nonclinical reviewer (Partially excerpted from NDA 212268, Section 2.6.6. Toxicology Written Summary, Table 28 p. 92)

5.5.5. Other Toxicology Studies

HP-3070 Local Tolerance

Local tolerance studies of HP-3070 patch included assessments of skin irritation and sensitization, as well as of skin phototoxicity potential. The primary skin irritation, skin sensitization and skin photosensitization were assessed in rabbits, guinea pigs and hairless guinea pigs, respectively. HP-3070 phototoxicity was assessed in vitro, in a photochemical study of asenapine (b) (4) and in EpiDerm phototoxicity test. In these tests, HP-3070 patch (both with and without asenapine) was found to be a mild skin irritant, without skin sensitization, photosensitization, or phototoxic potential. These studies were reviewed by E. Chalecka-Franaszek, Ph.D. under IND 125707 (SDN 10, review date June 23, 2016).

In addition, on 14 July 2017, the Division granted the Applicant a waiver from conducting additional photosafety studies (such as photocarcinogenicity and photoallergenicity), based on adequate supportive evidence provided in IND 125707 (as reviewed by S. Tabacova under IND 125707, SDN 31, review date March 30, 2017).

The key findings of HP-3070 local tolerance studies are described below.

Study title/ number: A primary skin irritation study of HP-3070 patch in rabbits (Study No. I-4099)

Key Study Findings: HP-3070 patch containing asenapine (b) (4) at (b) (4) mg/cm² and HP-3070 control patch (without asenapine), applied to intact and abraded skin of female rabbits for 24 hours, caused very slight to well defined erythema at the application site; the erythema gradually decreased and was no longer observed by Day 4 after application in abraded skin and by Day 5 in intact skin. Therefore, both patches were classified as a mildly irritant under the conditions of this study.

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Study title/ number: A skin sensitization study of HP-3070 patch in guinea pigs (Buehler test) (Study No. I-4100)

Key study findings: HP-3070 patch containing asenapine (b) (4) at (b) (4) mg/cm² and HP-3070 control patch without asenapine, applied to the skin of female white guinea pigs for 24 hours, did not cause erythema, edema, or other skin reactions at any observation point in any animal at the sites of challenge. Therefore, both the HP-3070 patch and the HP-3070 control patch showed no skin sensitization potential.

Study title/ number: Evaluation of sensitization following dermal administration of HP-3070 patch and ultraviolet exposure in guinea pigs (Study No. S13598)

Key study findings: Dermal topical administration of the HP- 3070 patch to hairless guinea pigs co-exposed to ultraviolet UVA & UVB radiation along with visible light caused slight erythema at the test article application site at 1 and 24 h following administration, compared to the negative control patch application site.

Study title/ number: Photochemical study of asenapine (Study No. 150723)

Key study findings: Asenapine (b) (4) (in methanol solution at a concentration of 10.4 mcg/mL) did not absorb light at any wavelength between 290 and 700 nm. The molar extinction coefficient of asenapine (b) (4) was not greater than 1000 L mol⁻¹ cm⁻¹ at any wavelength between 290 and 700 nm.

Study title/ number: Phototoxicity assay using the Epiderm Skin Model Multi-dose assay (Study No. 16A149.050067)

Key study findings: Evaluation of the phototoxicity potential of HP-3070 patch extract on human keratinocytes in the EpiDerm Skin Model (MatTek Corporation, MA, USA) in the presence and absence of UVA/UVB/visible light demonstrated that the test article (HP-3070 extractant) did not show phototoxic effects at any of the tested dilutions. The assay was valid since the positive control induced at least a 30% decrease in tissue viability in the presence of UVA/UVB exposure, compared to the viability in the absence of UVA/UVB exposure.

Evaluation of HP-3070 patch excipients

HP-3070 is a multi-layered patch that contains three consecutive layers:

1. The backing film consists of colorless and translucent polyester film.
2. The adhesive (b) (4) consists of asenapine (b) (4) ((b) (4) styrene-isoprene-styrene block copolymer, polyisobutylene (b) (4), polyisobutylene, alicyclic

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saturated hydrocarbon resin, mineral oil, sodium acetate anhydrous, isopropyl palmitate and butylated hydroxytoluene.

- The release liner consists of a silicon-treated polyester film, and the film is scored to facilitate user removal.

A comprehensive safety evaluation is provided for the HP-3070 excipients, based on the general toxicity and phototoxicity studies with HP-3070 patch and HP-3070 control (placebo) patch without asenapine, as well as on published data and human safety experience [reviewed by E. Chalecka-Franaszek, Ph.D. under IND 125707 (SDN 15-19, review date November 9, 2016) and by S. Tabacova, under IND 125707 (SDN 31, review date March 30, 2017)].

General toxicity assessment of HP-3070 patch excipients

The HP-3070 inactive components are listed in the following Applicant’s table.

Table 4. List of inactive components contained in the HP-3070 transdermal system

Inactive ingredient	Concentration (%)	Amount (mg)	US FDA (IID) Maximum Potency Transdermal	New Inactive ingredient
Styrene- Isoprene- Styrene Block Copolymer	(b) (4)			
Polyisobutylene (b) (4)				
Polyisobutylene				
Alicyclic saturated hydrocarbon resin				
Mineral oil				
Sodium acetate anhydrous				
Isopropyl palmitate				
Butylated hydroxytoluene				

Source: Nonclinical reviewer (Partially excerpted from NDA 212268, Section 2.6.6. Toxicology Written Summary, Table 14, p. 69)

Based on the highest dose patch ((b) (4) asenapine (b) (4)), the majority of the components are within the limits of the FDA IID for transdermal use, are used in FDA approved products and/or have been previously qualified for safe use in toxicity studies. Of the eight excipients present in the HP-3070 patch, one excipient, sodium acetate anhydrous, has been qualified by FDA’s IID for the subcutaneous route of administration but not for transdermal route and one other excipient, alicyclic saturated hydrocarbon resin, is not listed in IID. The remaining six excipients (styrene-isoprene-styrene block copolymer, polyisobutylene (b) (4), polyisobutylene, isopropyl palmitate, mineral oil and butylated hydroxytoluene) are present at levels that are within the limits provided by the FDA IID for topical/transdermal use.

For the two unqualified excipients (sodium acetate anhydrous and alicyclic saturated hydrocarbon resin), safety evaluations, described in more detail below, provided adequate

assessment of the systemic and local toxicity potential supporting the safety of these excipients for chronic dermal administration at the levels present in the HP-3070 patch.

Sodium Acetate Anhydrous:

The HP-3070 patch contains sodium acetate anhydrous (CAS No. 127-09-3) for which the maximum daily dose is 0.210 mg/kg/day (14.72 mg/patch/human/day, human body weight: 70 kg). Sodium acetate anhydrous for the transdermal route of administration is not listed in the IID, but it is listed as a pharmaceutical excipient for intravenous, oral, and subcutaneous administration at potencies up to 17.7%, 177 mg, and 0.16%, respectively. In addition, sodium acetate is a GRAS food substance with an ADI of “Not limited”. The safety of sodium acetate anhydrous in the HP-3070 patch is supported by the toxicity studies conducted by the Applicant using the HP-3070 control (placebo) patch, as well as by published literature data. Repeat-dose toxicity studies of HP-3070 have shown no adverse effects, and local toxicity studies indicate that sodium acetate anhydrous does not cause skin sensitization, skin phototoxicity, skin photo-irritation or skin photosensitization; published literature on toxicity studies with sodium acetate anhydrous have shown it to be of a low systemic and local toxicity, since it has high LD₅₀, high NOAEL in repeat-dose toxicity studies, and no evidence of a genotoxic or phototoxic potential. Based upon these safety evaluations of the HP-3070 patch and sodium acetate anhydrous, sodium acetate anhydrous is safe for use as an excipient in the HP-3070 patch at (b) (4) % level.

Alicyclic Saturated Hydrocarbon Resin:

The HP-3070 patch contains alicyclic saturated hydrocarbon resin (CAS No. 69430-35-9) which is an excipient that acts as a tackifier [concentration: 55.01% (=220.04 mg/40 cm² of the HP-3070 patch), maximum daily dose: 3.14 mg/kg/day (=220.04 mg/patch/human/day, human body weight: 70 kg)]. No general or local toxicity were observed in repeat-dose studies with the HP-3070 control (placebo) patch in rats, dogs or minipigs; it produced no irritation, sensitization or photosensitization of the skin in local toxicity studies. Additionally, the literature review of the toxicity profile of alicyclic saturated hydrocarbon resin (a high LD₅₀, a high NOAEL in repeat-dose toxicity studies, and no evidence of a genotoxic potential) is consistent with a low toxicity risk. Furthermore, alicyclic saturated hydrocarbon resin is expected to be poorly absorbed due to relatively high molecular weight (MW: 1260), since larger molecules cannot pass the corneal layer. Based upon these safety evaluations of the HP-3070 patch and alicyclic saturated hydrocarbon resin, alicyclic saturated hydrocarbon resin is safe for use as an excipient in the HP-3070 patch at (b) (4) % level.

The totality of excipients in the HP-3070 patch formulation were qualified in the pivotal GLP repeat-dose toxicity studies summarized in the following Applicant’s table:

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Table 5. Toxicology studies qualifying HP-3070 patch excipients

Toxicology studies qualifying HP-3070 Patch Excipients			
Study Name (Study Number)	GLP/ Non-GLP	Doses/Formulations Evaluated	Key Findings
A 13-week repeated dose percutaneous toxicity study of HP-3070 patch in rats (B-7552)	GLP	HP-3070: 2, 4, 6 mg/kg/day, (b) (4) cm ² /kg/day), for 24-hour daily (two rotated site) / percutaneous	NOAEL: Male: < 2 mg/kg/day, Female: 4 mg/kg/day
		HP-3070 placebo: (b) (4) cm ² /kg/day (b) (4) mg/kg/day)*, for 24-hour daily (two rotated site) / percutaneous	No toxicological findings were observed except for mild skin irritation.
A 26-week repeated dose percutaneous toxicity study of HP-3070 patch in rats with a recovery period of 6 weeks (B-7755)	GLP	HP-3070: 0.72, 1.2, 2 mg/kg/day, (b) (4) cm ² /kg/day), for 24 hours daily (two rotated site) / percutaneous	NOAEL: Male: < 0.72 mg/kg/day, Female: 1.2 mg/kg/day
		HP-3070 placebo: (b) (4) cm ² /kg/day (b) (4) mg/kg/day)*, for 24-hour daily (two rotated site) / percutaneous	No toxicological findings were observed except for mild skin irritation.
A 13-week repeated dose percutaneous toxicity study of HP-3070 patch in beagle dogs (B-7551)	GLP	HP-3070: 0.855, 2.61, 7.88 mg/kg/day, (b) (4) cm ² /kg/day), for 24-hour daily (two rotated site) / percutaneous	NOAEL: Male: 7.88 mg/kg/day, Female: 2.61 mg/kg/day
		HP-3070 placebo: (b) (4) cm ² /kg/day (b) (4) mg/kg/day)*, for 24-hour daily (two rotated site) / percutaneous	No toxicological findings were observed.
A 39-week repeated dose dermal toxicity study of HP-3070 patch in Gottingen minipigs with a 4-week recovery period (967-029)	GLP	HP-3070: 0.6, 1.8, 5.4 mg/kg/day, (b) (4) cm ² /kg/day), for 24 hours daily (two rotated site) / percutaneous	NOAEL: Male: 5.4 mg/kg/day, Female: 5.4 mg/kg/day
		HP-3070 placebo: (b) (4) cm ² /kg/day (b) (4) mg/kg/day)*, for 24-hour daily (two rotated site) / percutaneous	No toxicological findings were observed except for mild skin irritation.
Study for effects of the percutaneous administration of HP-3070 patch on fertility and early embryonic development to implantation in rats (R-1147)	GLP	HP-3070: 0.72, 1.2, (b) (4) 2.0 mg/kg/day, (b) (4) cm ² /kg/day), 4 weeks (males: 2 weeks before mating and during the period from mating through the day before necropsy. Females: 2 weeks before mating and during the period from mating to gestation day 7) for 24-hour daily (two rotated site) / percutaneous	NOAEL: for general toxicity in males and females; 0.72 mg/kg/day, for fertility and early embryonic development: < 0.72 mg/kg/day
		HP-3070 placebo: (b) (4) cm ² /kg/day (b) (4) mg/kg/day)*, for 24-hour daily (two rotated site) / percutaneous	No toxicological findings were observed.

GLP = Good Laboratory Practice; NOAEL = no observed adverse effect level *: The dosage as butylated hydroxytoluene

Source: Nonclinical reviewer (Partially excerpted from NDA 212268, Section 2.6.6. Toxicology Written Summary, p. 88, Table 27: Summary of completed Hisamitsu/Noven studies with the HP-3070 patch or patch extract)

To support the chronic use of HP-3070, the Applicant performed a 39-week dermal study in minipigs to evaluate the long-term systemic and dermal safety of the patch (Study 967-029). This study is in accordance with the FDA guidance “Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route” which states that if a new formulation contains a drug substance that has not been used by the dermal route, the repeat-dose local toxicity study should be conducted in a nonrodent species (preferably minipig). The results from this study showed no toxicological findings for the HP-3070 patch and placebo patch when compared to the “sham” control. This study qualifies the test article and excipients in the HP-3070 transdermal system for chronic dermal use.

Phototoxicity assessment of HP-3070 patch excipients

Consistent with the ICH Guidance: S10 Photosafety Evaluation of Pharmaceuticals, the UV absorption spectrum was determined for all methanol-soluble components and nonmethanol/non-water-soluble inactive components, to support the photosafety qualification of the HP-3070 final formulation and its individual components.

None of the methanol-soluble components (sodium acetate anhydrous, isopropyl palmitate, or butylated hydroxytoluene) showed a molar extinction coefficient in the UV range that would suggest the potential for phototoxicity.

None of the non-methanol/non-water-soluble components (styrene-isoprene-styrene block copolymer, polyisobutylene (b) (4), polyisobutylene, alicyclic saturated hydrocarbon resin) demonstrated phototoxicity when assessed using the EpiDerm system skin model. These results are consistent with the findings from the photosensitization study in guinea pigs (S13598).

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant has developed asenapine transdermal system at the dosage strengths of 3.8 mg/24 hours (b) (4) on 20 cm² patch), 5.7 mg/24 hours (b) (4) on 30 cm² patch) and 7.6 mg/24 hours (b) (4) on 40 cm² patch). This new formulation is intended to improve adherence to medication in patients with schizophrenia and provide innate advantages including the reduction of total daily doses of medication, no eating or drinking restrictions, ability to perform visual compliance checks, and an alternative option for patients who are averse to taking oral medications or injectables.

In this submission, one pivotal relative bioavailability study was conducted in healthy adult volunteers. The effects of application site and external heat on the PK of the formulation were also evaluated. In addition, three more phase 1 studies to assess single/multiple dose PK, dose proportionality, ethnic effect (Japanese and Caucasian healthy adults) were conducted. The 3.8

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mg/24 hours and 7.6 mg/24 hours patches were selected to be carried forward into the phase 3 program for evaluation of efficacy and safety.

6.1.1. **Recommendations**

The Office of Clinical Pharmacology (OCP) has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of asenapine transdermal system. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreements with the Sponsor
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	Primary evidence of effectiveness for this product comes from pivotal trial HP-3070-GL-04 (6-week in-patient study in schizophrenia patients). In addition, clinical efficacy and safety information is extended from LD based on AUC similarity of asenapine.
Proposed dose for general patients	☒ Yes ☐ No ☐ NA	The Sponsor proposed that HP-3070 can be initiated at a dose of 3.8 mg/24 hours, 5.7 mg/24 hours or 7.6 mg/24 hours depending on the individual patient's needs. However, to be consistent with LD which was approved with a starting dose of 5 mg BID and a maximum dose of 10 mg BID for the indication of schizophrenia, HP-3070 is recommended to be initiated at a dosage of 3.8 mg/24 hours with a maximum dose of 7.6 mg/24 hours. Based on the average exposure (AUC), HP-3070 3.8 mg/ 24 hours and 7.6 mg/24 hours correspond to Saphris 5 mg BID and 10 mg BID, respectively.
Labeling	☒ Yes ☐ No ☐ NA	Pending satisfactory agreement with the sponsor

6.2. Summary of Clinical Pharmacology Assessment

- The total asenapine exposure for HP-3070 (b) (4) 24 hours, measured as AUC_{0-t} and AUC_{0-inf}, was similar to that of the Saphris 5 mg sublingual tablet (within bioequivalence limits). However, peak exposure (C_{max}) for the HP-3070 was significantly lower and not statistically equivalent to Saphris.
- The steady-state C_{max}, C_{min}, and AUC_{0-tau} for asenapine after 7-day multiple applications of HP-3070 increased with increasing dose, dose-proportionality was established across the (b) (4) 24 hours to 7.6 mg/24 hours dose range of HP-3070
- Application of a heating pad on the HP-3070 (b) (4) /24 hours for 8 continuous hours led to a faster absorption rate (median t_{max} ~8 hours) as compared with asenapine without a heating pad (median t_{max} ~ 16 hours).
- There is no effect on asenapine PK with regard to HP-3070 3.8 mg/24 hours application site (upper arm, upper back, abdomen, upper chest, and hip area) or ethnic group comparison between Japanese and Caucasian subjects.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The HP-3070 clinical pharmacology program includes five phase 1 studies in both healthy adult subjects and in adult subjects with schizophrenia. The proposed dosing was determined based on one pivotal efficacy and safety study and supported by one PK bridging study for HP-3070 and Saphris. In addition, the impact of external factors such as application site and heat on the PK profile were assessed. Dose proportionality of the proposed clinical doses has also been demonstrated.

Absorption: On average, approximately 60% of the asenapine is released from the transdermal over 24 hours. Asenapine PK at the steady state is dose-proportional in the dose range of (b) (4) 24 hours to 7.6 mg/24 hours following application of asenapine patch. Steady-state plasma concentrations are achieved in about 72 hours after the first application of the patch, with peak to trough ratio of 1.5. There is no effect on asenapine PK with regards to the patch application site (upper arm, upper back, abdomen, upper chest, and hip area) or ethnic group comparison between Japanese and Caucasian subjects. Application of a heating pad on the asenapine patch (b) (4) 24 hours) for 8 hours led to a faster absorption rate (median t_{max} about 8 hours) as compared with asenapine patch without a heating pad (median t_{max} about 16 hours). Mean asenapine exposure, calculated as partial AUC₀₋₈, following asenapine patch application, was about 3.9 times greater than that without a heating pad, indicating the apparent heat effect in absorption during the time period of heating pad application.

Distribution: Asenapine is rapidly distributed and has a large volume of distribution (~20 - 25 L/kg), indicating extensive extravascular distribution. Asenapine is highly bound (95%) to plasma proteins, including albumin and α 1-acid glycoprotein.

Metabolism and Elimination: Direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2) are the primary metabolic pathways for asenapine. Asenapine is a high clearance drug with a clearance after intravenous administration of 52 L/h. In this circumstance, hepatic clearance is influenced primarily by changes in liver blood flow rather than by changes in the intrinsic clearance, i.e., the metabolizing enzymatic activity. After administration of a single dose of [14C]-labeled asenapine, about 90% of the dose was recovered; approximately 50% was recovered in urine, and 40% recovered in feces. About 50% of the circulating species in plasma have been identified. The predominant species was asenapine N -glucuronide; others included N-desmethyiasenapine, N-desmethyiasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. Pharmacological activity is primarily due to the parent drug.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosage by Applicant:

Depending on the individual patient's needs, treatment with HP-3070 can be initiated at a dose of 3.8 mg/24 hours, 5.7 mg/24 hours or 7.6 mg/24 hours. The safety of doses above 7.6 mg/24 hours has not been evaluated in clinical studies.

However, Saphris was approved with a starting dose of 5 mg BID and a maximum dose of 10 mg BID for the indication of schizophrenia. The pivotal relative bioavailability study and the dose proportionality study showed that AUCs of HP-3070 3.8 mg/24 hours and 7.6 mg/24 hours are comparable to those of Saphris 5 mg BID and 10 mg BID, respectively.

To be consistent with Saphris, the recommended dosage by Agency is as follows:

Initiate HP-3070 at a dosage of 3.8 mg/24 hours. In a short-term, placebo-controlled trial, there was no suggestion of added benefit at a dosage of 7.6 mg/24 hours, but there was an increase in certain adverse events. The dosage may be increased to 5.7 mg/24 hours or 7.6 mg/24 hours, as needed, after one week. The safety of doses above 7.6 mg/24 hours has not been evaluated in clinical studies.

Based on the average exposure (AUC) of asenapine, HP-3070 3.8 mg/24 hours corresponds to 5 mg twice daily of sublingual asenapine and HP-3070 7.6 mg/24 hours corresponds to 10 mg twice daily of sublingual asenapine.

Therapeutic Individualization

There are no dedicated studies conducted to investigate CYP inducers/inhibitors, organ dysfunctions on HP-3070 PK. Therapeutic individualization is based on the information from Saphris.

Strong CYP1A2 inhibitors: asenapine is metabolized by CYP1A2. Marginal increase of asenapine exposure was observed when asenapine is used with fluvoxamine at 25 mg administered twice daily. However, the tested fluvoxamine dose was suboptimal. Full therapeutic dose of fluvoxamine is expected to cause a greater increase in asenapine exposure. Dosage reduction for asenapine based on clinical response may be necessary.

CYP2D6 substrates and inhibitors: asenapine may enhance the inhibitory effects of paroxetine on its own metabolism. Concomitant use of paroxetine with asenapine increased the paroxetine exposure by 2-fold as compared to use paroxetine alone. Reduce paroxetine dose by half when paroxetine is used in combination with asenapine

Hepatic impairment: asenapine exposure for patients with mild to moderate hepatic impairment is similar to patients with normal hepatic function. In patients with severe hepatic impairment, asenapine exposure is 7-fold higher compared to subjects with normal hepatic function. Therefore, no dose adjustment required in patients with mild to moderate hepatic impairment. asenapine is contraindicated in patients with severe hepatic impairment.

Renal impairment: asenapine exposure is similar in subjects with varying degrees of renal impairment and normal function. As asenapine and N-desmethylenapine excretion into urine is <0.1%, urinary elimination can be considered negligible. Therefore, no dose adjustment is required in patients with renal impairment.

Outstanding Issues: None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Refer to section 6.2.1.

6.3.2. Clinical Pharmacology Questions

Is appropriate PK bridge established between HP-3070 and Saphris?

Yes, a pivotal phase 1 study (HP-3070-US-05) was conducted to assess the relative bioavailability between HP-3070 and Saphris in healthy adult subjects. The subjects were randomly assigned to receive either one HP3070^{(b) (4)} /24 hours on upper arm for 24 hours or a single dose of Saphris 5 mg under fasting conditions. The results showed that the total

asenapine exposure (AUC_{0-t} and AUC_{0-inf}) for HP-3070^{(b) (4)} /24 hours is statistically equivalent to that of Saphris 5-mg sublingual tablet. Geometric LS means ratios for both parameters were approximately 1.1, with 90% CIs of the geometric LS means falling within the 0.8 to 1.25 limit (Table 6). However, HP-3070 has a significantly lower peak (C_{max} ~ 1.72 ng/mL) and a more gradual increase and sustained concentration after reaching t_{max} (~ 16 hours) (Figure 1 and Table 7).

Table 6: Statistical Analysis of Asenapine Relative Exposure

Parameter (unit)	Treatment ^a	N ^b	Geometric LS Means	Ratio of Geometric LS Means (ratio)	90% CI of the Ratio (ratio)	Inter-Subject CV	Intra-Subject CV
AUC _{0-t} (ng•h/mL)	B	17	28.7	1.10	(1.00, 1.21)	16.0	15.9
AUC _{0-inf} (ng•h/mL)	B	17	31.8	1.13	(1.03, 1.24)	17.9	15.1
C _{max} (ng/mL)	B	17	1.12	0.291	(0.245, 0.346)	15.4	29.2
	C	16	3.85				

Source: Table 14.2.7.

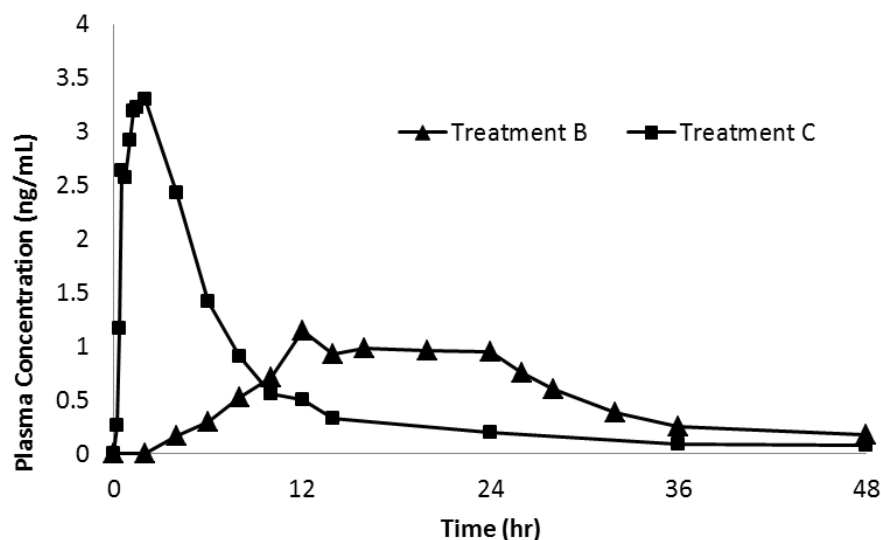
Abbreviations: CV=coefficient of variation; LS=least squares.

^a B=HP-3070^{(b) (4)} patch without a heating pad applied, C=Saphris 5-mg sublingual tablet.

^b N is the number of subjects with estimable pharmacokinetic parameter.

Source: Applicant's study report (Study HP-3070-US-05), Page 82, Table 11-4

Figure 1: Mean asenapine concentration-time profiles by treatment – HP-3070^{(b) (4)} (b) (4) patch and sublingual Saphris 5 mg



Study Treatment B = HP-3070^{(b) (4)} patch without a heating pad applied.

Study Treatment C = Saphris 5 mg sublingual tablet.

Source: Applicant's summary of clinical pharmacology studies, Page 28, Figure 8

Table 7: Mean (CV) Plasma Pharmacokinetic Parameters of Asenapine by Treatment

Parameter (unit)	Treatment B HP-3070 ^{(b) (4)} without heating pad applied (n=17)	Treatment C Saphris 5-mg sublingual tablet (n=16)
AUC ₀₋₈ (ng•h/mL)	1.46 (54.8)	NA
AUC _{0-t} (ng•h/mL)	29.7 (23.5)	26.0 (20.6)
AUC _{0-inf} (ng•h/mL)	32.8 (25.7) ^b	27.8 (18.9)
%AUC (%)	8.82 (44.2) ^b	6.62 (54.0)
C _{max} (ng/mL)	1.27 (67.3)	3.96 (27.8)
t _{max} (h) ^a	16.1 (12.0, 24.0)	1.25 (0.500, 2.00)
λ _z (h)	0.0266 (46.8)	0.0453 (30.3)
t _{1/2} (h)	33.9 (59.0)	17.7 (53.0)
CL/F (L/h)	102 (20.1) ^b	186 (17.1)

Abbreviations: CV=coefficient of variation; h=hours; NA=not applicable.

^a For t_{max}, the median (minimum, maximum) values are presented.

^b n=16.

Source: Applicant's study report (Study HP-3070-US-05), Page 79, Table 11-1

The dose proportionality for the HP-3070 at dose levels of ^{(b) (4)} 24 hours, 3.8 mg/24 hours, 5.7 mg/24 hours and 7.6 mg/24 hours following multiple 24 hours applications was evaluated in Study HP-3070-US-02b. Each subject received a total of seven patches (one patch per day) at seven different sites among eight application sites (the upper arm, upper back, upper chest, and hip area; right and left sides for each application site). The result suggested that steady-state exposure (C_{max}, C_{min}, and AUC_{0-tau}) of HP-3070 increased proportionally with increasing dose.

**Table 8. Summary Statistics of Pharmacokinetic Parameters for Asenapine and Desmethyl-
asenapine in Plasma**

Analyte	Treatment	N	C ^{ss} _{max} (ng/mL)	t ^{ss} _{max} [#] (h)	C ^{ss} _{min} (ng/mL)	AUC ^{ss} _{0-tau} (ng.h/mL)
Asenapine	HP-3070 (b) (4)	22	1.14 (30.3%) (0.500 – 2.14)	16.0 (2.00 – 23.8)	0.745 (32.4%) (0.350 – 1.47)	22.3 (28.2%) (10.6 – 40.6)
	HP-3070	21	2.26 (23.9%) (1.48 – 3.27)	16.0 (2.00 – 24.0)	1.57 (25.8%) (0.907 – 2.46)	45.8 (24.7%) (26.8 – 68.0)
	HP-3070	20	3.40 (18.6%) (2.44 – 5.25)	14.0 (2.00 – 23.8)	2.33 (20.6%) (1.59 – 3.89)	69.3 (20.0%) (48.4 – 110)
	HP-3070	20	4.68 (17.3%) (3.04 – 6.29)	12.0 (4.03 – 24.0)	3.25 (22.5%) (1.83 – 4.45)	96.2 (18.7%) (62.3 – 126)
Desmethyl- Asenapine	HP-3070 (b) (4)	22	0.142 (40.1%) (0.0572 – 0.288)	4.00 (2.00 – 23.8)	0.106 (41.5%) (0.0374 – 0.216)	2.96 (41.6%) (1.10 – 6.28)
	HP-3070	21	0.279 (37.3%) (0.139 – 0.524)	12.0 (2.00 – 23.8)	0.207 (40.5%) (0.0940 – 0.451)	5.80 (38.7%) (2.80 – 11.6)
	HP-3070	20	0.445 (37.9%) (0.245 – 0.989)	12.0 (1.98 – 20.0)	0.330 (37.2%) (0.168 – 0.707)	9.38 (36.9%) (5.24 – 20.5)
	HP-3070	20	0.604 (39.8%) (0.311 – 1.17)	12.0 (1.98 – 24.0)	0.454 (38.5%) (0.211 – 0.889)	12.8 (39.6%) (6.77 – 25.7)

N = number of subjects

Note: Arithmetic mean (coefficient of variation [%CV]) and (minimum- maximum) are presented.

[#] For t^{ss}_{max} the median (range) is presented instead of mean (%CV) and (minimum- maximum).

Source: Applicant's study report (Study HP-3070-US-02b), Page 82, Table 8

According to the results of relative bioavailability study and the dose proportionality study, we can conclude that appropriate PK bridge has been established between HP-3070 and Saphris. Based on the average exposure (AUC), HP-3070 3.8 mg/ 24 hours and 7.6 mg/24 hours correspond to Saphris 5 mg BID and 10 mg BID, respectively.

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

No, the proposed dosage is based on the efficacy and safety study (HP-3070-GL-04) in patients with schizophrenia that both HP-3070 3.8 mg/24 hours and HP-3070 7.6 mg/24 hours (without titration) showed statistically significantly better than placebo for primary efficacy endpoint (change of PANSS total score between baseline and week 6). However, Saphris was approved with a titration scheme for the indication of schizophrenia. The recommended starting dose is 5 mg BID and maximum dose is 10 mg BID. Given the efficacy and safety information is extended from Saphris based on AUC similarity of asenapine, the following dosage is recommended by the FDA to be consistent with Saphris dosage:

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Initiate HP-3070 at a dosage of 3.8 mg/24 hours. In a short-term, placebo-controlled trial, there was no suggestion of added benefit at a dosage of 7.6 mg/24 hours, but there was an increase in certain adverse events. The dosage may be increased to 5.7 mg/24 hours or 7.6 mg/24 hours, as needed, after one week. The safety of doses above 7.6 mg/24 hours has not been evaluated in clinical studies.

Considering switch may occur between HP-3070 and Saphris, the following information is added based on the established PK bridge between HP-3070 and Saphris and dose proportionality of HP-3070:

Based on the average exposure (AUC) of asenapine, HP-3070 3.8 mg/24 hours corresponds to 5 mg twice daily of sublingual asenapine and HP-3070 7.6 mg/24 hours corresponds to 10 mg twice daily of sublingual asenapine.

What are the PK properties of asenapine after single dose administration of asenapine?

Based on the Study HP-3070-US-05 results, the PK profile of asenapine following a single HP-3070 application is shown in Figure 1 and Table 7. After HP-3070 application, asenapine concentrations increase over time typically reaching their maximum between 12 and 24 hours and exhibiting sustained concentrations through the duration of patch wear time (24 hours). Following patch removal, the apparent elimination half-life was about 34 hours. The lower (relative to LD sublingual Saphris) early plasma concentrations with equivalent total exposure achieved with the HP-3070 will translate to a lower peak to trough ratio with once daily patch application.

Does heat affect the PK of Asenapine?

Yes, the asenapine PK following a single 24-hour application of HP-3070 (b) (4) -mg patch with a heating pad for the first 8 hours displayed a faster absorption rate, as the median t_{max} was 8 hours earlier with a heating pad as compared with HP-3070 without a heating pad. Also, mean asenapine exposure following HP-3070 application measured over the course of heat application (8 hours), calculated as AUC₀₋₈ for asenapine, was significantly greater than that without a heating pad. The mean C_{max} , AUC_{0-t}, and AUC_{0-inf} for asenapine following application with a heating pad were slightly higher than those without a heating pad. Following application of HP-3070 with or without a heating pad, plasma concentrations of asenapine appeared to decline in a multiphasic manner, with a mean elimination half-life ($t_{1/2}$) of 27.1 hours for HP-3070 with a heating pad and 33.9 hours for HP-3070 without a heating pad (Table 9 and Figure 2).

Table 9: Mean (CV) Plasma Pharmacokinetic Parameters of Asenapine by Treatment

Parameter (unit)	Treatment A	Treatment B	Treatment C
	HP-3070 ^{(b) (4)} with heating pad applied for 8 hours (n=16)	HP-3070 ^{(b) (4)} without heating pad applied (n=17)	Saphris 5-mg sublingual tablet (n=16)
AUC ₀₋₈ (ng•h/mL)	5.37 (49.8)	1.46 (54.8)	NA
AUC _{0-t} (ng•h/mL)	33.0 (28.3)	29.7 (23.5)	26.0 (20.6)
AUC _{0-inf} (ng•h/mL)	35.7 (29.2)	32.8 (25.7) ^b	27.8 (18.9)
%AUC (%)	7.54 (32.0)	8.82 (44.2) ^b	6.62 (54.0)
C _{max} (ng/mL)	1.34 (33.0)	1.27 (67.3)	3.96 (27.8)
t _{max} (h) ^a	8.00 (4.00, 24.0)	16.1 (12.0, 24.0)	1.25 (0.500, 2.00)
λ _z (/h)	0.0303 (37.6)	0.0266 (46.8)	0.0453 (30.3)
t _{1/2} (h)	27.1 (45.8)	33.9 (59.0)	17.7 (53.0)
CL/F (L/h)	94.9 (21.7)	102 (20.1) ^b	186 (17.1)

Source: Table 14.2.3.

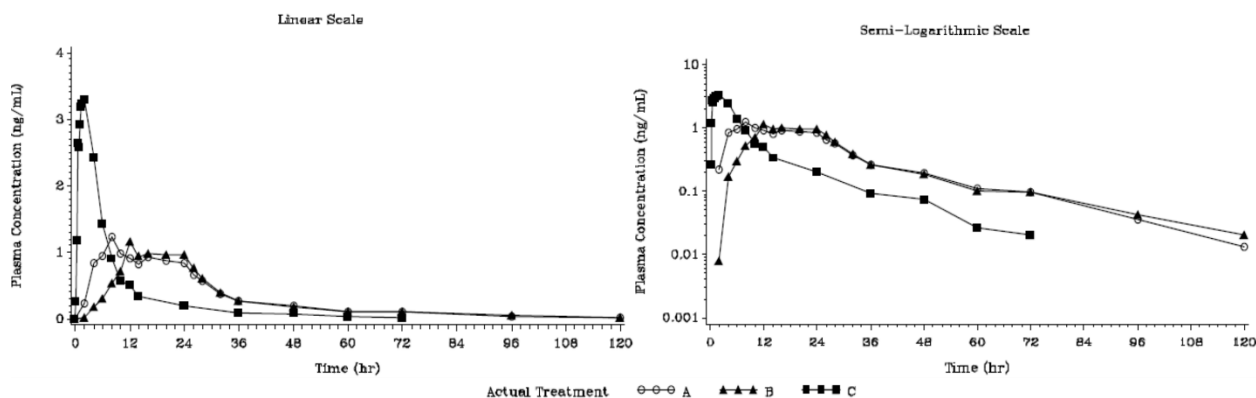
Abbreviations: CV=coefficient of variation; h=hours; NA=not applicable.

^a For t_{max}, the median (minimum, maximum) values are presented.

^b n=16.

Source: Applicant's study report (Study HP-3070-US-05), Page 79, Table 11-1

Figure 2: Arithmetic Mean Plasma Concentrations of Asenapine versus Time Profile by Treatment (Linear and Semi-logarithmic)



Source: Applicant's study report (Study HP-3070-US-05), Page 76, Figure 11-1

Based on the relative exposure analysis for asenapine, the asenapine exposure during heating pad application (AUC₀₋₈) was 3.9-fold higher than that without heat, indicating the apparent heat effect in absorption during heating pad application. C_{max}, AUC_{0-t}, and AUC_{0-inf} after HP-3070 application with a heating pad were approximately 1.1-fold higher than those without a heating pad; however, because the 90% CIs of the geometric least squares (LS) means AUC_{0-t} and AUC_{0-inf} fell within the 0.8 to 1.25 limit and the upper limit for C_{max} was slightly above

1.25, it is therefore considered that the application of HP-3070 with a heating pad for the first 8 hours had no significant effect on total asenapine exposure as measured by AUC_{0-t} and AUC_{0-inf} (Table 10).

Table 10: Statistical Analysis for Effect of Heat on Asenapine Exposure

Parameter (unit)	Treatment ^a	N ^b	Geometric LS Means	Ratio of Geometric LS Means (ratio)	90% CI of the Ratio (ratio)	Inter-Subject CV	Intra-Subject CV
AUC ₀₋₈ (ng•h/mL)	A	16	4.83	3.90	(2.93, 5.20)	26.7	48.0
	B	17	1.24				
AUC _{0-t} (ng•h/mL)	A	16	31.4	1.09	(0.995, 1.20)	16.0	15.9
	B	17	28.7				
AUC _{0-inf} (ng•h/mL)	A	16	34.2	1.07	(0.981, 1.18)	17.9	15.1
	B	16	31.8				
C _{max} (ng/mL)	A	16	1.25	1.11	(0.936, 1.32)	15.4	29.2
	B	17	1.12				

Source: Table 14.2.6.

Abbreviations: CV=coefficient of variation; LS=least squares.

^a A=HP-3070 (b) (4) patch with heating pad applied for 8 hours, B=HP-3070 (b) (4) patch without heating pad applied.

^b N is the number of subjects with estimable pharmacokinetic parameter.

Source: Applicant's study report (Study HP-3070-US-05), Page 81, Table 11-3

Does different application site affect the bioavailability of asenapine?

No, application site does not affect asenapine exposure based on HP-3070-US-03 study. Asenapine exposure was equivalent across all application sites (upper arm, upper back, abdomen, upper chest, and hip area), with the exception of the abdomen compared to the upper arm, for which the lower boundary for the 90% CI for C_{max} is slightly below the 80% limit. Values for the geometric mean ratios and the mean asenapine concentration-time profiles by application site are presented in Figure 3 and Table 11, respectively.

Table 11 Summary of Statistical Analysis of Relative Exposure for Asenapine by Application Site

Treatment Comparison [HP-3070 ^{(b) (4)} (20 cm ²) patch]	Parameter	Geometric mean ratio (%)	90% CI		Intra-Subject CV%
			Lower	Upper	
Upper back vs Upper arm	C _{max} (ng/mL)	98.8	93.6	104	14.7
	AUC _{0-t} (ng.h/mL)	100	95.3	105	13.2
	AUC _{0-inf} (ng.h/mL)	99.6	94.9	104	13.1
Abdomen vs Upper arm	C _{max} (ng/mL)	81.9	77.6 ^a	86.5	14.7
	AUC _{0-t} (ng.h/mL)	85.8	81.7	90.0	13.2
	AUC _{0-inf} (ng.h/mL)	85.9	81.9	90.2	13.1
Upper chest vs Upper arm	C _{max} (ng/mL)	88.2	83.6	93.1	14.7
	AUC _{0-t} (ng.h/mL)	91.2	86.9	95.8	13.2
	AUC _{0-inf} (ng.h/mL)	90.9	86.6	95.3	13.1
Hip area vs Upper arm	C _{max} (ng/mL)	93.5	88.6	98.7	14.7
	AUC _{0-t} (ng.h/mL)	95.1	90.6	99.8	13.2
	AUC _{0-inf} (ng.h/mL)	95.6	91.1	100	13.1

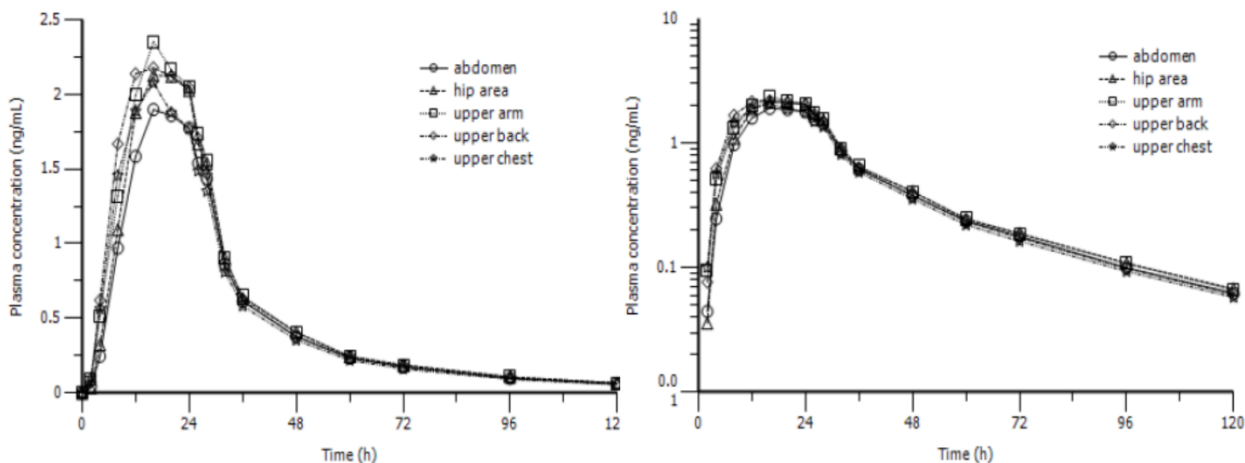
Source: Study HP-3070-US-03 CSR, Table 9

^a 90% CI not entirely within the critical region.

Abbreviations: CI=confidence interval; CV%=percent coefficient of variation.

Source: Applicant's study report (Study Hp-3070-US-03), Page 69, Table 9

Figure 3 Mean Asenapine Concentration-Time Profiles by All Five Application Sites on Linear (Left) and Semi-logarithmic (Right) Scales



Source: Applicant's study report (Study Hp-3070-US-03), Page 60, Figure 1

6.3.3 Financial Disclosure

See Appendix 17.1.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

A total of nine clinical studies comprise the development program for the asenapine TDS. These studies are summarized in the table below.

Table 12: Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
HP-3070-GL-04	02876900	R, DB, PC, parallel group, fixed-dose	Asenapine TDS (b) (4) qDay Asenapine TDS (b) (4) x2 qDay Placebo TDS qDay	Change PANSS total score Change CGI-Severity score	6 wks treatment 30 day follow-up	614	Adults with DSM-5 schizophrenia mod ill or worse	59 centers in 5 countries/U.S. and eastern Europe
Studies to Support Safety								
HP-3070-US-06	None	Group 1 Single-blind induction & challenge phase. Rechallenge if needed. Group 2 Single-blind cumulative irritation phase.	Group 1 Asenapine TDS (b) (4) 3x/week Placebo TDS 3x/week Saline TDS 3x/week Then: Rest period. Then: Single application of above. Group 2 Asenapine TDS (b) (4) 3x/week Placebo TDS 3x/week Saline TDS 3x/week	Skin irritation using the Berger & Bowman scale.	Group 1 Induction: 22 days Rest: 2 weeks Challenge: 48 hrs Rechallenge: 48 hr Group 2 22 consecutive days	Group 1 N=220 Group 2 N=42	Healthy males & females ages 18 to 50 years.	Single center/U.S.
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
HP-3070-US-01	None	Single dose, open label, 3-way crossover	Sycrest 5 mg sublingual tablet Asenapine TDS (b) (4) Asenapine TDS (b) (4)	Cmax, Tmax, AUC to evaluate relative BA	Single dose Follow-up 7 to 10 days	N=18	Healthy males & females ages 18 to 45 years.	Singlecenter/ The Netherlands
HP-3070-US-02	None	Part 1 Open label, 2-period, single ascending dose study Part 2 7-day multiple dose PK study	Part 1 Asenapine TDS (b) (4) Asenapine TDS (b) (4) Part 2 Asenapine TDS (b) (4) once daily x7 days	Part 1 Single dose PK and dose proportionality Part 2 Multiple dose PK	Part 1 24 hours Part 2 7 days Follow-up after 7 to 10 days	N=24	Healthy males & females ages 18 to 45 years.	Singlecenter/ The Netherlands
HP-3070-US-02b	None	Open label, 4-period, multiple ascending dose study	Each TDS strength once daily for 7 days: Asenapine TDS (b) (4) Asenapine TDS (b) (4) Asenapine TDS (b) (4) Asenapine TDS (b) (4)	Multiple dose PK D2 receptor occupancy via PET scan	7 days Follow-up after 7 to 10 days	N=24	Males & females ages 18 to 65w/ schizophrenia or schizoaffective disorder	Singlecenter/U.K.
HP-3070-US-03	None	Open label, 5-period, single dose crossover study	Asenapine TDS (b) (4) single application in one of 5 locations: upper arm, upper chest, upper back, abdomen, and hip.	BA by application site and by ethnicity (Japanese or Caucasian)	24 hours Follow-up after 7 to 10 days	N=40	Healthy males & females ages 20 to 40 yrs. Ethnicity: 50% Caucasian & 50% Japanese	Singlecenter/U.K.

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
HP-3070-US-05	None	Single dose, 4-period, 3-way crossover study	Asenapine TDS (b) (4) w/heat x8 hrs Asenapine TDS (b) (4) without heat Saphris 5 mg sublingually after fasting Asenapine TDS (b) (4) w/heat x24 hrs	Effect of external heat on PK. Relative exposure of asenapine from the TDS versus sublingual Saphris.	24 hours Follow-up after 7 days	N=18	Healthy males & females ages 18 to 45 yrs	Singlecenter/U.S.
HP-3070-US-08	None	Open label, single TDSapplication	Asenapine TDS (b) (4) Asenapine TDS (b) (4) TDS was applied to one of 5 locations (upper chest, upper arm, hip, upper back, abdomen)	Adhesion score (0 to 4): 0 = ≥90% adhered to 4 = 0% (detachment)	24 hours Follow-up after 7 days	N=100 (50/dose & 10/location)	Males and females ages 18 to 65 years with schizophrenia on stable treatment	Two centers/U.S.
HP-3070-US-09	None	Test session involving the TDS, packaging, and Instructions For Use.	Application of 2 TDS sizes (identical to the (b) (4) and (b) (4) strengths) that contained no active drug.	Percentage of subjects who passed critical task performance	Test session lasted up to 1 hour.	N=45 subjects (15/group)	Three groups: 1) Caregivers 2) Adults with schizophrenia 3) Healthcare providers	Two centers/U.S.

Source: Extracted from Table 1 in the Applicant's Clinical Overview.

7.2. Review Strategy

The review of efficacy was based on a single trial, Study HP-3070-GL-04. Yang (Kelly) Yang, PhD, the Biometrics Reviewer, reviewed the efficacy results. Gregory M. Dubitsky, MD, the Clinical Reviewer, reviewed the trial design (including patient selection criteria and study endpoints), financial disclosure information, baseline demographic and illness severity, protocol violations and deviations, and effects on a patient-reported outcome (PRO).

Dr. Dubitsky performed the review of safety data. The strategy for that portion of the review is discussed under [Section 8.2.1](#).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study HP-3070-GL-04

Trial Design

This was a 6-week, randomized, double-blind, placebo-controlled, fixed dose, inpatient study in 614 adult patients with schizophrenia (by DSM-5 criteria) in acute exacerbation, as indicated by all of the following at screening and baseline:

- PANSS total score ≥ 80 .
- Score of four or more in at least two of the following items of the PANSS: conceptual disorganization, delusions, hallucinatory behavior, and unusual thought content.
- CGI-Severity score ≥ 4 (moderately ill).

Duration of the current episode was required to be eight weeks or less and length of hospitalization 21 days or less. Important exclusion criteria were:

- First episode of schizophrenia.
- Diagnosed with schizophrenia less than six months before screening.
- Presence of a DSM-5 diagnosis other than schizophrenia.
- Any skin abnormality at possible application sites that was likely to be aggravated.
- A significant skin disorder such as atrophy, psoriasis, or vitiligo.

During a 3- to 14-day screening/run-in period, patients wore a single-blind placebo TDS. Eligible

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patients were then randomized in a 1:1:1 ratio to one of the following study treatments at baseline (Day 0):

- Asenapine TDS (b) (4) and one placebo TDS.
- Asenapine TDS (b) (4) (two (b) (4) TDSs).
- Placebo TDS (2 placebo TDSs).

To maintain blinding, all patients wore two TDSs during the 6-week treatment period. TDSs were applied in close proximity, without overlapping, to one of the following sites: abdomen, hip, upper arm, upper back, or upper chest. TDSs were applied daily and removed after 24 hours. Patients were assessed weekly during the treatment period. A follow-up visit or phone call was completed 30 days after removal of the last TDS to assess adverse events.

Antipsychotics, antidepressants, and mood stabilizers were prohibited during the study.

Study Endpoints

The primary efficacy endpoint was the change from baseline to Week 6 in the Positive and Negative Symptom Scale (PANSS) total score. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (seven items), negative symptoms of schizophrenia (seven items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme). The total PANSS scores range from 30 to 210. This is a valid and reliable endpoint for assessing the effect of antipsychotic medication on psychotic symptomatology in patients with schizophrenia.

The key secondary endpoint was the change from baseline to Week 6 in the Clinical Global Impression-Severity (CGI-S) assessment scale. The CGI-S is a single-item scale that rates the severity of mental illness on a scale from 1 (normal) to 7 (among the most extremely ill) based on the total clinical experience of the rater in treating patients with schizophrenia. The CGI-S is a widely accepted measure of global illness severity.

Statistical Analysis Plan

The Full Analysis Set (FAS) was used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment. The FAS included all randomized subjects who had at least one TDS of double-blind study medication applied and who have a Baseline PANSS total score and at least one post-Baseline assessment of the primary efficacy measure (PANSS total score).

The change from Baseline to Week 6 in the PANSS total score for each of the three treatment arms was analyzed using an MMRM analysis. The MMRM-based approach assumed that data were missing at random (MAR). The MMRM model included change from Baseline in PANSS total score as the repeated dependent variable, with country, treatment (HP-3070 (b) (4) HP-

3070 (b) (4), and placebo), visit (Weeks 1, 2, 3, 4, 5, and 6), treatment by visit interaction, and the Baseline PANSS total score as covariates. An unstructured covariance matrix was assumed. The Restricted Maximum Likelihood (REML) method was used for the estimation of the covariance parameters. The Kenward-Rogers method was used to estimate the denominator degree of freedom. The treatment-by-time interaction term allows for comparisons of the treatment groups at each time point. Treatment comparisons of each HP-3070 dose to placebo at Week 6 was used for the primary analysis. Missing PANSS total scores were not imputed for primary analysis.

The blinded sample size recalculation was performed after approximately 50% of the desired number of patients have been randomized and completed up to 6 weeks of study treatment. The sample size would be recalculated based on whether the estimated pooled SD from all available subjects at sample size re-assessment was considerably larger than the assumption (SD=20). This SSR was directed and conducted by an independent statistician from QuintilesIMS, who was not involved in the trial conduct other than this SSR.

The change from Baseline in CGI-S score at Week 6 (the key secondary efficacy endpoint) was analyzed in the same way as described for the primary endpoint, with the only difference that the MMRMs used Baseline value of CGI-S as covariate instead of Baseline PANSS total score. Missing data for the key secondary endpoint of change in CGI-S score between Baseline and Week 6 were treated in the same way as for the primary efficacy endpoint.

A matched parallel gatekeeping procedure was used to control the overall Type I error rate in a strong sense at the level of 0.05 for the following two hierarchical families.

- Family 1 was the HP-3070 (b) (4) versus placebo (Hypothesis 1) and the HP-3070 (b) (4) versus placebo (Hypothesis 2), based on the primary endpoint PANSS total score.
- Family 2 was the HP-3070 (b) (4) versus placebo (Hypothesis 3) and the HP-3070 (b) (4) versus placebo (Hypothesis 4), based on the key secondary endpoint CGI-S.

The hypothesis testing used in this gatekeeping procedure was based on truncated and regular Hochberg procedure.

Exploratory subgroup analyses were also conducted in primary and key secondary endpoints on the FAS.

Protocol Amendments

The original study protocol (dated November 16, 2015) was amended twice:

Amendment 1 (dated January 20, 2016) included removal of the proportion of CGI-

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Improvement score responders as a key secondary endpoint and addition of a skin irritation assessment daily between 30 and 60 minutes after TDS removal.

Amendment 2 (dated November 21, 2016) included clarification of the exclusion criteria for patients with cancer and provision of Columbia-Suicide Severity Rating Scale (C-SSRS) criteria for excluding patients at risk for suicidal behavior.

8.1.2. Study Results

Compliance with Good Clinical Practices

This study was completed in accordance with applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Financial Disclosure

See Appendix 17.1.

Patient Disposition

The study was conducted at 59 centers in the US, Russia, Bulgaria, Serbia, and Ukraine. A total of 616 subjects were randomized and 607 subjects were included in the primary analysis set (full analysis set). The dropout rate in the full analysis set was near 22% .

Table 13: Number of Subjects (Study HP-3070-GL-04)

	Placebo n (%)	(b) (4) n (%)	(b) (4) n (%)
Randomized	206	204	204
Full Analysis Set	203 (98.5)	201 (98.5)	203 (98.5)
Completers	162 (78.6)	166 (81.4)	158 (77.5)

Source: Biostatistics Reviewer's Analysis

Protocol Violations/Deviations

The use of concomitant antipsychotic medication was prohibited during the treatment phase of this trial, per the study protocol. This use was the most common protocol violation, occurring in 55% (332/607) of the FAS population based on the Clinical Reviewer's examination of the dataset ADCM.xpt. (Please see the subsection below regarding concomitant medications for further details.)

The next most common category of protocol deviation was compliance with the investigation product, which was reported in 14%, 15%, and 16% of patients in the Full Analysis Set who were treated with asenapine TDS (b) (4) (b) (4) , and placebo, respectively. These deviations included

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product detachment during exercise, inconsistent time of product application, and product applied to the same location on two consecutive days.

Deviations involving study eligibility and entry criteria were reported in 1%, 1%, and 3% of patients who received asenapine TDS (b) (4), (b) (4) and placebo, respectively. The Clinical Reviewer reviewed these deviations and judged that they are unlikely to have impacted on the study results.

Table of Demographic Characteristics

Demographic characteristics of the FAS are shown in the following table. Most patients were under age 65 years. Treatment arms were balanced with respect to age, race, ethnicity, and world region (U.S. versus rest of the world). The asenapine (b) (4) group had a lower proportion of males than the other groups.

Table 14: Study HP-3070-GL-04: Demographic Characteristics of the FAS

Demographic Parameters	Asenapine TDS (b) (4) N=203 n (%)	Asenapine TDS (b) (4) N=201 n (%)	Placebo N=203 n (%)	Overall N=607 n (%)
Sex				
Male	110 (54%)	128 (64%)	129 (64%)	367 (60%)
Female	93 (46%)	73 (36%)	74 (36%)	240 (40%)
Age				
Mean years (SD)	42 (12)	42 (12)	42 (12)	42 (12)
Median (years)	42	41	42	42
Min, max (years)	18, 69	18, 69	18, 67	18, 69
Age Group				
< 65 years	197 (97%)	199 (99%)	201 (99%)	597 (98%)
≥ 65 years	6 (3%)	2 (1%)	2 (1%)	10 (2%)
Race				
White	157 (77%)	155 (77%)	150 (74%)	462 (76%)
Black or African American	44 (22%)	46 (23%)	53 (26%)	143 (24%)
American Indian or Alaska Native	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Unspecified	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Ethnicity				
Hispanic or Latino	5 (2%)	9 (5%)	1 (<1%)	15 (3%)
Not Hispanic or Latino	198 (98%)	192 (95%)	202 (100%)	592 (97%)
Region				
United States	60 (30%)	59 (29%)	61 (30%)	180 (30%)
Rest of the World	143 (70%)	142 (71%)	142 (70%)	427 (70%)

Source: Created by the Clinical Reviewer from the dataset ADSL.xpt using JMP 11.1.1.

Baseline Disease Characteristics

The mean time since first diagnosis of schizophrenia was 15.7 years (range 0 to 48 years). The mean duration of the current psychotic episode was 4.9 weeks (range 1.1 to 9.3 weeks). Seventy-five percent of patients had a baseline PANSS total score of 90 or greater. There was no major difference in these baseline characteristics across the three treatment arms.

Concomitant Medications and Treatment Compliance

The Clinical Reviewer manually examined the concomitant medication analysis dataset (ADCM.xpt) to identify any patients who took concomitant antipsychotic medication during the blinded phase of this trial, in apparent violation of the study protocol. This dataset was screened using EPOCH=Blinded Treatment and FASFL=Y. Medications listed under the variable CMTRT were reviewed.

Although the proportions of patients with such use were approximately equal across the three treatment arms, the proportions were high: 55% (112/203), 56% (112/201), and 53% (108/203) of patients received a concomitant antipsychotic drug during blinded treatment in the asenapine TDS (b) (4), (b) (4), and placebo treatment groups, respectively. Because of this finding, the efficacy data were re-analyzed after exclusion of these patients from the FAS by the Biometrics Reviewer to evaluate the impact of this use on the efficacy results. Statistical superiority of both asenapine treatment groups over placebo on the primary endpoint was maintained after exclusion of patients who took a concomitant antipsychotic drug. The results are shown in Appendix 17.5.

In addition, an Information Request was issued to the Applicant on August 9, 2019, to permit them to respond to this finding. The Applicant responded on August 16, 2019, and explained that, because of the methodology for categorizing the time of concomitant medication use by study phase, concomitant antipsychotic medication that was started on the final day of the double-blind treatment phase was enumerated as occurring in the blinded treatment phase. Initiating treatment with an antipsychotic drug on the last day of the treatment phase is reasonable to prevent relapse of illness after stopping the study drug. The Clinical Reviewer investigated this explanation by comparing the variables TR02EDT (last date of study drug exposure in the double-blind treatment period) with CMSTDTC (first date of concomitant medication use) for all patients whom he identified as having used a concomitant antipsychotic drug during blinded treatment.¹ These two dates were not identical for only three patients, all in the asenapine TDS (b) (4) treatment group.² Two of these patients started a concomitant antipsychotic the day prior to the last day of exposure to study drug and the third patient

¹ The time for the last exposure to study drug in the double-blind treatment period (TR02EDT) was approximately 24 hours after the time of last TDS application (LSTPCDTM).

² Patients (b) (6)

started an antipsychotic one month (31 days) before the final day of exposure. Thus, the corrected proportions of patients who received a concomitant antipsychotic drug during blinded treatment were 1% (3/203), 0% (0/201), and 0% (0/203) of patients in the asenapine TDS (b) (4) (b) (4) and placebo treatment groups, respectively. This use is unlikely to have biased the efficacy findings of this trial, given the strong statistically significant superiority over placebo TDS.

To ensure treatment compliance, TDSs were applied and removed by designated staff. In addition, TDS adhesion was assessed throughout the day. Compliance was calculated at weekly intervals as the number of TDSs applied divided by the number of TDSs prescribed and defined as $\geq 80\%$ and $\leq 120\%$ of study medication. Overall, the compliance rate during the double-blind treatment period was 84% and roughly the same across the three treatment groups.

Efficacy Results – Primary Endpoint

The primary analysis result is summarized on Table 15.

As shown in Figure 4, the LS mean decreases in the PANSS total score in both HP-3070 groups were numerically greater than placebo beginning at Week 1 and continuing through Week 6. However, the mean decreases in HP-3070 (b) (4) group was numerically greater than (b) (4) group at later visits. Overall, compared to placebo, the plot supported that both doses of HP-3070 improved the PANSS total score after 6 weeks of treatment.

Figure 5 shows the percentages of subjects with different magnitudes of improvement on the primary endpoint in the HP-3070 (b) (4), HP-3070 (b) (4) and placebo groups. A patient can have one of three types of response: symptom improvement (measured as a negative change at week 6 in PANSS Total), worsening, or dropout out of the study. Dropout rates are similar among the three study arms. Both HP-3070 groups have fewer patients with worsening PANSS Total or no change in PANSS Total compared to placebo. The response distributions of both HP-3070 groups are shifted towards greater magnitude of improvement in PANSS Total scores compared to the placebo arm's response distribution displays the histogram of the magnitude of improvement from baseline in PANSS Total Score at Week 6.

The HP-3070 (b) (4) HP-3070 (b) (4) and placebo groups had similar mean (SD) PANSS total scores at Baseline. The LSM estimates (SE) of the treatment comparison (HP-3070-placebo) for the change from Baseline at Week 6 was -4.8 (1.634) and -6.6 (1.630) for the (b) (4) (b) (4) and (b) (4) groups, respectively, compared with placebo. Both doses showed statistically significant improvement in change from baseline in PANSS total score at Week 6 compared with placebo.

Table 15: Primary Analysis Results on Change from Baseline in PANSS Total Score at Week 6 (Full Analysis Set)

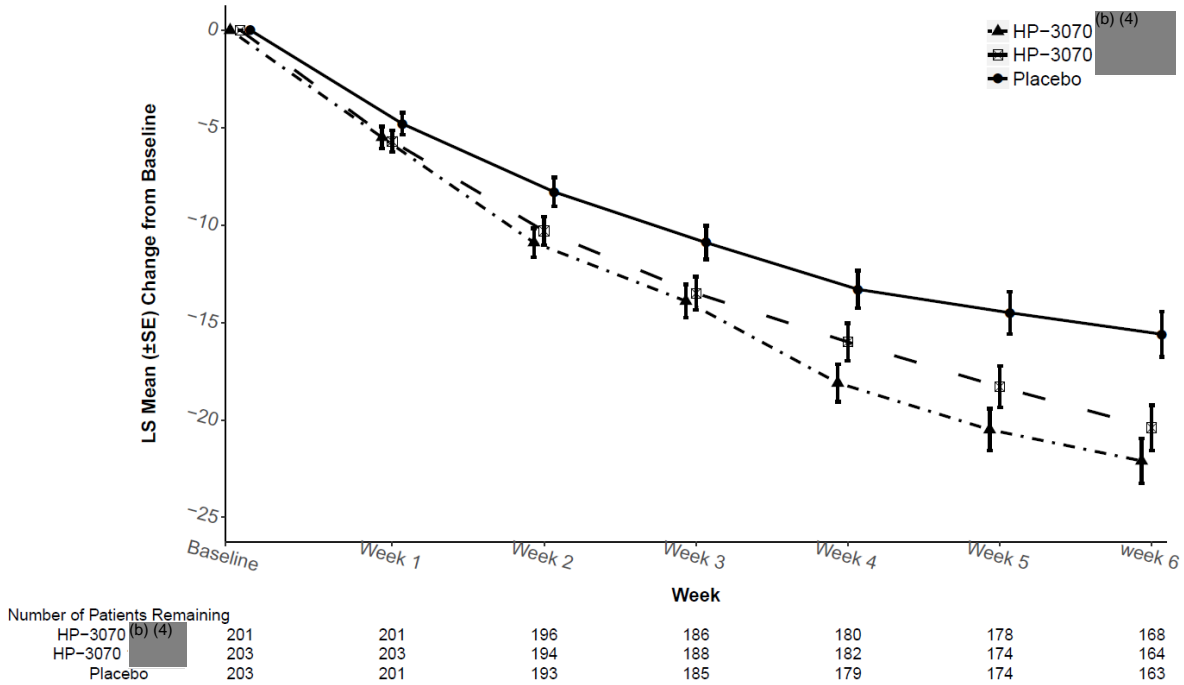
	Placebo (n=203)	HP-3070 (b) (4) (n=201)	HP-3070 (b) (4) (n=203)
Mean score at Baseline (SD)	97.4 (10.07)	97.0 (9.78)	95.6 (8.68)
Mean Score at Week 6 (SD)	78.5 (17.76)	73.3 (15.80)	74.0 (15.63)
LS Mean Change from Baseline (SE)	-15.5 (1.166)	-22.1 (1.158)	-20.4 (1.162)
Placebo -subtracted Difference (95% CI)		-6.6 (-9.81, -3.40)	-4.8 (-8.06, -1.64)
Unadjusted P-value		<0.001	0.003
Adjusted P-value		<0.001	0.003

Abbreviations: CI = Confidence Interval; LS = least squares; Max = maximum; Min =minimum; N = number of subjects in the Full Analysis Set by treatment group; n = number of subject in calculation; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = Standard Error

Notes: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication. The mixed model for repeated measures includes treatment, country, visit, treatment by visit interaction, and Baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degree of freedom.

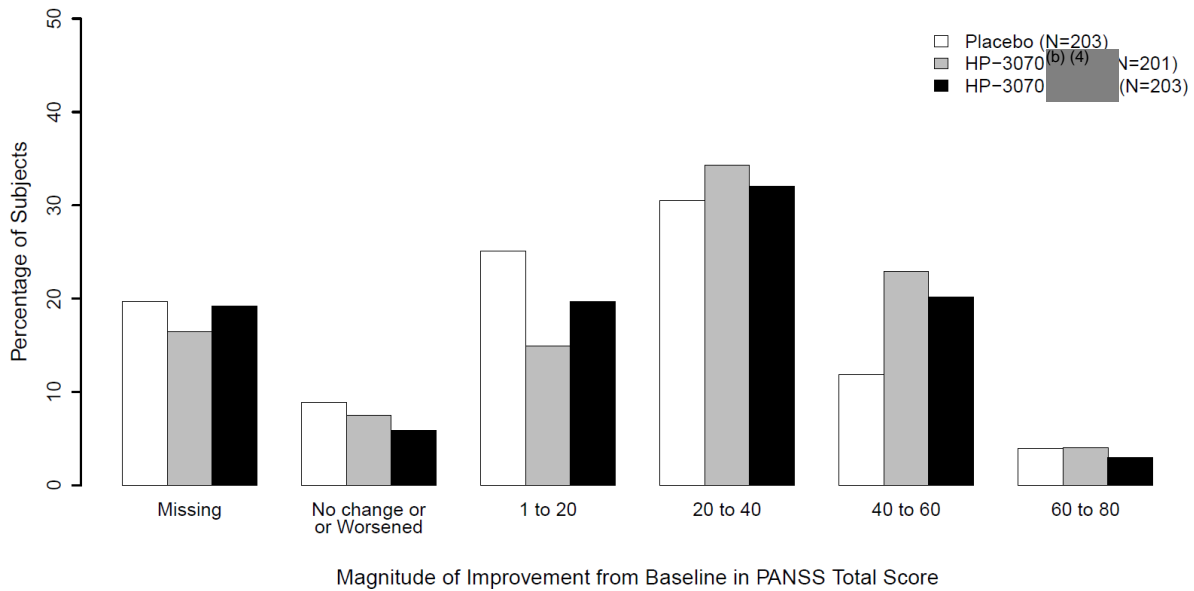
Source: Applicant's Analysis (Table 15 of CSR), confirmed by Biostatistics Reviewer

Figure 4: Least Squared Mean ($\pm$ SE) Change-from-Baseline over Time in PANSS Total Score.



Abbreviations: SE = Standard Error
 Source: Biostatistics Reviewer's Analysis.

Figure 5: Histogram of the Magnitude of Improvement from Baseline in PANSS Total Score at Week 6.



Source: Biostatistics Reviewer's Analysis.

At the interim look on April 10, 2017, 306 subjects had been randomized and 221 subjects had data on both baseline and Week 6. The estimated SD was 14.9 based on those 221 subjects with data at both baseline and Week 6. Given that the estimated pooled SD was smaller than the assumed SD=20, the independent statistician from QuintilesIMS recommended that no increase in the planned sample size was required. As there was no analysis of drug effect and Noven was kept blinded to the data and uninformed of the interim results (i.e., response rates) until final database lock, no statistical adjustment was made to the level of significance for hypothesis testing at the end of the study.

The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of the subgroup analyses, those p-values are not presented here.

Most subjects were aged <55 years. Only one patient was neither White nor Black; that patient was included with the white patients in a “White and Other Races” category for the subgroup analysis on race. The results are presented in Table 16. There is only one subgroup showing a different treatment direction on primary endpoints from that of the overall population. The high dose treatment group (b) (4) has smaller overall treatment effect compared to the low dose treatment group (b) (4). Therefore, different treatment directions may be expected for some subgroups in high dose treatment group.

Table 16: Subgroup Analysis Results

Dose		Subgroup	HP-3070 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (95% CI) (HP-3070-Placebo)
(b) (4)	Overall		-22.1 (1.16) (201)	-15.5 (1.17) (203)	-6.6 (-9.81, -3.40)
	Gender	F	-24.2 (1.91) (62)	-15.3 (1.98) (54)	-8.8 (-14.23, -3.45)
		M	-20.9 (1.46) (106)	-15.7 (1.45) (111)	-5.2 (-9.21, -1.25)
	Age	<55	-22.0 (1.30) (137)	-15.2 (1.30) (135)	-6.9 (-10.44, -3.31)
		≥55	-21.8 (2.61) (31)	-16.9 (2.67) (30)	-4.9 (-12.24, 2.49)
	Race	Black/African American	-21.0 (2.60) (34)	-15.1 (2.39) (43)	-5.9 (-12.91, 1.07)
		White and Other Races	-22.8 (1.28) (134)	-16.3 (1.32) (122)	-6.5 (-10.11, -2.95)
	Region	US	-21.1 (2.24) (46)	-13.9 (2.20) (49)	-7.1 (-13.32, -0.91)
		Russia	-22.8 (2.13) (48)	-10.8 (2.18) (44)	-12.1 (-18.10, -6.03)
		Rest of World	-22.7 (1.61) (74)	-20.7 (1.63) (72)	-2.0 (-6.49, 2.52)
(b) (4)	Overall		-20.4 (1.16) (203)	-15.5 (1.17) (203)	-4.8 (-8.06, -1.64)
	Gender	F	-20.8 (1.71) (75)	-15.3 (1.98) (54)	-5.4 (-10.55, -0.29)
		M	-20.1 (1.58) (89)	-15.7 (1.45) (111)	-4.4 (-8.56, -0.23)
	Age(years)	<55	-20.3 (1.28) (140)	-15.2 (1.30) (135)	-5.2 (-8.70, -1.60)
		≥55	-20.8 (2.82) (24)	-16.9 (2.67) (30)	-3.9 (-11.52, 3.77)
	Race	Black/African American	-21.9 (2.73) (29)	-15.1 (2.39) (43)	-6.8 (-13.98, 0.37)
		White and Other Races	-20.2 (1.27) (135)	-16.3 (1.32) (122)	-4.0 (-7.53, -0.39)
	Region	US	-20.6 (2.34) (37)	-13.9 (2.20) (49)	-6.6 (-12.97, -0.30)
		Russia	-23.1 (2.09) (49)	-10.8 (2.18) (44)	-12.3 (-18.30, -6.32)
		Rest of World	-18.4 (1.60) (78)	-20.7 (1.63) (72)	2.3 (-2.20, 6.78)

Abbreviations: CI = Confidence Interval; LS = least squares; Max = maximum; Min =minimum; N = number of subjects in the Full Analysis Set by treatment group; n = number of subject in calculation; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = Standard Error

Notes: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication. The mixed model for repeated measures includes treatment, country, visit, treatment by visit interaction, and Baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degree of freedom.

Source: Applicant's Analysis (Table 14.2.4.1, Table 14.2.4.2, Table 14.2.4.3, Table 14.2.4.4, Table 14.2.4.5, Table 14.2.4.6, Table 14.2.4.9 and Table 14.2.4.10 of CSR,), confirmed by Biostatistics Reviewer

Data Quality and Integrity

See [Section 4.1](#) for information regarding the OSI inspection of this trial.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint was the change in CGI-S score from Baseline to Week 6. Because the primary objective was met for both HP-3070 doses, confirmative testing for the key

secondary endpoint was performed. The improvement in the CGI-S scores at Week 6 were statistically significantly different from placebo for both the HP-3070 (b) (4) and HP-3070 (b) (4) treatment groups. Thus, treatment with HP-3070 demonstrated a statistically significant improvement over placebo in the CGI-S after 6 weeks of treatment.

Table 17: Key Secondary Analysis Results on Change from Baseline in CGI-S Score at Week 6 (Full Analysis Set)

	Placebo (n=203)	HP-3070 (b) (4) (n=201)	HP-3070 (b) (4) (n=203)
Mean score at Baseline (SD)	4.9 (0.58)	4.9 (0.54)	4.9 (0.50)
Mean Score at Week 6 (SD)	4.0 (1.01)	3.6 (0.93)	3.7 (0.96)
LS Mean Change from Baseline (SE)	-0.8 (0.071)	-1.2 (0.071)	-1.1 (0.071)
Placebo-subtracted Difference (95% CI)		-0.4 (-0.64, -0.25)	-0.4 (-0.55, -0.16)
Unadjusted P-value		<0.001	<0.001
Adjusted P-value		<0.001	<0.001

Source: Applicant's Analysis (Table 15 of CSR), confirmed by Biostatistics Reviewer

Dose/Dose Response

This trial evaluated the efficacy of two fixed doses of the asenapine TDS, (b) (4) and (b) (4). There was no evidence on either the primary efficacy endpoint or the key secondary efficacy endpoint that the higher dose conferred an added benefit over the lower dose.

Durability of Response

Durability of response in the treatment of schizophrenia is inferred from a double-blind, placebo-controlled maintenance study of asenapine sublingual tablets with a randomized withdrawal design.³ In that study, 700 patients entered a 26-week, open label treatment phase with asenapine sublingual tablets. A total of 386 patients who met criteria for stability were then randomized to double-blind, placebo-controlled treatment during a randomized withdrawal phase. Asenapine sublingual tablets were statistically superior to placebo in time to relapse or impending relapse.⁴

³ This study was submitted and reviewed under NDA 22117 S-003, which was approved on September 3, 2010.

⁴ See Section 14.1 of Saphris labeling.

Efficacy Results – PRO endpoints

One patient-reported outcome (PRO), the Medication Satisfaction Questionnaire (MSQ), was assessed in this trial. The MSQ consists of one question: “Overall, how satisfied are you with your current antipsychotic medication?” Patients rate their satisfaction on a 7-point scale from 1 (extremely dissatisfied) to 7 (extremely satisfied). A one-point change on the MSQ may be considered clinically meaningful.⁵ The MSQ was administered at Weeks 2, 4, and 6 in this trial. Mean scores by visit are shown below.

Table 18: Mean MSQ Scores

	Asenapine TDS ^{(b) (4)}	Asenapine TDS ^{(b) (4)}	Placebo TDS
Week 2			
N	199	194	192
Mean (SD)	4.7 (1.3)	4.7 (1.3)	4.5 (1.3)
Week 4			
N	184	182	181
Mean (SD)	5.1 (1.2)	5.0 (1.3)	4.7 (1.5)
Week 6			
N	160	169	164
Mean (SD)	5.2 (1.3)	5.3 (1.3)	4.9 (1.5)

Source: Extracted from Table 14.2.3.10 in the CSR for Study HP-3070-GL-04.

The range in each treatment group at each visit was 1 to 7. The only statistically significant difference between either active drug group and placebo (at a nominal alpha level of 0.05) was at Week 4 for the asenapine TDS ^{(b) (4)} group (p=0.04). However, this difference in means was only 0.4, which the Clinical Reviewer does not consider clinically meaningful. On average, patients in each treatment arm were “somewhat satisfied” (score of 5) with their medication.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

This application contained only one efficacy trial (Study HP-3070-GL-04).

⁵ Vernon MK, et al, 2010, Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients, Schizophr Res, 118:271-278.

8.1.4. **Integrated Assessment of Effectiveness**

The efficacy results from Study HP-3070-GL-04, together with the results from two short-term trials of asenapine sublingual tablets in adult patients with schizophrenia, support the effectiveness of the asenapine transdermal delivery system in the treatment of adult patients with schizophrenia.⁶

8.2. **Review of Safety**

8.2.1. **Safety Review Approach**

The safety review strategy consisted of the following:

- A review of serious adverse events, including deaths, across eight of the nine studies in the development program. Because Study HP-3070-US-09 (the Summative Usability Test) involved only a placebo TDS and, therefore, was not capable of providing useful information regarding the safety of the asenapine TDS, it was excluded from the safety review.
- A review of all standard safety analyses of data from the pivotal safety and efficacy trial for this application (Study HP-3070-GL-04). This included an examination of adverse events that led to premature discontinuation, common adverse events, vital sign data, laboratory test results, ECG findings, and assessments of suicidal ideation and behavior as well as movement disorder symptoms.
- In addition, the Division of Dermatology and Dental Products (DDDP) was consulted to review Study HP-3070-US-06 (the Cumulative Skin Irritation and Sensitization Study). Their review is also summarized in this document.

8.2.2. **Review of the Safety Database**

Overall Exposure

A total of 866 subjects were exposed to asenapine TDS across all clinical studies. The primary source of safety data was Study HP-3070-GL-04. The Safety Analysis Set (SAF) for this study was defined as all patients who had at least one double-blind, study-medication TDS applied and had at least one post-application safety measurement during the double-blind treatment period. The SAF was comprised of 614 patients. Duration of exposure by treatment arm is shown in the table below.

⁶ See Saphris labeling.

Table 19: Exposure (Days) to Double-Blind Study Medication

	Asenapine TDS (b) (4) N=204	Asenapine TDS (b) (4) N=204	Placebo N=206
Mean (SD)	40.2 (5.7)	40.5 (5.6)	40.2 (6.0)
Median	42	42	42
Minimum, Maximum	2, 42	1, 42	1, 42

Source: Extracted from Table 21 in the CSR for Study HP-3070-GL-04.

The total number of TDS applications during the double-blind treatment phase were 6107, 6608, and 6219 for patients in the asenapine TDS (b) (4), asenapine TDS (b) (4) and placebo TDS arms, respectively.

Adequacy of the safety database:

This safety database, together with safety data from trials and postmarketing experience with asenapine sublingual tablets, is adequate to assess the safety of asenapine TDS. It is expected that the only major difference in safety findings will be those relevant to dermal application site reactions given that systemic exposure to asenapine is comparable between asenapine TDS and asenapine sublingual tablets. Such reactions were adequately monitored in the pivotal trial (HP-3070-GL-04) and the potential for dermatological adverse reactions was systematically evaluated in Study HP-3070-US-06. Because these reactions are expected to occur with short-term treatment and the long-term safety of asenapine has been established in previous trials with the sublingual tablets, no long-term safety studies of the asenapine TDS are considered necessary.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Clinical reviewer performed an audit that examined the Narrative Summaries, Case Report Forms, and adverse event analysis dataset (ADAE.xpt) to evaluate the consistency of adverse event data across these three documents for five randomly selected patients.⁷ No inconsistencies were found for any of these patients.

He noted no significant issues with data integrity or submission quality overall.

See also [Section 4.1](#) for information regarding the OSI inspection of this trial.

⁷ Subject numbers (b) (6), and (b) (6).

Categorization of Adverse Events

For Study HP-3070-GL-04, the Clinical Reviewer examined the adverse event (AE) analysis dataset (ADAE.xpt) to evaluate the coding of reported AE terms (AETERM) to MedDRA Preferred Terms (AEDECOD), which was done by the Applicant using MedDRA version 20.1. Out of 1,266 adverse event reports in this dataset, only three instances (in two patients) of inaccurate coding were found. In these cases, the reported term “Akathisia” was coded to “Extrapyramidal Disorder” instead of the more specific Preferred Term “Akathisia.” One of the patients was in the asenapine TDS (b) (4) group and the other in the placebo TDS group. Given only three errors out of 1,266 reports, no correction to the dataset was requested from the Applicant. Otherwise, the AE coding appeared to be accurate.

Several MedDRA Preferred Terms were felt to represent closely related clinical events. These were combined into common AE terms for purposes of calculating AE reporting rates. Table 20 displays which Preferred Terms were combined into common terms in calculating AE incidence rates for labeling.

Table 20: Re-Categorization of MedDRA Preferred Terms

Common AE Term	Subsumed MedDRA Preferred Terms
Tachycardia	Tachycardia, sinus tachycardia, heart rate increased.
Bradycardia	Bradycardia, sinus bradycardia.
Abdominal Pain	Abdominal discomfort, abdominal pain, abdominal pain upper.
Application Site Reaction	Application site dermatitis, discoloration, discomfort, dryness, erythema, exfoliation, induration, irritation, edema, pain, papules, pruritus, reaction.
Upper Respiratory Infection	Upper respiratory tract infection, acute sinusitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, otitis media, oropharyngeal pain.
Hepatic Enzyme Increased	Hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased.
Blood Glucose Increased	Blood glucose increased, blood insulin increased, glycosylated hemoglobin increased, hyperglycemia, type 2 diabetes mellitus, diabetes mellitus, hyperinsulinemia.
Weight Increased	Weight increased, obesity.
Hyperlipidemia	Blood cholesterol increased, blood triglycerides increased, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia.
Hypertension	Hypertension, blood pressure increased, diastolic hypertension, hypertensive crisis.
Dyskinesia	Dyskinesia, tardive dyskinesia.

Common AE Term	Subsumed MedDRA Preferred Terms
Extrapyramidal Disorder	Extrapyramidal disorder, akathisia, dyskinesia, tardive dyskinesia, dystonia, parkinsonism, muscle spasms, musculoskeletal stiffness.
Somnolence	Somnolence, sedation, lethargy, hypersomnia.
Anxiety	Anxiety, nervousness, tension, restlessness.
Depression	Depression, depressive symptom.
Insomnia	Insomnia, initial insomnia, terminal insomnia.
Mania	Mania, hypomania.
Abnormal Dreams	Abnormal dreams, nightmare.
Psychotic Disorder	Psychotic disorder, schizophrenia, suspiciousness.
Agitation	Agitation, aggression, irritability.
Suicidal Ideation	Suicidal ideation, overdose.

Source: Created by the Clinical Reviewer based on examination of the dataset ADAE.xpt.

Routine Clinical Tests

In Study HP-3070-GL-04, the following safety assessments were performed at baseline (Day 0 of the double-blind treatment period) and at Weeks 1, 2, 3, 4, 5, and 6 of treatment:

- Body weight.
- 12-lead ECG.
- Movement disorder scales.⁸
- Columbia-Suicide Severity Rating Scale.
- Vital signs.

Vital signs included measurement of blood pressure, pulse rate, and temperature. These were recorded weekly at 6 and 12 hours post-application and immediately prior to removal of the previous day's TDSs. Assessment for orthostatic hypotension consisted of measurement of blood pressure and pulse after 5 minutes in the supine position and again after standing for approximately 1 to 3 minutes.

Laboratory testing included standard hematology, chemistry, and urinalysis parameters as well as TSH and HbA_{1c}. Fasting blood samples for laboratory tests were obtained at baseline and Weeks 3 and 6.

Irritation at the TDS application site was assessed daily between 30 and 60 minutes after TDS removal. Also, patients were asked to report any discomfort or skin irritation due to the TDS

⁸ Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS).

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and these spontaneous reports were recorded as AEs.

TDS adhesion was evaluated at 6 and 12 hours post-application and immediately prior to removal. In addition, patients were requested to check adhesion throughout the day and immediately report any complete or partial detachment.

The TDS application site was assessed weekly for adhesive residue.

The Clinical Reviewer considers the safety assessments to be adequate to evaluate the safety of asenapine TDS.

8.2.4. Safety Results

Deaths

There were no deaths in this clinical development program.

Serious Adverse Events

Serious adverse events (SAEs) were defined in accordance with 21 CFR 312.32(a) and occurred only in Study HP-3070-GL-04.

Nine patients experienced serious adverse events, as tabulated below.

Table 21: Serious Adverse Events

SAE	Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo
Schizophrenia exacerbation	1	2	2
Gastrointestinal ulcer hemorrhage	1	0	0
Acute coronary syndrome/HTN Crisis	0	1	0
Drug Overdose	0	0	1
Seizure/Contusion/Facial fractures	0	0	1

Source: Extracted from Table 24 in the CSR for Study HP-3070-GL-04.

The event of schizophrenia exacerbation likely represents worsening of the underlying condition due to lack of efficacy in individual patients as opposed to a reaction to study drug.

Patient (b) (6) was a 68 year old male who experienced a gastrointestinal ulcer hemorrhage manifested by black feces, hypotension, anemia, weakness, dizziness, and loss of consciousness on Day 19. A gastric ulcer and chronic duodenal ulcers were diagnosed on endoscopy and study drug was stopped the following day. He was medically treated and

recovered. His medical history was remarkable for gastric and duodenal ulcers and concomitant use of aspirin.

Patient (b) (6) was a 64 year old female who experienced T-wave inversion and evidence of anterolateral wall ischemia on ECG on Day 21. On Day 24, her ECG was reportedly improved but she experienced a hypertensive crisis (blood pressure of 220/120). She was medically treated and her blood pressure improved (140/90). However, the following day, her ECG again revealed T-wave inversion suggestive of ischemia. Study drug was stopped and an acute coronary syndrome was diagnosed. She was hospitalized and medically treated, with resolution of the event one week later. Her medical history was remarkable for coronary artery disease and hypertension.

The Clinical Reviewer considers the SAEs experienced by these two patients as more likely caused by the medical conditions or concomitant medication use than to asenapine TDS.

Patient (b) (6) was treated with placebo TDS and took an overdose of amitriptyline 10 days after removal of the final TDS. Patient (b) (6) also received the placebo TDS and had sustained a head injury in an attack prior to enrollment, which was not reported to the investigator because the patient considered it insignificant. On Study Day 5, he experienced a seizure and fell, striking his head and face and resulting in a contusion. He was hospitalized and a CT scan revealed closed fractures of facial bones. In neither case could the SAEs be attributed to asenapine TDS because the patients were treated only with the placebo TDS.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study HP-3070-GL-04, the incidence of dropout due to an adverse event was roughly comparable across the three treatment arms:

Asenapine TDS (b) (4)	8% (16/204)
Asenapine TDS (b) (4)	5% (10/204)
Placebo TDS	7% (14/206)

The rates at which specific adverse events led to withdrawal of study drug in more than one asenapine TDS-treated patient are displayed in Table 22.

Table 22: Enumeration of Adverse Events Leading to Premature Discontinuation⁹

	Asenapine TDS (b) (4) (N=204)	Asenapine TDS (b) (4) (N=204)	Placebo TDS (N=206)
Extrapyramidal Disorder ¹⁰	5 (2%)	1 (<1%)	1 (<1%)
Psychotic Disorder ¹¹	4 (2%)	4 (2%)	8 (4%)
Application Site Reaction ¹²	1 (<1%)	1 (<1%)	0 (0%)

Source: Created by the Clinical Reviewer based on analysis of the dataset ADAE.xpt using JMP 11.1.1.

The most common AE resulting in dropout was exacerbation of psychosis, which was twice as likely in the placebo group as in the asenapine TDS groups. This most likely represents lack of efficacy and exacerbation of the underlying illness. Otherwise, the adverse event that most commonly led to dropout was akathisia, in 1.5% (3/204), 0.0% (0/204), and 0.5% (1/206) of patients who received asenapine TDS (b) (4), asenapine TDS (b) (4), and placebo TDS, respectively.

Significant Adverse Events

See the discussion of application site reactions under Section 8.2.5 below.

Treatment Emergent Adverse Events and Adverse Reactions

Adverse events associated with the use of asenapine TDS that occurred at an incidence of $\geq 2\%$ in either asenapine TDS arm and greater than the placebo incidence in Study HP-3070-GL-04 are shown below. Adverse events that were common and drug-related (i.e., events with a reporting rate $\geq 5\%$ in either asenapine TDS arm and at least twice the placebo rate) were extrapyramidal disorder, application site erythema, application site pruritus, and weight increased.

⁹ Only those AEs that led to dropout in more than one asenapine TDS-treated patient are enumerated in this table. Non-serious AEs that resulted in dropout in only one asenapine TDS-treated patient are headache, lethargy, mania, depressive symptom, nausea, vomiting, non-cardiac chest pain, ALT increased, urticaria, and vertigo.

¹⁰ Extrapyramidal disorder also includes the Preferred Terms akathisia and dystonia.

¹¹ Psychotic disorder also includes the Preferred Terms schizophrenia and suspiciousness.

¹² Application site reaction includes the Preferred Terms application site discoloration and pruritus.

Table 23: Percentage of Patients Reporting Treatment-Emergent Adverse Events

System Organ Class/ Preferred Term	Placebo N = 206	Asenapine TDS	
		(b) (4) N = 204	(b) (4) N = 204
Gastrointestinal disorders			
Constipation	4	5	4
Dyspepsia	1	1	3
Diarrhea	1	3	1
General Disorders			
Any Application Site Reaction ¹³	4	15	14
Application site erythema	2	9	10
Application site pruritus	2	5	4
Application site irritation	1	2	0
Investigations			
Blood glucose increased ¹⁴	1	3	1
Weight Increased	2	4	6
Hepatic enzyme increased ¹⁵	0	2	2
Infections and Infestations			
Nasopharyngitis	2	3	1
Upper respiratory tract infection	2	3	1
Metabolism disorders			
Increased appetite	0	3	1
Nervous System Disorders			
Headache	6	9	9
Any Extrapyrmidal disorder ¹⁶	4	10	16
Akathisia	2	4	4
Somnolence ¹⁷	2	4	3
Dystonia	0	1	3

¹³ Includes application site dermatitis, discoloration, discomfort, dryness, edema, erythema, exfoliation, induration, irritation, pain, papules, pruritus, and reaction.

¹⁴ Includes blood glucose increased, blood insulin increased, glycosylated hemoglobin increased, hyperglycemia, Type 2 diabetes mellitus, diabetes mellitus, and hyperinsulinemia.

¹⁵ Includes hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, and gamma-glutamyltransferase increased.

¹⁶ Includes akathisia, dyskinesia, dystonia, extrapyramidal disorder, parkinsonism, tardive dyskinesia, muscle spasm, and musculoskeletal stiffness.

¹⁷ Includes somnolence, sedation, lethargy, and hypersomnia.

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Vascular Disorders			
Hypertension ¹⁸	1	2	2

Source: Extracted from Table 23 in the CSR for Study HP-3070-GL-04 and, for combined MedDRA terms, based on the Clinical Reviewer's analysis of the dataset ADAE.xpt using JMP 11.1.1.

The incidence of any extrapyramidal disorder and weight gain appeared to be dose-related.

Extrapyramidal Symptoms

In addition to monitoring for extrapyramidal symptoms (EPS) in Study HP-3070-GL-04, movement disorder scales were completed during this trial to systematically quantify such events. Specifically, the Abnormal Involuntary Movement Scale (AIMS) rates dyskinesia, the Simpson-Angus Scale (SAS) rates symptoms of parkinsonism, and the Barnes Akathisia Rating Scale (BARS) rates akathisia. The total scores on the AIMS, SAS, and BARS range from 0 to 40, 0 to 40, and 0 to 9, respectively. Higher scores indicate more severe symptoms for each scale. Baseline scores and mean changes from baseline to Week 6 in these scales are shown in the following table. Baseline mean scores were low and mean changes were small for each scale in every treatment arm.

Table 24: Mean Changes from Baseline in EPS Scales

		Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo
AIMS Total Score				
Baseline	N	204	204	206
	Mean Score	0.5	0.3	0.3
Week 6	N	163	168	166
	Mean Change	0.0	-0.1	0.1
SAS Total Score				
Baseline	N	204	204	206
	Mean Score	0.4	0.4	0.5
Week 6	N	163	168	166
	Mean Change	0.0	-0.1	-0.2
BARS Total Score				
Baseline	N	204	204	206
	Mean Score	0.0	0.1	0.1
Week 6	N	163	168	166
	Mean Change	0.0	0.0	-0.1

Source: Extracted from Tables 14.3.5.1, 14.3.5.2.2, and 14.3.5.3.1 in the CSR for Study HP-3070-GL-04.

¹⁸ Includes hypertension, blood pressure increased, diastolic hypertension, and hypertensive crisis.

Suicidal Thoughts and Behavior

The C-SSRS was used to detect and assess any treatment-emergent suicidal ideation or behavior during double-blind treatment. No patient in either asenapine TDS treatment arm experienced suicidal behavior (suicide attempt, interrupted suicide, aborted suicide, or preparatory acts for suicide) compared to one patient in the placebo TDS arm. During double-blind treatment, the incidence of suicidal ideation was low across the treatment arms and slightly higher in the placebo arm: 0.0% (0/204), 1.0% (2/204), and 1.5% (3/206) of patients in the asenapine TDS (b) (4), asenapine TDS (b) (4) and placebo TDS groups, respectively, experienced suicidal ideation. The highest reported level of suicidal ideation was active ideation but without a specific plan or intent to act, which was experienced by one patient in the asenapine TDS (b) (4) arm and one patient in the placebo TDS arm.

These data do not indicate an increased risk of suicidal ideation or behavior associated with asenapine TDS.

Laboratory Findings

Laboratory abnormalities associated with sublingual asenapine include increases in liver transaminases, CPK levels, serum prolactin, and metabolic parameters as well as decreases in white blood cell and neutrophil counts. Observed effects of asenapine TDS on these parameters are discussed below. Mean changes and shifts from normal to abnormal values after study drug treatment in Study HP-3070-GL-04 were unremarkable for other chemistry, hematology, and urinalysis parameters.

Mean changes from baseline to Week 6 in relevant laboratory parameters are shown in the table below. Asenapine TDS treatment was associated with larger mean changes from baseline in liver transaminases and creatine kinase. Mean changes in bilirubin, WBC count, and neutrophil count do not suggest hyperbilirubinemia, leukopenia, or neutropenia associated with asenapine TDS in this trial.

Table 25: Mean Changes from Baseline to Week 6 in Laboratory Parameters

	Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo TDS
ALT (U/L)	+3.8	+6.0	-1.1
AST (U/L)	+1.1	+1.9	-1.0
GGT (U/L)	+3.3	+2.4	-2.4
Bilirubin (total) (mg/dL)	-0.01	-0.05	+0.04
Creatine Kinase (U/L)	+7.2	+4.8	-10.2
Prolactin (ng/mL)	+0.2	-0.8	-2.0
WBC (count/mm ³)	+170	+320	-170
Neutrophil (count/ mm ³)	+134	+209	-217

Source: Extracted from Tables 14.3.2.1 and 14.3.2.2 in the CSR for Study HP-3070-GL-04.

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Changes from baseline and shifts from baseline to Week 6 in urinalysis parameters were unremarkable.

The Clinical Reviewer analyzed the laboratory dataset LB.xpt to determine the number of patients who experienced an outlier value for relevant laboratory parameters at any time during double-blind treatment using the criteria below.

Table 26: Laboratory Outlier Criteria

Liver	Hematology
ALT ≥168 U/L (3X ULN)	White Blood Cells ≤2800/mm ³
AST ≥120 U/L (3X ULN)	Neutrophils <1000/mm ³
GGT ≥183 U/L (3X ULN)	Prolactin
Bilirubin (total) ≥2 mg/dL	Prolactin (males) ≥1506 mIU/L (4X ULN)
CK	Prolactin (females) ≥2485 mIU/L (4X ULN)
Creatine Kinase (males) ≥924 U/L (3X ULN)	
Creatine Kinase (females) ≥576 U/L (3X ULN)	

Source: Based on the Clinical Reviewer’s examination of reference ranges in the dataset LB.xpt.

The percentages of patients who met any of these criteria at any time during blinded treatment are shown below. Outlier liver transaminase values were observed in more patients in the asenapine TDS arms than in the placebo arm. One patient in the asenapine TDS (b) (4) group (Subject (b) (6)) experienced a very low neutrophil count at Week 3 of treatment (200/mm³); the count was in the normal range one week later (2270/mm³) and at Week 6 (2490/mm³).

Table 27: Proportions of Patients with an Outlier Laboratory Value At Any Point

Laboratory Parameter	Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo TDS
ALT	3%	2%	0%
AST	1%	1%	0%
GGT	1%	1%	0%
Bilirubin (Total)	1%	0%	1%
Creatine Kinase	2%	2%	2%
Prolactin	1%	0%	2%
White Blood Cells	1%	1%	1%
Neutrophils	0%	1%	0%

Source: Created by the reviewer based on analysis of the dataset LB.xpt using JMP 11.1.1.

One patient who received asenapine TDS (b) (4) dropped out because of elevated ALT levels

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which ranged from 173 to 239 U/L. ALT returned to normal range after stopping study treatment. There was no associated elevation in bilirubin levels or other adverse events in this patient.

No patient met the criteria for a potential Hy's law case (i.e., ALT or AST >3x ULN, alkaline phosphatase <2x ULN, and total bilirubin $\geq$ 2x ULN).

No patient experienced an AE related to increased prolactin levels (i.e., impotence, gynecomastia, or amenorrhea).

Effects on Metabolic Parameters

In addition to the above effects on laboratory endpoints, atypical antipsychotics are associated with alterations in metabolic parameters. Assessments of metabolic effects with asenapine TDS are discussed below.

Mean changes in fasting glucose from baseline to endpoint were:

Asenapine TDS (b) (4)	+3.72 mg/dL (N=172)
Asenapine TDS (b) (4)	+3.28 mg/dL (N=174)
Placebo TDS	+0.03 mg/dL (N=174)

The proportions of patients with shifts in glucose from normal and borderline values to high values are shown in the table below. These data suggest a tendency for asenapine TDS to cause hyperglycemia in a small fraction of patients.

Table 28: Proportion of Patients with Shifts in Fasting Glucose Levels

Shift	Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo TDS
Normal to High <100 to $\geq$ 126 mg/dL	3.0%	3.1%	0.0%
Borderline to High ($\geq$ 100 to <126) to $\geq$ 126 mg/dl	1.0%	1.0%	2.0%

Source: Extracted from Appendix Table 2 in the Applicant's Summary of Clinical Safety.

No patient had a baseline HbA1C value of 7% or higher. During double-blind treatment, an HbA1C value of 7% or greater was reported in 1%, 2%, and 1% of patients treated with asenapine TDS (b) (4), asenapine TDS (b) (4) and placebo TDS, respectively.

Changes from baseline in serum lipid levels are displayed below.

Table 29: Mean Change from Baseline to Endpoint in Lipid Parameters

	Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo TDS
Total Cholesterol (mg/dL)	+4.5	+5.1	+0.7
LDL (mg/dL)	+4.2	+1.4	+1.6
HDL (mg/dL)	-0.7	+0.2	-0.8
Fasting Triglycerides (mg/dL)	+6.7	+17.3	-2.6

Source: Extracted from Table 29 in the Applicant's Summary of Clinical Safety.

The proportions of patients with shifts in lipid measures from normal values to high values are shown in Table 30. **Table 20. Table 20**

Table 30: Proportions of Patients with Shifts in Lipid Parameters

Shift	Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo TDS
Tot. Cholesterol Normal to High (<200 to ≥ 240 mg/dL)	1.0%	2.6%	1.0%
LDL Normal to High (<100 to ≥ 160 mg/dL)	0.0%	1.0%	0.5%
HDL Normal to Low (≥ 40 to <40 mg/dL)	12.1%	10.7%	8.1%
Fasting TGs Normal to High (<150 to ≥ 200 mg/dL)	3.2%	7.0%	1.1%

Source: Extracted from Appendix Table 2 in the Applicant's Summary of Clinical Safety.

Mean changes from baseline to endpoint in body weight were greater with asenapine TDS than with placebo treatment, with no evidence of a dose-response effect:

Asenapine TDS (b) (4)	+2.0 kg (N=164)
Asenapine TDS (b) (4)	+2.1 kg (N=168)
Placebo TDS	+0.6 kg (N=167)

Also, the percentages of subjects who experienced a 7% or greater increase in body weight from baseline to endpoint were greater with asenapine TDS than with placebo treatment:

Asenapine TDS (b) (4)	14%
Asenapine TDS (b) (4)	18%
Placebo TDS	4%

Similarly, mean changes from baseline to Week 6 in BMI were greater with asenapine TDS than

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with placebo treatment:

Asenapine TDS (b) (4)	+0.7 kg/m ²
Asenapine TDS (b) (4)	+0.7 kg/m ²
Placebo TDS	+0.2 kg/m ²

The pattern of changes in metabolic measures and body weight were similar to those observed with asenapine sublingual tablets.

Vital Signs

Mean changes from baseline in blood pressure, pulse rate, and body temperature were remarkable only for increases in pulse rate with asenapine TDS compared to placebo. These changes were noticeable beginning at Week 1 but were less prominent by Week 6, as shown below for supine pulse rate.

Table 31: Mean Changes from Baseline in Supine Pulse Rate (bpm)

	Asenapine TDS (b) (4)		Asenapine TDS (b) (4)		Placebo TDS	
	N	Mean Δ	N	Mean Δ	N	Mean Δ
Week 1	203	+3.8	202	+3.0	203	+1.0
Week 6	164	+2.0	168	+0.9	167	+0.7

Source: Extracted from Table 14.3.4.1 in the CSR for Study HP-3070-GL-04.

The proportions of patients who had a markedly abnormal vital sign measurement at any time during double-blind treatment are displayed in the following table. Rates were low and there were no major differences between the asenapine TDS groups and placebo-treated patients.

Table 32: Proportion of Patients with Markedly Abnormal Vital Signs

Criteria ¹⁹	Asenapine TDS (b) (4)	Asenapine TDS (b) (4)	Placebo TDS
	N=204	N=204	N=206
Systolic Blood Pressure			
≤90 mmHg and decr. ≥20 mmHg	0.5%	0.0%	0.0%
≥180 mmHg and incr. ≥20 mmHg	0.5%	0.5%	0.0%
Diastolic Blood Pressure			
≤50 mmHg and decr. ≥15 mmHg	0.0%	0.0%	0.0%
≥105 mmHg and incr. ≥15 mmHg	0.5%	0.5%	1.0%

¹⁹ Increases and decreases are relative to baseline.

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Heart Rate			
≤50 bpm and decr. ≥15 bpm	0.0%	0.0%	0.5%
≥120 bpm and incr. ≥15 bpm	0.5%	0.5%	1.5%
Body Temperature			
≥38.3° and incr. ≥1.1°C	0.0%	0.5%	0.5%

Source: Extracted from Table 14.3.4.3 in the CSR for Study HP-3070-GL-04.

Atypical antipsychotics are associated with orthostatic hypotension and syncope, with the highest risk during initial dose titration or dose increases. A small percentage of patients treated with sublingual asenapine tablets in clinical trials experienced syncope. Orthostatic hypotension was defined as a ≥30 mmHg decrease in systolic blood pressure or a ≥20 mmHg decrease in diastolic blood pressure after three minutes of standing compared to supine values. During Study HP-3070-GL-04, in the asenapine TDS (b) (4) arm, one patient at Week 2 and two patients at Week 3 met this criterion. One placebo TDS-treated patient met this criterion at Week 5. No patients in the asenapine TDS (b) (4) arm met this criterion at any assessment.

No patient in this trial experienced an adverse event coded to the MedDRA Preferred Terms syncope, presyncope, syncope vasovagal, loss of consciousness, or drop attacks.

Electrocardiograms (ECGs)

Mean changes from baseline in ECG parameters were remarkable only for increases in heart rate (consistent with the increases in pulse rate noted above) and QTc. Changes from baseline at Weeks 1 and 6 in these measures are shown below.

Table 33: Mean Changes from Baseline in ECG Parameters

	Asenapine TDS (b) (4)		Asenapine TDS (b) (4)		Placebo TDS	
	N	Mean Δ	N	Mean Δ	N	Mean Δ
Heart Rate (bpm)						
Week 1	203	+5.2	202	+3.7	202	+1.8
Week 6	164	+4.8	166	+1.5	165	+0.7
QTcB (msec)						
Week 1	202	+5.8	201	+3.1	201	-1.0
Week 6	163	+4.5	164	+1.8	164	-0.8
QTcF (msec)						
Week 1	202	+1.1	201	-0.3	201	-2.7
Week 6	163	+0.1	164	+0.6	164	-1.7

Source: Extracted from Table 14.3.3.1 in the CSR for Study HP-3070-GL-04.

The proportions of patients who had a markedly abnormal ECG parameter at any time during double-blind treatment are displayed below. A slightly higher proportion of asenapine TDS-

treated patients than placebo TDS-treated patients experienced abnormal increases in QTc values, heart rate, PR interval, and QRS interval. No patient had a QTc value above 500 msec.

Table 34: Proportion of Patients with Markedly Abnormal ECG Results

Criteria	Asenapine TDS	Asenapine TDS	Placebo TDS
	(b) (4) N=204	(b) (4) N=204	N=206
QTcB			
>500 msec	0.0%	0.0%	0.0%
Incr. ≥30 msec	29.9%	25.0%	24.3%
Incr. ≥60 msec	0.5%	2.5%	1.5%
QTcF			
>500 msec	0.0%	0.0%	0.0%
Incr. ≥30 msec	7.4%	6.9%	4.4%
Incr. ≥60 msec	0.0%	1.0%	0.5%
Heart Rate ≥100 bpm	15.2%	12.3%	12.1%
PR Interval ≥210 msec	3.4%	2.0%	1.5%
QRS Interval ≥120 msec	1.0%	0.5%	0.0%

Source: Extracted from Table 30 in the CSR for Study HP-3070-GL-04.

One patient treated with asenapine TDS (b) (4) was diagnosed with an “acute coronary syndrome” based on ECG findings. This patient ((b) (6)), who had a history of coronary artery disease and hypertension, is discussed above under Serious Adverse Events. One placebo TDS-treated patient dropped out due to a prolonged QTcB interval (maximum 464 msec at Week 3). Other reported AEs related to ECG abnormalities were first-degree AV block and sinus arrhythmia, both in patients treated with placebo TDS. No patient had an AE related to a ventricular arrhythmia.²⁰

QTc data are consistent with data with asenapine sublingual tablets. In a dedicated QT study with sublingual asenapine at doses up to 20 mg BID, there were increases in the QTc interval ranging from 2 to 5 msec compared to placebo. No patient had a QTc ≥500 msec, an increase from baseline in QTc ≥60 msec, or Torsade de Pointes or any other AE associated with delayed ventricular repolarization.

8.2.5. Analysis of Submission-Specific Safety Issues

Dermatologic reactions are a safety issue specific to this asenapine product. Application site

²⁰ AEs that were coded to the MedDRA Preferred Terms accelerated idioventricular rhythm, rhythm idioventricular, Torsade de Pointes, ventricular arrhythmia, ventricular bigeminy, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, ventricular tachycardia, or ventricular trigeminy.

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reactions (ASRs) were a common and drug-related adverse reaction in both asenapine TDS treatment arms, with about 15% of asenapine TDS-treated patients experiencing an ASR:

Asenapine TDS (b) (4)	14% (28/204)
Asenapine TDS (b) (4)	15% (31/204)
Placebo TDS	4% (8/206) ²¹

Although the asenapine TDS rates were higher than the placebo TDS rate, there was no indication of a dose-response relationship. None of these reactions was classified as serious. Among the 336 treatment-emergent ASRs reported in patients comprising the SAF, 78% (262/336) were rated as mild and 22% (73/336) were rated as moderate in severity. Only one ASR (erythema) was rated as severe (in one patient in the asenapine TDS (b) (4) arm). Of all ASRs, 96% (321/336) resolved without sequelae.

Two patients dropped out because of an ASR, one in the asenapine TDS (b) (4) group because of application site pruritus and one in the asenapine TDS (b) (4) group because of multiple occurrences of moderate skin hyperpigmentation. The latter event occurred in Patient (b) (6) a 26 year old white female. Hyperpigmentation was noted at five application sites on four different days (Days 6, 14, 16, and 21 of double-blind treatment). Study drug was stopped and AmbiFade Cream was applied.²² Three of the five reactions were reported as “not resolved” as of 27 days after the last TDS removal. This patient’s past medical history was remarkable only for a dust allergy.

Four patients experienced papules: in three cases, the reaction were rated as mild (after the asenapine (b) (4) TDS) and one reaction was moderate (after the asenapine (b) (4) TDS). None resulted in dropout and all resolved.

Erythema was the most common type of ASR reported: 9.8%, 9.3%, and 1.5% of patients in the asenapine TDS (b) (4), asenapine TDS (b) (4), and placebo arms, respectively, reported erythema. Other types of ASRs were dermatitis, discomfort, dryness, exfoliation, induration, irritation, edema, pain, papules, and pruritus.

The following table presents an overall enumeration of patients by maximum rating of skin irritation by visual inspection after TDS removal.

²¹ Rates were calculated based on combined Preferred Terms, as described in [Section 8.2.3](#).

²² AmbiFade cream contains topical hydroquinone (a depigmenting agent).

Table 35: Enumeration of Patients (n(%)) by Maximum Skin Irritation

Maximum Skin Irritation Score	Asenapine TDS (b) (4) (N=204)	Asenapine TDS (b) (4) (N=204)	Placebo (N=206)
0= No evidence of irritation	112 (55%)	121 (59%)	168 (82%)
1= Minimal irritation	62 (30%)	54 (27%)	30 (15%)
2= Definite erythema, readily visible; minimal edema or minimal papular response	25 (12%)	25 (12%)	6 (3%)
3= Erythema and papules	2 (1%)	1 (<1%)	0
4= Definite edema	1 (<1%)	0	1 (<1%)
5= Erythema, edema, and papules	0	1 (<1%)	0
6= Vesicular eruption	0	0	0
7= Strong reaction spreading beyond the application site	0	0	0

Source: Table 28 in the CSR for Study HP-3070-GL-04.

A dedicated study to systematically evaluate skin irritation and sensitization was conducted and is described in Section 8.2.8.

The number of complete TDS detachments was roughly the same in each treatment arm and, overall, was 0.2% (37/18934). The occurrence of partial TDS detachments was higher at 1.9% (368/18934) overall.

An overall enumeration of patients by maximum adhesive residue score is provided in the table below.

Table 36: Enumeration of Patients (n(%)) by Maximum Adhesive Residue

Maximum Adhesive Residue	Asenapine TDS (b) (4) (N=202)	Asenapine TDS (b) (4) (N=198)	Placebo (N=197)
0= None	137 (68%)	133 (67%)	126 (64%)
1= Mild	50 (25%)	57 (29%)	53 (27%)
2= Medium	15 (7%)	6 (3%)	17 (9%)
3= Heavy	0	2 (1%)	1 (<1%)

Source: Extracted from Table 27 in the CSR for Study HP-3070-GL-04.

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

No COA analyses were necessary to evaluate safety.

8.2.7. Safety Analyses by Demographic Subgroups

An exploratory analysis of the incidence of all AEs under the common AE term “Application Site Reaction” (ASR) by the demographic variables age, sex, and race revealed that patients of the Black race experienced higher rates of ASRs across all treatment arms compared to White patients, as shown on Table 37.²³

Table 37: Incidence (n/N(%)) of ASRs by Age, Sex, and Race

	Asenapine TDS ^{(b) (4)}	Asenapine TDS ^{(b) (4)}	Placebo TDS
AGE			
<50 years	19/144 (13%)	21/146 (14%)	6/141 (4%)
≥50 years	9/60 (15%)	10/58 (17%)	2/65 (3%)
SEX			
Male	17/110 (15%)	18/131 (14%)	6/131 (5%)
Female	11/94 (12%)	13/73 (18%)	2/75 (3%)
RACE			
White	16/158 (10%)	21/157 (13%)	2/152 (1%)
Black	11/44 (25%)	10/47 (21%)	6/54 (11%)

Source: Created by the reviewer based on analysis of the dataset ADAE.xpt using JMP 11.1.1.

In the asenapine TDS^{(b) (4)} and placebo TDS arms, the racial difference was statistically significant (p-values = 0.02 and <0.01, respectively, using a two-tailed Fisher’s exact test). Erythema was the most common ASR report in whites and blacks (54% and 49% of all reports, respectively), followed by pruritus (24% and 29% of all reports, respectively).

8.2.8. Specific Safety Studies

Cumulative Skin Irritation and Sensitization Study

Study HP-3070-US-06 was a single-center, phase 1 study conducted in the U.S. to assess cumulative skin irritation and sensitization of the asenapine TDS in healthy adults. Maryjoy Mejia, MD, Clinical Reviewer in the Division of Dermatology and Dental Products (DDDP), completed a review of this study on July 3, 2019. Her review is summarized below.

This study was comprised of two groups:

²³ The number of patients from other race subgroups (N=2) was too small to meaningfully analyze.

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- Group 1: Evaluation of cumulative irritation and sensitization potential. The treatment phase consisted of induction, rest, challenge, and rechallenge periods.
- Group 2: Evaluation of cumulative irritation. The treatment phase consisted of a two-week cumulative irritation period.

Test products were:

- Treatment A: Asenapine TDS ([REDACTED] (b) (4) TDS).
- Treatment B: Placebo (0.0 mg/[REDACTED] (b) (4) TDS).
- Treatment C: Negative control TDS (0.9% saline TDS).

Subjects were healthy females and males, ages 18 to 50 years. Subjects with a history of significant allergies and those using medications that would alter inflammatory or immune response to the test products were excluded. A history of sensitivity to asenapine or adhesive dressings was also exclusionary.

Group 1

During induction, the three test products were applied to the back three times per week for three weeks. Applications were to the same site as the previous application unless precluded by skin irritation at the site. This was followed by a 10- to 17-day rest period. In the challenge period, the three test products were applied to treatment-naïve skin and worn for 48 hours to assess for sensitization. In subjects with suspected sensitization, there was a 3-week rest period followed by rechallenge to treatment-naïve skin. A total of 201 subjects completed this part of the study. The proportion of subjects with a meaningful degree of dermal response was substantially higher for the asenapine TDS (21%) compared to placebo TDS (1%) and 0.9% saline (6%).²⁴ Two subjects had equivocal sensitization at the sensitization assessment (one subject with placebo and saline TDSs and one subject with the asenapine TDS). On rechallenge, it was determined that sensitization had occurred in neither subject.

Group 2

The three test products were applied to the same respective application sites on the back daily for 21 days. A total of 33 subjects completed this treatment. The proportion of subjects with a meaningful degree of dermal response was much higher for the asenapine TDS (97%) compared to placebo TDS (9%) and 0.9% saline (0%).

Dr. Mejia concluded that the asenapine (b) (4) TDS was found to be more irritating than the placebo TDS or saline TDS in this study. However, the observed irritation in Group 2 (following

²⁴ A meaningful dermal response was defined by degree of irritation as well as other effects, such as skin glazing, film of exudate, or scabbing.

daily application to the same site) does not reflect intended use of the to-be-marketed product. Contact sensitization was not observed in this study. The proposed product labeling addresses the potential for skin irritation.

8.2.9. Additional Safety Explorations

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no overdoses involving asenapine TDS. There were no reports of adverse events that suggested abuse potential, withdrawal, or rebound symptoms associated with asenapine TDS treatment in Study HP-3070-GL-04.²⁵

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No postmarketing safety data are available for asenapine TDS.

Postmarketing safety experience with sublingual asenapine is notable for reports of application site reactions, primarily in the sublingual area. These reactions include oral ulcers, blisters, peeling/sloughing, and inflammation. In addition, there have been reports of choking in patients who may also have experienced oropharyngeal muscular dysfunction or hypoesthesia.²⁶ These reactions are unlikely with asenapine TDS because of the transdermal route of administration.

Expectations on Safety in the Postmarket Setting

Postmarketing experience with asenapine TDS will likely be remarkable for skin ASRs. (b) (5)

Otherwise, postmarketing adverse event reports are expected to be consistent with those for other atypical antipsychotic drugs.

8.2.11. Integrated Assessment of Safety

The most prominent safety concern with asenapine TDS is the frequent occurrence of ASRs, which occurred in approximately 20% of patients treated with asenapine TDS in Study HP-3070-

²⁵ This conclusion is based on a search by the Clinical Reviewer of the adverse event database AE.xpt for any of the following MedDRA Preferred Terms: drug tolerance, habituation, drug withdrawal syndrome, substance related disorder, euphoric mood, elevated mood, feeling drunk, feeling of relaxation, withdrawal psychosis, and rebound psychosis.

²⁶ From Section 6.2 of Saphris labeling.

GL-04. None of these reactions was classified as serious and most were rated as mild (78%) or moderate (22%) in severity. Erythema was the most common type of ASR. Two patients dropped out because of ASRs, one because of pruritus and a second because of hyperpigmentation, which persisted well after stopping asenapine TDS treatment. The potential for asenapine TDS to cause skin irritation was confirmed in Study HP-3070-US-06, which systematically evaluated cumulative dermal irritation and sensitization. No evidence of skin sensitization was seen in that study. Information regarding ASRs will be labeled under Warnings and Precautions. Given that no ASR was serious, most were mild, and most resolved without sequelae, the Clinical Reviewer does not recommend a REMS or an enhanced pharmacovigilance (EPV) program because of the potential for these reactions.

Otherwise, the major safety findings with asenapine TDS are consistent with the systemic effects of sublingual asenapine and other oral atypical antipsychotics, such as metabolic effects (like weight gain and dyslipidemia) and extrapyramidal symptoms.

Increases from baseline in liver transaminases, pulse and heart rate, and QTc interval were also observed. These changes were relatively small, not associated with adverse events, and are consistent with observed findings with sublingual asenapine.

8.3. Statistical Issues

Both HP-3070 treatment groups showed statistical significance when compared with the placebo group on the primary and the key secondary endpoint. However, the results did not suggest additional benefit of the (b) (4) over the (b) (4) dose whether on the primary or the key secondary endpoint (see Table 15 and Table 17). In addition, the observed treatment differences in CGI-S appeared to be very small.

8.4. Conclusions and Recommendations

The Applicant has provided sufficient evidence that asenapine TDS, under the conditions of use described in labeling, is efficacious in treating adult patients with an exacerbation of schizophrenia. Although asenapine TDS is clearly associated with ASRs, those reactions are not deemed to be of such severity that they would preclude approval of this product. The Clinical Reviewer recommends that this application be approved.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting or other external consultation was not deemed necessary as part of the application review.

10 Pediatrics

Schizophrenia has a very low prevalence in pediatric patients 12 years of age and younger and, thus, studies in that age range have not been required to satisfy the Pediatric Research Equity Act (PREA). Therefore, the Agreed initial Pediatric Study Plan (iPSP) for asenapine TDS, dated March 17, 2017, included the following deferred clinical studies only for adolescents with schizophrenia:

- A Modeling and Simulation study of pharmacokinetics to determine appropriate dosing.
- A short-term safety and efficacy trial.
- A long-term, open label safety extension study.

This plan was reviewed by the Division on June 20, 2019, and by the Pediatric Review Committee (PeRC) on July 10, 2019. Because an adequate and well controlled trial of sublingual asenapine in the treatment of adolescents with schizophrenia failed to demonstrate statistical superiority over placebo and given the possibility that the transdermal route of administration of asenapine TDS may be associated with poor treatment compliance in adolescents with schizophrenia (because the TDS can be removed at any time), the Division decided to not require an adolescent study. This decision was affirmed by the PeRC as part of the PREA Assessment of this application on August 14, 2019.

(b) (4)



A response from the Applicant is pending at this time.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Clinical Comments

Clinical comments on the Applicant's proposed labeling were discussed at Labeling Meetings on the following dates: July 1, July 15, July 25, July 29, August 12, and August 26, 2019. The Clinical Reviewer has added revisions with explanatory comments to draft labeling in SharePoint.

Other Prescription Drug Labeling

Clinical Comments

DMEPA has recommended several clarifications to the Instructions For Use (IFU) based on findings from the Summative Usability Study (Study HP-3070-US-09). The Clinical Review Team was consulted on these changes and provided feedback to DMEPA on July 31 and August 6.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not needed for this product.

13 Postmarketing Requirements and Commitment

There are no Postmarketing Requirements or Commitments planned for this application.

Asenapine TDS will likely be used chronically in the treatment of patients with schizophrenia. Hence, provision or a requirement to provide information on the maintenance of efficacy over the long-term is needed to support approval for this indication. However, because long-term efficacy in treating patients with schizophrenia was established for sublingual asenapine and the bioavailability of asenapine is comparable between the sublingual and transdermal products, long-term efficacy may be extrapolated from sublingual asenapine to asenapine TDS. Therefore, no maintenance study of asenapine TDS in patients with schizophrenia is required.

As discussed in Section 10 above, the Division decided not to require studies of asenapine TDS in adolescent patients with schizophrenia.

14 Division Director (OCP) Comments

15 Division Director (OB) Comments

16 Division Director (Clinical) Comments

This 505(b)(2) application includes data in support of Secuado, a transdermal delivery system (TDS) for the atypical antipsychotic, asenapine, referencing the Agency's previous findings of safety and effectiveness of the listed drug, Saphris (NDA 22117). Saphris is approved for the treatment of adult patients with schizophrenia and patients age 10 years and older with manic or mixed mood episodes associated with bipolar I disorder. Secuado is intended for once daily application to treat adult patients with schizophrenia. As described in the review above, based on a PK bridge to the listed drug and a single adequate and well-controlled clinical study, the Applicant has provided substantial evidence of effectiveness for the treatment of adults with schizophrenia and this application will be approved.

17 Appendices

17.1. Financial Disclosure

Covered Clinical Study: HP-3070-US-05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>5</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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Covered Clinical Study: HP-3070-GL-04

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>59</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.2. Nonclinical Pharmacology/Toxicology

Not applicable.

17.3. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable.

17.4. Additional Clinical Outcome Assessment Analyses

No additional clinical outcome assessment analyses were performed.

17.5. Additional Statistical Sensitivity Analyses

The statistics reviewer conducted the sensitivity analysis on the primary endpoint to evaluate the impact of concomitant antipsychotic medication use on the efficacy results. The primary model was performed on the FAS patients who didn't take any concomitant antipsychotic drug. A total number of 332 patients were removed from the FAS for the sensitivity analysis. The results still supported superiority of both asenapine treatment groups over placebo after exclusion of patients who took a concomitant antipsychotic drug.

Table 38: Primary Analysis Results on Change from Baseline in PANSS Total Score at Week 6 (patients without taking concomitant antipsychotic medication)

	Placebo (n=91)	HP-3070 (b) (4) (n=89)	HP-3070 (b) (4) (n=95)
Mean score at Baseline (SD)	95.7 (9.49)	97.9 (10.90)	94.7 (8.36)
Mean Score at Week 6 (SD)	76.3 (18.1)	73.1 (15.70)	72.1 (15.4)
LS Mean Change from Baseline (SE)	-16.5 (1.64)	-23.7 (1.68)	-21.9 (1.69)
Placebo-subtracted Difference (95% CI)		-7.25 (-11.79, -2.71)	-5.4 (-9.94, -0.86)
Unadjusted P-value		0.002	0.02

Abbreviations: CI = Confidence Interval; LS = least squares; Max = maximum; Min = minimum; N = number of subjects in the Full Analysis Set by treatment group; n = number of subject in calculation; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = Standard Error

Notes: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication. The mixed model for repeated measures includes treatment, country, visit, treatment by visit interaction, and Baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degree of freedom.

Source: Biostatistics Reviewer's Analysis

The Applicant conducted the sensitivity analysis to verify the missing at random (MAR) assumption underlying the primary efficacy MMRM analyses (FAS population). A PMM using a placebo-based multiple imputation method was performed to explore the robustness of the MMRM results for the primary efficacy variable for the ITT population.

1: The treatment comparison analysis of change from Baseline in PANSS total score at Week 6 by the Pattern-Mixture Model for dropout Pattern 1 (using a placebo-based multiple imputation) is summarized for the FAS population.

Table 39: Primary Analysis Results on Change from Baseline in PANSS Total Score at Week 6 (Full Analysis Set)

	Placebo (n=203)	HP-3070 (b) (4) (n=201)	HP-3070 (b) (4) (n=203)
Mean score at Baseline (SD)	97.4 (10.07)	97.0 (9.78)	95.6 (8.68)
Mean Score at Week 6 (SD)	75.4 (16.58)	75.0 (16.67)	74.0 (15.63)
LS Mean Change from Baseline (SE)	-14.2 (1.67)	-20.1 (1.67)	-18.4 (1.66)
Placebo -subtracted Difference (95% CI)		-5.9 (-9.11, -2.76)	-4.3 (-7.44, -1.09)
Unadjusted P-value		<0.001	0.009

Abbreviations: CI = Confidence Interval; LS = least squares; Max = maximum; Min =minimum; N = number of subjects in the Full Analysis Set by treatment group; n = number of subject in calculation; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = Standard Error

Notes: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication. A pattern-mixture model approach using a placebo-based multiple imputation has been used for this analysis. Imputed datasets are analyzed with a mixed model for repeated measures including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degree of freedom.

Source: Applicant’s Analysis (14.2.1.2.1.1of CSR), confirmed by Biostatistics Reviewer

The Applicant also performed PMM analysis for the patterns 2 and 3 below. For these analyses, only the discontinuation reasons considered as informative will be imputed using the placebo-based imputation model; discontinuations for non-informative reasons will be multiply imputed using the MAR assumption within each treatment arm.

2: The treatment comparison analysis for Pattern 2 (using a placebo-based multiple imputation for discontinuation due to lack of efficacy, AE, or death) is summarized for the FAS.

Table 40: Primary Analysis Results on Change from Baseline in PANSS Total Score at Week 6 (Full Analysis Set)

	Placebo (n=203)	HP-3070 (b) (4) (n=201)	HP-3070 (b) (4) (n=203)
Mean score at Baseline (SD)	97.4 (10.07)	97.0 (9.78)	95.6 (8.68)
Mean Score at Week 6 (SD)	75.4 (16.58)	75.0 (16.67)	74.0 (15.63)
LS Mean Change from Baseline (SE)	-14.3 (1.65)	-20.2 (1.66)	-18.5 (1.65)
Placebo -subtracted Difference (95% CI)		-6.0 (-9.12, -2.80)	-4.2 (-7.36, -1.06)
Unadjusted P-value		<0.001	0.009

Abbreviations: CI = Confidence Interval; LS = least squares; Max = maximum; Min =minimum; N = number of subjects in the Full Analysis Set by treatment group; n = number of subject in calculation; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = Standard Error

Notes: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication. A pattern-mixture model approach using a placebo-based multiple imputation has been used for this analysis. Imputed datasets are analyzed with a mixed model for repeated measures including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degree of freedom.

Source: Applicant's Analysis (14.2.1.2.1.2 of CSR), confirmed by Biostatistics Reviewer.

3: The treatment comparison analysis for Pattern 3 (using a placebo-based multiple imputation for discontinuation due to lack of efficacy) is summarized for the FAS.

Table 41: Primary Analysis Results on Change from Baseline in PANSS Total Score at Week 6 (Full Analysis Set)

	Placebo (n=203)	HP-3070 (b) (4) (n=201)	HP-3070 (b) (4) (n=203)
Mean score at Baseline (SD)	97.4 (10.07)	97.0 (9.78)	95.6 (8.68)
Mean Score at Week 6 (SD)	75.4 (16.58)	75.0 (16.67)	74.0 (15.63)
LS Mean Change from Baseline (SE)	-14.3 (1.66)	-20.2 (1.66)	-18.6 (1.65)
Placebo -subtracted Difference (95% CI)		-6.0 (-9.15, -2.83)	-4.3 (-7.46, -1.14)
Unadjusted P-value		<0.001	0.008

Abbreviations: CI = Confidence Interval; LS = least squares; Max = maximum; Min =minimum; N = number of subjects in the Full Analysis Set by treatment group; n = number of subject in calculation; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = Standard Error

Notes: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication. A pattern-mixture model approach using a placebo-based multiple imputation has been used for this analysis. Imputed datasets are analyzed with a mixed model for repeated measures including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degree of freedom.

Source: Applicant's Analysis (14.2.1.2.1.3 of CSR), confirmed by Biostatistics Reviewer

The results of this analysis, shown in Table 39 through Table 41 were in line with MMRM results for the primary efficacy variable; thus, the Applicant concluded that the MMRM results (primary analyses) were robust.

In addition, the Applicant performed a second sensitivity (supplementary) analysis based on rank-transformed PANSS total score data to assess the impact on treatment group comparisons. The ANCOVA allowed for a comparison of the changes from Baseline at Week 6, adjusting for Baseline and country.

4: The ANCOVA on rank-transformed PANSS total score data at Week 6 analyses for the FAS population is summarized in Table 42.

Table 42: ANCOVA on Rank-Transformed PANSS Total Score Data at Week 6 Full Analysis Set

	Placebo (n=203)	HP-3070 (b) (4) (n=201)	HP-3070 (b) (4) (n=203)
Rank-Transformed Change from Baseline to Week 6	0.55 (0.29)	0.45 (0.28)	0.49 (0.28)
LS Mean Change from Baseline (SE)	0.00 (0.074)	-0.1 (0.078)	-0.1 (0.082)
Unadjusted P-value		0.002	0.027

Abbreviations: CI = Confidence Interval; LS = least squares; Max = maximum; Min = minimum; N = number of subjects in the Full Analysis Set by treatment group; n = number of subject in calculation; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = Standard Error

Notes: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication. The values of the change from baseline variable as well as baseline covariate are transformed to standardized ranks within each country, using fractional ranks and mean method for ties. Before performing the rank transformation, subjects with missing data at week 6 due to discontinuation for any reason are imputed with a change from baseline equal to the largest change from baseline in observed data plus 1, so that these subjects have the highest rank after the transformation. Separate regression models are fit for each country using a regression model for change from baseline with baseline as predictor. P-value is based on the Cochran-Mantel-Haenszel test, controlling for country. The hypothesis tested is the Row Mean Score Differ statistic, using the values of the residuals as scores.

Source: Applicant's Analysis (14.2.1.2.6 of CSR), confirmed by Biostatistics Reviewer

As with the primary analysis, for both dose levels of HP-3070, the Applicant claimed that the treatment difference achieved statistical significance ($p < 0.05$) in favor of HP-3070 at Week 6.

Reviewer's Note: *This reviewer opines that the ANCOVA on rank-transformed PANSS total score data should be considered as an analysis to shed some light on how useful the treatment is. That is, if the treatment is beneficial (in term os efficacy) but the patient dropped out of study or discontinued the treatment, the question is how useful the treatment is. In this approach, it is not clear whether the Applicant's approach to handling missing data is sensible because the dropouts were ranked without considering the dropout time.*

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/s/

SHIN-YE CHANG
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SONIA A TABACOVA
10/11/2019 06:18:15 AM

AISAR H ATRAKCHI
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LUNING ZHUANG
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YANG YANG
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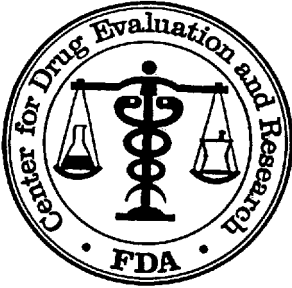
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GREGORY M DUBITSKY
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Recommend approval with agreed labeling.

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US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics
Division of Biometrics VI

STATISTICAL REVIEW AND EVALUATION

NDA NO.	212268
SERIAL NO.	1
DATE RECEIVED BY THE CENTER	01/08/2019
DRUG NAME	Asenapine TDS
DOSAGE FORM	TDS
INDICATION	Schizophrenia
SPONSOR	Hisamitsu Pharmaceutical Co., Inc.
REVIEW FINISHED	08/08/2019
STATISTICAL REVIEWER	Chao Wang, Ph.D.
SECONDARY REVIEWER	Meiyu Shen, Ph.D.
PROJECT MANAGER	Teshara Bouie

Chao Wang, Ph.D., Mathematical Statistician, CDER/OTS/OB/DBVI
Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DBVI

Concur: _____
Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DBVI

CC List:
Teshara Bouie, OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI

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1 Executive summary

I evaluated the applicant's in vivo adhesion data collected in the clinical study HP-3070-US-08 for NDA 212268.

- The adhesion data were collected from 99 patches used by 99 subjects for HP-3070 in two strengths (b) (4) [REDACTED]
- Exploratory analysis showed that the (b) (4) strength appeared to adhere better than the (b) (4) strength.
- The formal statistical analysis was performed in terms of the probability that a randomly selected TDS maintains at least 75% adhesion throughout the entire wear period.
- Using all data for HP-3070 (b) (4) in the per protocol population, the estimated probability that a randomly selected TDS of HP-3070 (b) (4) maintains at least 75% adhesion was 0.96 and the 95% lower confidence limit for this probability was 0.89.
- Using all data for HP-3070 (b) (4) in the per protocol population, the estimated probability that a randomly selected TDS of HP-3070 (b) (4) maintains at least 75% adhesion was 0.86 and the 95% lower confidence limit for this probability was 0.76.
- The analysis of such probability for each combination of application site and strength showed that upper chest was the application site with the worst adhesion for both strengths.
- After we excluded the adhesion data from upper chest, the estimated probability that a randomly selected TDS of HP-3070 (b) (4) maintains at least 75% adhesion changed to 1 and the 95% lower confidence limit for this probability changed to 0.95.
- After we excluded the adhesion data from upper chest, the estimated probability that a randomly selected TDS of HP-3070 (b) (4) maintains at least 75% adhesion changed to 0.92 and the 95% lower confidence limit for this probability changed to 0.83.

2 Introduction

On January 8, 2019, FDA Office of Pharmaceutical Quality, Office of New Drug Products requested the Division of Biometrics VI, Office of Biostatistics to evaluate the applicant's in vivo adhesion data of a transdermal delivery system (TDS) product in the clinical study HP-3070-US-08 in Section 5.3.5.4 of the NDA 212268 application package dated December 13, 2018.

In this evaluation, I reviewed the study and analyzed the in vivo adhesion data.

3 Statistical reviewer's analysis

3.1 Overview

The study was a randomized, open-label, Phase I study, assessing the adhesion performance of 2 strengths of HP-3070 (b) (4) and (b) (4) for 24 hours in adults with schizophrenia.

The applicant planned a total of 100 subjects and randomly assigned them to 1 of the 2 treatment arms (b) (4) or (b) (4). One TDS was placed at 1 of 5 randomly assigned application sites: upper chest, abdomen, upper arm, upper back, and hip by clinic staff and measured according to the scoring system defined by the FDA guidance, *Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs*:

- 0: $\geq 90\%$ adhered (essentially no lift off the skin),
- 1: $\geq 75\%$ to $< 90\%$ adhered (some edges only lifting off the skin),
- 2: $\geq 50\%$ to $< 75\%$ adhered (less than half of the TDS lifting off the skin),
- 3: $> 0\%$ to $< 50\%$ adhered (not detached, but more than half of the TDS lifting off the skin without falling off),
- 4: = 0% adhered (TDS detached; completely off the skin).

In addition to the score, percent adhesion was also recorded. Clinic staff assessed patch adhesion throughout the day at 4, 8, 12, 16, and 24 hours (± 15 minutes) after patch application. Photographs were also taken immediately after each adhesion assessment.

One subject (Subject (b) (6) with HP-3070 (b) (4) applied on hip) had to leave the clinic prior to the scheduled TDS removal time. The patch was applied at 16:30, May 16, 2018 and removed at 14:35, May 17, 2018. The subject was considered withdrawn and all end of study assessments were conducted at that time. Thus Subject (b) (6) was removed from the per protocol population. No other patches were removed early. The per-protocol population consisted of 99 subjects whose TDS was not intentionally removed early or who were not discontinued prior to the end of the labeled duration of patch wear for reasons unrelated to adhesion. In this evaluation, I only analyzed the data from the per protocol population.

There was one case of complete detachment. The TDS of Subject (b) (6) (HP-3070 (b) (4) on hip) was found to have completely detached at the 8-hour post application adhesion assessment which was conducted at 23:00, June 1, 2018. The patch was applied at 15:00, June 1, 2018. The exact time of detachment was unknown. The subject was sleeping in bed and upon waking the patch was found detached on the subject's bed.

In the following analysis, I did not transform the original measured scores by the worst score carry forward method.

3.2 Study design and conduct

There were no significant issues regarding the study design and conduct which may impact the data quality adversely.

3.3 Exploratory data analysis

There were 68 (68.69%) TDSs which had scores 0 throughout the entire wear period, including 42 (84%) for HP-3070 (b) (4) and 26 (53.06%) for HP-3070 (b) (4).

The frequency of adhesion scores (AS) at each time point of measurement are summarized for each strength separately in Tables 1 and 2. The tables showed that in general the TDSs for both strengths performed better at the early stage after application than at the end of wear period. In addition, the product with (b) (4) strength seems to adhere better than the (b) (4) strength product.

	AS=0	AS=1	AS=2	AS=3	AS=4
Hour=4	49	0	1	0	0
Hour=8	48	1	1	0	0
Hour=12	47	2	1	0	0
Hour=16	44	4	2	0	0
Hour=24	44	5	1	0	0

Table 1: Summary of frequency of adhesion scores at each time point of measurement after application for HP-3070 (b) (4).

	AS=0	AS=1	AS=2	AS=3	AS=4
Hour=4	48	0	0	1	0
Hour=8	40	6	0	2	1
Hour=12	36	7	2	3	1
Hour=16	34	8	2	4	1
Hour=24	31	14	0	3	1

Table 2: Summary of frequency of adhesion scores at each time point of measurement after application for HP-3070 (b) (4).

It is also of interest to see the first time for a TDS to be observed with a given non-zero score. These frequencies are summarized in Tables 3 and 4 for (b) (4) and (b) (4) strength respectively.

	AS=1	AS=2	AS=3	AS=4
Hour=4	0	1	0	0
Hour=8	1	0	0	0
Hour=12	2	0	0	0
Hour=16	2	1	0	0
Hour=24	2	0	0	0

Table 3: Summary of frequency of time of a TDS firstly observed with a given adhesion score after application for HP-3070 (b) (4).

	Score=1	Score=2	Score=3	Score=4
Hour=4	0	0	1	0
Hour=8	6	0	1	1
Hour=12	4	2	1	0
Hour=16	3	1	1	0
Hour=24	6	0	0	0

Table 4: Summary of frequency of time of a TDS firstly observed with a given adhesion score after application for HP-3070 (b) (4).

3.4 The probability that a randomly selected TDS maintains at least 75% adhesion throughout the entire wear period

I summarized the estimated probability and 95% lower confidence limits (CL) that a randomly selected TDS maintains at least 75% adhesion (i.e., adhesion score 1 or less) throughout the entire wear period for each strength in Table 5. Note that the applicant used Clopper Pearson method to compute the confidence limit. However, it has been shown to have very wide coverage probability and the Jeffreys and second order corrected (SOC) are recommended (Cai, 2005). Thus I reported the 95% lower confidence limits calculated by the Clopper Pearson method, Jeffreys method, and SOC method. Note that the estimated probability that the HP-3070 (b) (4) maintains at least 75% adhesion was larger than that of HP-3070 (b) (4) (0.96 versus 0.86). The Jeffreys and SOC CLs for the case of HP-3070 (b) (4) were close to 0.9. However, those for HP-3070 (b) (4) were 0.76.

Treatment	Sample size	Point estimate	Clopper Pearson CL	Jeffreys CL	SOC CL
HP-3070 (b) (4)	49	0.86	0.75	0.76	0.76
HP-3070 (b) (4)	50	0.96	0.88	0.89	0.89

Table 5: Summary of the point estimate and 95% lower confidence limits of the probability that a TDS maintains at least 75% adhesion during the entire wear period for each strength.

Because there were 5 different sites in the study, to assess the possible effect of application site on adhesion performance, similar probabilities and confidence limits for all combinations of strengths and application sites were computed, as shown in Table 6. The small lower confidence limits for the probabilities are due to the small sample sizes.

Treatment	Application site	Count	Sample size	Point estimate	Clopper Pearson CL	Jeffreys CL	SOC CL
HP-3070 (b) (4)	UPPER CHEST	8	10	0.80	0.49	0.55	0.55
HP-3070	UPPER BACK	10	10	1.00	0.74	0.83	0.82
HP-3070	UPPER ARM	10	10	1.00	0.74	0.83	0.82
HP-3070	HIP	10	10	1.00	0.74	0.83	0.82
HP-3070	ABDOMEN	10	10	1.00	0.74	0.83	0.82
HP-3070	UPPER CHEST	6	10	0.60	0.30	0.35	0.35
HP-3070	UPPER BACK	10	10	1.00	0.74	0.83	0.82
HP-3070	UPPER ARM	9	10	0.90	0.61	0.67	0.67
HP-3070	HIP	8	9	0.89	0.57	0.64	0.64
HP-3070	ABDOMEN	9	10	0.90	0.61	0.67	0.67

Table 6: Summary of point estimate and 95% lower confidence limits of the probability that a TDS maintains at least 75% adhesion throughout the entire wear period for each combination of strength and application site.

3.5 The probability that a randomly selected TDS maintains at least 70% adhesion throughout the entire wear period

In order to assess the robustness of the data, I also summarized the point estimate and 95% lower confidence limits of the probability that the TDS maintains at least 70% adhesion during the entire wear period for each

application site and for each strength. Note that in a draft guidance by European Medicines Agency (EMA) (European Medicines Agency, 2012), it stated that “less than 70 % adheres or patch detachment is regarded as significant patch adhesion failure.” The results are reported in Tables 7 and 8. There is no change for the results for HP-3070 (b) (4). For HP-3070 (b) (4), the difference between the estimated probabilities using 70% and using 75% was due to one TDS with adhesion percentage between 70% and 75%.

Treatment	Sample size	Point estimate	Clopper Perason CL	Jeffreys CL	SOC CL
HP-3070 (b) (4)	49	0.86	0.75	0.76	0.76
HP-3070 (b) (4)	50	0.98	0.91	0.92	0.92

Table 7: Summary of the point estimate and 95% lower confidence limits of the probability that a TDS maintains at least 70% adhesion during the entire wear period for each strength.

Treatment	Application site	Count	Sample size	Point estimate	Clopper Pearson CL	Jeffreys CL	SOC CL
HP-3070 (b) (4)	UPPER CHEST	9	10	0.90	0.61	0.67	0.67
HP-3070	UPPER BACK	10	10	1.00	0.74	0.83	0.82
HP-3070	UPPER ARM	10	10	1.00	0.74	0.83	0.82
HP-3070	HIP	10	10	1.00	0.74	0.83	0.82
HP-3070	ABDOMEN	10	10	1.00	0.74	0.83	0.82
HP-3070	UPPER CHEST	6	10	0.60	0.30	0.35	0.35
HP-3070	UPPER BACK	10	10	1.00	0.74	0.83	0.82
HP-3070	UPPER ARM	9	10	0.90	0.61	0.67	0.67
HP-3070	HIP	8	9	0.89	0.57	0.64	0.64
HP-3070	ABDOMEN	9	10	0.90	0.61	0.67	0.67

Table 8: Summary of the point estimate and 95% lower confidence limits of the probability that a TDS maintains at least 70% adhesion during the entire wear period for each strength and application site.

3.6 Adhesion performance of the TDS when the adhesion data from upper chest were excluded

Tables 6 and 8 showed that upper chest was the site with the worst adhesion performance. One may be interested in the overall performance of product when upper chest is excluded. The estimated probability and lower 95% confidence limits are shown in Table 9. The results using 70% as threshold were the same. When upper chest was excluding from the application sites, the point estimate of the probability that the TDS maintaining at least 75% adhesion for (b) (4) strength product increased to 1 and the 95% lower confidence limit increase to 0.95.

Treatment	Sample size	Point estimate	Clopper Perason CL	Jeffreys CL	SOC CL
HP-3070 (b) (4)	39	0.92	0.81	0.83	0.83
HP-3070 (b) (4)	40	1.00	0.93	0.95	0.95

Table 9: Summary of the point estimate and 95% lower confidence limits of the probability that a TDS maintains at least 75% adhesion during the entire wear period for each strength excluding upper chest.

Should one perform a hypothesis test with the following hypotheses,

$$H_0 : p \leq p_0 \text{ versus } H_a : p > p_0. \quad (1)$$

where p denote the probability that the product maintains at least 75% adhesion throughout its wear period. The null hypothesis H_0 can be rejected at a nominal size of 0.05 if the the 95% lower confidence limit of p at least p_0 . If $p_0 = 0.9$, then the (b) (4) strength passed the above hypothesis test but not the (b) (4) strength.

4 Conclusion

In summary, I evaluated the in vivo adhesion performance of HP-3070 in two strengths (b) (4) and (b) (4)). Exploratory analysis showed that the (b) (4) strength appeared to adhere better than the (b) (4) strength. The formal statistical analysis was performed in terms of the probability that a randomly selected TDS maintains at least 75% adhesion throughout the entire wear period. The analysis of such probability for all combinations of application sites and strengths showed that upper chest was the application site showing the worst adhesion. When the adhesion data from the upper chest were excluded, the estimated probability that a randomly selected TDS of HP-3070 (b) (4) maintains at least 75% adhesion changed to 1 and the 95% lower confidence limit for this probability changed to 0.95. Similarly, the estimated probability that a randomly selected TDS of HP-3070 (b) (4) maintains at least 75% adhesion changed to 0.92 and the 95% lower confidence limit for this probability changed to 0.83.

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