Office of Clinical Pharmacology Review

NDA or BLA Number	217927
Link to EDR	\\cdsesub1\evsprod\NDA217927\0001
Submission Date	12/22/2022;
Submission Type	Standard; 505(b)(2) to DAYPRO® (oxaprozin) 600 mg caplets (NDA 018841)
Brand Name	Coxanto™ (oxaprozin) Capsule, 300 mg
Generic Name	--
Dosage Form and Strength	Capsule, 300 mg
Route of Administration	Oral
Proposed Indication	Relief of signs and symptoms of Osteoarthritis (OA); Relief of signs and symptoms of Rheumatoid Arthritis (RA); Relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)
Dosage Regimen	• Use the lowest effective dosage for shortest duration consistent with individual patent treatment goals • OA: 1,200 mg (four 300 mg capsules) given orally once a day • RA: 1,200 mg (four 300 mg capsules) given orally once a day • JRA: 600 mg once daily in patients 22- to 31 kg. 900 mg once daily in patients 32- to 54 kg. 1,200 mg once daily in patients ≥greater than 55 kg
Applicant	Solubiomix, LLC
Associated IND	IND 145336
OCP Review Team	Hongwu Shen, Ph.D. (DNP Clinpharm Reviewer) Michael Bewernitz, Ph.D. (DPM Reviewer) Atul Bhattaram, Ph.D. (DPM Team Lead) Srikanth C. Nallani, Ph.D. (DNP Clinpharm Secondary Reviewer)

Reference ID: 5249158

Table of Contents

Reference ID: 5249158

List of Figures

List of Tables

Reference ID: 5249158

1. EXECUTIVE SUMMARY

Solubiomix LLC submitted this 505 (b) (2) application with a food effect study and a single-dose comparative bioavailability (BA) study under fasting conditions, comparing their Coxanto (oxaprozin) Capsule to the listed drug Daypro. The results of the single-dose BA study demonstrated comparable AUC0-72h between the two products, but the Cmax of Coxanto was about 34% higher than that of Daypro after receiving a single-dose of 600 mg. The safety concern of the higher Cmax after the first Coxanto dose can be mitigated through labeling by limiting the maximum daily dose from 1800 mg to 1200 mg and removal of the one-time loading dose of 1800 mg, compared to Daypro. Therefore, from clinical pharmacology perspective, this application is acceptable.

1.1 Recommendations

From the Clinical Pharmacology perspective, NDA 217927, submitted on December 22, 2022, is acceptable. Overall, adequate information has been provided characterizing the clinical pharmacology aspects of oxaprozin including to guide dosing in special populations. When this review is documented in DARRTS, the internal labeling meetings were held, however the labeling changes have not been negotiated with the applicant.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Clinical Pharmacology studies provide the pivotal evidence of effectiveness.
General dosing instructions	•Use the lowest effective dosage for shortest duration consistent with individual patent treatment goals •Osteoarthritis (OA): 1,200 mg (four 300 mg capsules) given orally once a day •Rheumatoid Arthritis (RA): 1,200 mg (four 300 mg capsules) given orally once a day • Juvenile Rheumatoid Arthritis (JRA): 600 mg once daily for patients 22 to 31 kg; 900 mg once daily for patients 32 to 54 kg; 1,200 mg once daily for patients greater than 55 kg
Dosing in patient subgroups (intrinsic and extrinsic factors)	Same as Daypro (oxaprozin) caplet, 600 mg (NDA 018841)
Labeling	Edits are made in Sections 2.5 and 12.3 of the proposed label. See section 2.4 of this review for more details.
Bridge between the to-be-marketed and clinical trial formulations	To-be-marketed formulation was used in the clinical studies.
Other (specify)	

Reference ID: 5249158

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Solubiomix LLC submitted NDA 217927 for Oxaprozin Capsule (brand name Coxanto)[1], 300 mg, under section 505 (b)(2) of the Federal Food Drug and Cosmetic Act. The listed drug (LD) is Pfizer Inc.'s Daypro® (oxaprozin) Caplet, 600 mg (NDA 018841). The proposed indications are for relief of signs and symptoms of OA, RA, and JRA, which are the same as Daypro. The applicant also proposed to use similar dose and dosing regimen as Daypro. The safety and efficacy of Oxaprozin Capsule is based on the pharmacokinetic comparison or bioavailability comparison to Daypro. The applicant conducted two Phase 1 PK studies. Both studies were randomized, open-label, 2-way crossover studies conducted in healthy adult volunteers. The study #SBX-P0-750 assessed the comparative bioavailability of Oxaprozin Capsule to Daypro under fasting conditions, and the study #SBX-P0-194 assessed the food effect of Oxaprozin Capsule. The applicant did not conduct any efficacy or safety studies. Safety information was also collected from the two PK studies. Office of Study Integrity and Surveillance (OSIS) inspections for the clinical and bioanalytical portions were requested for the study #SBX-P0-750. A remote regulatory assessment (RRA) of the analytical portion was conducted and no objectionable conditions were observed during the RRA. OSIS concluded that the bioanalytical data from Study #SBX-P0-750 are reliable. The inspection of the clinical portion of the study did not find any objectionable conditions, but two inspection findings were discussed. One observation was related to the use of two stand-by subjects to replace two already randomized subjects but not meeting acceptance criteria before the first dosing, the other observation was related to the use of unspecified "SN" abbreviation for subjects in the meal intake record. From clinical pharmacology perspective, the two observations will not impact the data integrity of study and the OSIS conclusion is concurred.

Comparative bioavailability between Oxaprozin Capsule and Daypro caplet under fasted conditions (Study # SBX-P0-750):

In this study, thirty subjects were enrolled. Four subjects withdrew from the study due to COVID-19 positive. The remaining twenty-six subjects (13 males and 13 females ranged from 28 to 60 years old) completed the study and were included in the PK and statistical analysis. The mean ± SD plasma concentration time profiles of oxaprozin from Oxaprozin Capsule versus Daypro under fasted conditions are shown in Figure 1. The PK parameters are shown in Tables 1 and 2.

The results showed that under fasting conditions, Oxaprozin Capsule showed similar AUC0-72h comparing to Daypro, but the Cmax of Oxaprozin Capsule was 34% higher than that of Daypro. The point estimate of the geometric mean ratio (Oxaprozin Capsule/Daypro) for AUC0-72h was 113.58% and the

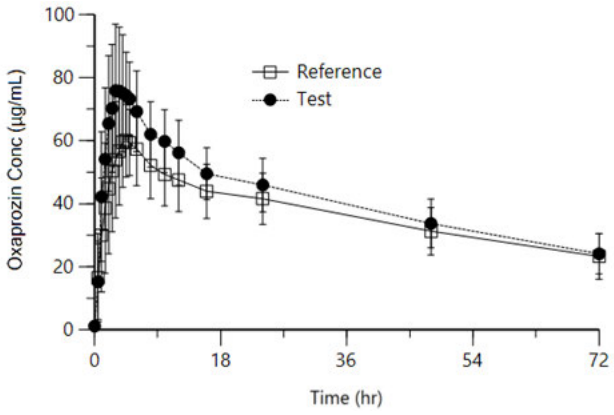
[1] The Oxaprozin Capsule and brand name COXANTO are interchangeable in the review.

Reference ID: 5249158

corresponding 90% CI was 110.33 to 116.92%. However, the point estimate of the geometric mean ratio for Cmax was 133.60% and the corresponding 90% CI was 129.68 to 137.63%, which is outside the BE criteria of 80.00-125.00%. The individual Cmax data demonstrated consistent higher Cmax, with a minimum of 16% and maximum of 59%, in all subjects after receiving Oxaprozin Capsule compared to Daypro. The median Tmax (min, max) for Oxaprozin Capsule was 3h (1.5, 5.0 h) compared to Daypro with a Tmax of 4.0 h (3.0, 6.0 h).

As the exposure to oxaprozin for Oxaprozin Capsule is comparable or higher than Daypro, the efficacy can be extrapolated from Daypro. To help address the potential safety concerns from the 34% higher Cmax, the applicant conducted PK modeling and simulation (Study # SBMX-IDD-OXAPROZIN-4341) to show that the Cmax difference will be reduced under steady state conditions which represents the chronic use of the product. In addition, in a response to Information Request, the applicant proposed to modify the dosing information in the label to address the safety risk cause by elevated Cmax, such as limiting the maximum daily and single dose to 1200 mg. Per Daypro label, "*The maximum recommended total daily dose of DAYPRO in adults is 1800 mg (26 mg/kg, whichever is lower) in divided doses*". In addition, "*In adults, in cases where a quick onset of action is important, the pharmacokinetics of oxaprozin allows therapy to be started with a one-time loading dose of 1200 mg to 1800 mg (not to exceed 26 mg/kg)*". The proposed labeling modification is considered sufficient to mitigate the potential safety concern.

Figure 1: Mean (±SD) plasm concentration-time profiles of oxaprozin after single-dose administration of Oxaprozin Capsule (Test) or Daypro (Reference) in Study #SBX-P0-750.



Reference ID: 5249158

Table 1: Summary of PK parameters of oxaprozin from Oxaprozin Capsule (Test) versus Daypro (Reference) under fasting conditions in Study #SBX-P0-750.

Parameter	Test (n=26)		Reference (n=26)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (µg/mL)	85.144	15.3	64.367	19.5
T_{max} (hours)[a]	3.00	1.50 – 5.00	4.00	3.00 – 6.00
AUC_{0-72} (µg·h/mL)	2939.697	18.2	2604.245	20.2
T_{lag} (hours)[a]	0.00	N/AP	0.00	0.00 – 0.50

Abbreviation: CV = coefficient of variation.
a. Median and range are presented.

Table 2: Summary of statistical analysis of oxaprozin from Oxaprozin Capsule (Test) versus Daypro (Reference) under fasting conditions in Study #SBX-P0-750

Parameter	Intra-subject CV (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Test (n=26)	Reference (n=26)		Lower	Upper
C_{max}	6.2	84.673	63.379	133.60	129.68	137.63
AUC_{0-72}	6.0	2890.332	2544.812	113.58	110.33	116.92

Abbreviations: CV = coefficient of variation; LSmeans = least-square means.
a. units are µg/mL for C_{max} and µg·h/mL for AUC_{0-72}
Source: Appendix 16.2.6.1.3

Food Effect Study for Oxaprozin Capsule (Study # SBX-P0-194):

In this study, thirty subjects were enrolled. Four subjects withdrew from the study due to COVID-19 positive, one subject withdrew due to personal reason and one subject did not show up for PCR test. The remaining 24 subjects (11 males and 13 females, ranged from 22 to 60 years old) completed the study and were included in the PK and statistical analysis. The mean ± SD plasma concentration time profiles of oxaprozin under fasting and fed conditions are shown in Figure 2. The PK parameters are shown in Table 3.

Comparing to the fasting conditions, food (high-fat, high-calorie meal) delayed the absorption of oxaprozin. The geometric mean of Cmax of oxaprozin under fed conditions was 16.8% lower than the Cmax under fasting conditions, and the median Tmax under fed conditions was 3 hours later than the Tmax under fasting conditions. The presence of food did not impact the AUC0-72h of oxaprozin. The statistical results showed that the 90% CI of AUC geometric mean ratio were within the range of 80.00 to 125.00%.

Based on the study results, high-fat, high-calorie meal reduced the rate of absorption of oxaprozin, but the extent of absorption was not changed. This result is consistent with the food impact of Daypro.

Reference ID: 5249158

Figure 2: Mean (±SD) plasm concentration-time profiles of oxaprozin after single-dose administration of Oxaprozin Capsule under fasting or fed conditions in Study #SBX-P0-194

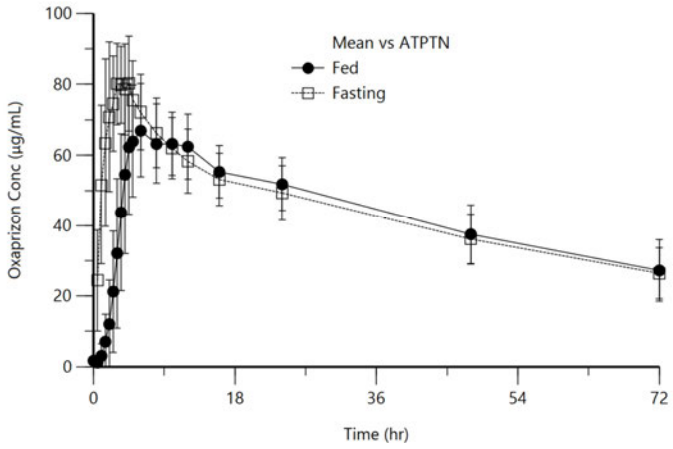


Table 3: Summary of PK parameters of oxaprozin under fasting and fed conditions in Study #SBX-P0-194

Parameter (Units)	Treatment-1 Fed Conditions (n=24)		Treatment-2 Fasting Conditions (n=24)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (µg/mL)	72.746	16.9	87.024	13.0
T_{max} (hours)[a]	6.00	4.00-24.00	3.00	1.00-4.63
AUC_{0-72} (µg·h/mL)	3072.818	16.6	3170.410	15.9
T_{lag} (hours)[a]	0.50	0.00-2.00	0.00	N/AP

Abbreviations: CV = coefficient of variation.
a. Median and range are presented.

PK modeling Study (Study SBMX-IDD-OXAPROZIN-4341):

The applicant conducted modeling and simulation study #SBMX-IDD-OXAPROZIN-4341 to predict the steady state PK profiles of Oxaprozin Capsule and Daypro and to support the bioequivalence (BE) between the two products after repeated doses. The applicant used PK data from a single dose study of 600 mg Oxaprozin Capsule (2x 300 mg) to develop the PK model. In order to account for known non-linear pharmacokinetics, the applicant leveraged oxaprozin steady-state PK from the literature. Please refer to section **4.3.2 Population PK Simulation** for details.

Reference ID: 5249158

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Use the lowest effective dosage for shortest duration consistent with individual patent treatment goals.

For OA, the dosage is 1200 mg (four 300 mg capsules) given orally once a day.

For RA, the dosage is 1200 mg (four 300 mg capsules) given orally once a day.

For JRA in patients 6-16 years of age, the recommended dosage given orally once per day should be based on body weight of the patient.

Body Weight Range (kg)	Dose (mg)	Number of Capsules[2]
22 to 31 kg	600 mg	two 300 mg capsules
32 to 54 kg	900 mg	three 300 mg capsules
55 kg or greater	1,200 mg	four 300 mg capsules

Different dose strengths and formulations (e.g., capsules, tablets) of oral oxaprozin are not interchangeable. This difference should be taken into consideration when changing strengths or formulations (see Osteoarthritis 2.2, Rheumatoid Arthritis 2.3, Juvenile Rheumatoid Arthritis 2.4, and pharmacokinetics 12.3). The highest daily dose for COXANTO is 1,200 mg a day.

2.2.2 Therapeutic individualization

After observing the response to initial therapy with Oxaprozin Capsules, the dose and frequency should be adjusted to suit an individual patient's needs. The maximum recommended total daily dose of Oxaprozin Capsules in adults is 1200 mg. In children, doses greater than 1200 mg have not been studied.

Patients with low body weight should initiate therapy with 600 mg once daily. Patients with severe renal impairment or on dialysis should also initiate therapy with 600 mg once daily. If there is insufficient relief of symptoms in such patients, the dose may be cautiously increased to 1200 mg, but only with close monitoring.

Physicians should ensure that patients are tolerating lower doses without gastroenterologic, renal, hepatic, or dermatologic adverse effects before advancing to the larger doses. Most patients will tolerate once-a-day dosing with Oxaprozin Capsules, although divided doses may be tried in patients unable to tolerate single doses.

2.3 Outstanding Issues

No.

[2] As the labeling negotiation is still ongoing, the recommended daily dose table may not represent the final recommended dose table in the Coxanto label.

2.4 Summary of Labeling Recommendations

As of 9/21/2023, labeling negotiation is still ongoing. Tentative labeling recommendations are shown below: recommended deletions are shown as ~~red strikethrough~~ and additions are shown as blue underlined text:

Under section **2.1 General Dosing Instruction**

Carefully consider the potential benefits and risks of COXANTO and other treatment options before deciding to use COXANTO. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].

Different dose strengths and formulations (e.g., capsules, tablets) of oral oxaprozin are not interchangeable. This difference should be taken into consideration when changing strengths or formulations (see (b) (4) 2.2, (b) (4) 2.3, (b) (4) 2.4, (b) (4) 12.3). The highest daily dose for COXANTO is 1,200 mg a day.

Comment: Because Oxaprozin Capsule (COXANTO) did not meet BE to Daypro in the fasting comparative bioavailability study, and showed 34% higher Cmax compared to Daypro, it is not interchangeable with Daypro even the total dose is the same. There is no study conducted between COXANTO and Daypro Alta (oxaprozin potassium) Tablet, 600 mg, no conclusion can be made between those two products. Therefore, the statement of non-interchangeability with other oxaprozin oral products is proposed to be added in the label. In addition, COXANTO is 300 mg strength, while Daypro, Daypro Alta, and other Oxaprozin Tablet products are all 600 mg strength. To reduce the risk of dosing error, in addition to add the number of capsules for each dose, the strength difference between COXANTO and other oxaprozin oral products is also emphasized.

Under section **2.5 Individualization of Dosage**

After observing the response to initial therapy with COXANTO, the dose and frequency should be adjusted to suit an individual patient's needs. In osteoarthritis and rheumatoid arthritis and juvenile rheumatoid arthritis, the dosage should be individualized to the lowest effective dose of COXANTO to minimize adverse effects. The maximum recommended total daily dose of COXANTO in adults is 1,200 mg (b) (4)

(b) (4)

Physicians should ensure that patients are tolerating lower doses (b) (4) without gastroenterologic, renal, hepatic, or dermatologic adverse effects before

advancing to the larger doses. Most patients will tolerate once-a-day dosing with COXANTO, although divided doses may be tried in patients unable to tolerate single doses.

Comment: The change in maximum recommended total daily dose from 1800 mg to 1200 mg and the removal of one-time loading dose of 1800 mg are recommended based on team discussion to reflect the risk mitigation strategy due to the 34% higher Cmax of Oxaprozin Capsule (COXANTO) compared to Daypro caplet observed in the single-dose comparative bioavailability study under fasting conditions (Study #SBX-P0-750). The other changes are to reflect the change of maximum daily dose from (b) (4) mg to 1200 mg.

Under section **12.3 Pharmacokinetics** General Pharmacokinetic Characteristics

In dose proportionality studies utilizing 600 mg, 1,200 mg, and 1800 mg doses, the pharmacokinetics of oxaprozin in healthy subjects demonstrated nonlinear kinetics of both the total and unbound drug in opposite directions, i.e., dose exposure related increase in the clearance of total drug and decrease in the clearance of the unbound drug. Decreased clearance of the unbound drug was related predominantly to a decrease in the volume of distribution of the unbound drug and not an increase in the elimination half-life. This phenomenon is considered to have minimal impact on drug accumulation upon multiple dosing. ~~The pharmacokinetic parameters of oxaprozin in healthy subjects receiving a single dose~~ (b) (4) ~~are presented in Table 3.~~

(b) (4)

Comment: Those PK parameters are from Daypro label and may not represent the PK parameters of COXANTO, therefore are deleted. As the labeling negotiation is ongoing, the applicant has the option to provide PK parameters of COXANTO based on the conducted studies.

Under section **12.3 Pharmacokinetics** Absorption

COXANTO is 95% absorbed after oral administration. Food may reduce the rate of absorption of oxaprozin, but the extent of absorption is unchanged. (b) (4)

(b) (4)

Under section **12.3 Pharmacokinetics** Distribution

The apparent volume of distribution (Vd/F) of total oxaprozin is approximately ~~11 to 17 L/70 kg~~. Oxaprozin is 99% bound to plasma proteins, primarily to albumin. At therapeutic drug concentrations, the plasma protein binding of oxaprozin is saturable, resulting in a higher proportion of the free drug as the total drug concentration is increased. With increases in single doses or following multiple once-daily dosing, the apparent volume of distribution and clearance of total drug increased, while that of unbound drug decreased due to the effects of nonlinear protein binding.

Comment: The applicant will be recommended to update the apparent volume of distribution based on PK studies conducted.

Under section **12.3 Pharmacokinetics** Drug Interaction Studies

(b) (4)

Comment: The deletion of (b) (4) is recommended for the (b) (4) (b) (4)

Reference ID: 5249158

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Solubiomix LLC submitted the 505(b)(2) NDA 217927 for Oxaprozin Capsule (Brand name Coxanto) which relies on the previous Agency's findings of safety and efficacy for the listed drug Daypro (oxaprozin) Caplet (NDA 018841). Daypro is indicated for relief of signs and symptoms of OA, RA, and JRA, and is marketed as 600 mg caplet. There are 13 approved generic products for Oxaprozin Tablet, 600 mg, with 5 generic products are still on the market.

Solubiomix intends to market Oxaprozin Capsule for the same indications as Daypro, and to market as 300 mg strength to provide convenience and accuracy of dosing for patients who use oxaprozin in 300 mg increments.

In a pre-IND meeting (IND 145336), Solubiomix discussed their development plan including detailed study design for the scientific bridging study as well as a partial waiver plan for JRA patients under 6 years old. The applicant's plan of only measuring total oxaprozin (unbound+ bound) in plasma and using truncated AUC0-72h for the planned fasting comparative bioavailability (BA) study and food effect study was accepted. The applicant then conducted the studies #SBX-P0-750 (fasting BA study) and #SBX-P0-194 (food effect study) accordingly.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Characteristic	**Drug Information**
Established Pharmacological Class	NSAID
Mechanism of Action	The mechanism of action, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2)
Active Moieties	oxaprozin
Bioanalysis	Oxaprozin is detected in plasma using a validated by LC-MS-MS method.
Pharmacokinetics	
Dose-proportionality	The pharmacokinetics of oxaprozin in healthy subjects demonstrated nonlinear kinetics.
Absorption	Oxaprozin is highly absorbed after oral administration. Food may reduce the rate of absorption of oxaprozin, but the extent of absorption is unchanged.
Tmax	Peak plasma concentration is noted at a median of 3 hours under fasting conditions and is delayed to 6 hours under fed conditions.
Distribution	Oxaprozin is 99% bound to plasma proteins, primarily to albumin. At therapeutic drug concentrations, the plasma protein binding of oxaprozin is saturable, resulting in a higher proportion of the free drug as the total drug concentration is increased. Oxaprozin penetrates into synovial tissues of rheumatoid arthritis patients with oxaprozin concentrations 2-fold and 3-fold greater than in plasma and synovial fluid, respectively. Oxaprozin is expected to be excreted in human

Reference ID: 5249158

	milk based on its physical-chemical properties; however, the amount of oxaprozin excreted in breast milk has not been evaluated.
Elimination	Terminal elimination half-life of oxaprozin is about 52 hours
Metabolism	Oxaprozin is primarily metabolized in the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). Ester and ether glucuronide are the major conjugated metabolites of oxaprozin.
Excretion	Approximately 5% of the oxaprozin dose is excreted unchanged in the urine. Sixty-five percent (65%) of the dose is excreted in the urine and 35% in the feces as metabolites. Biliary excretion of unchanged oxaprozin is a minor pathway, and enterohepatic recycling of oxaprozin is insignificant.
Bodyweight	Patients with low body weight should initiate therapy with 600 mg once daily.
Age	No statistically significant differences between young and elderly groups.
Renal impairment	Oxaprozin plasma protein binding may decrease in patients with severe renal deficiency. Dosage adjustment may be necessary in patients with renal insufficiency. Patients with severe renal impairment or on dialysis should also initiate therapy with 600 mg once daily. If there is insufficient relief of symptoms in such patients, the dose may be cautiously increased to 1200 mg, but only with close monitoring.
Hepatic impairment	Patients with well-compensated cirrhosis do not require reduced doses of oxaprozin as compared to patients with normal hepatic function.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical pharmacology submission provides pivotal support of effectiveness. Study #SBX-P0-750 provides evidence that the systemic exposure to oxaprozin after receiving single dose of 2 capsules of Oxaprozin Capsule, 300 mg, is similar or higher than that after receiving 1 caplet of Daypro (600 mg). The shape of the PK profiles of Oxaprozin Capsule and Daypro were comparable, with Oxaprozin Capsule reaching the peak plasma concentration 1 hour earlier than Daypro. Therefore, the effectiveness of Oxaprozin Capsule can be extrapolated from Daypro.

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

The applicant proposed to use the same dosing regimen for their Oxaprozin Capsule, 300 mg, as that for Daypro. The Oxaprozin Capsule formulation is an immediate release product with inactive ingredients that (b) (4) however, the dissolution studies showed that Oxaprozin Capsule dissolved slightly faster than Daypro at higher pH. The significance of this observation is unknown. The study SBX-P0-750 demonstrated a 34% higher mean Cmax with Oxaprozin Capsule without any statistically significant differences in AUC compared to Daypro. The Tmax of Oxaprozin Capsule was 1 hour earlier than that of Daypro. The applicant justified that the PK after a single dose

does not represent which occurs in normal medical use of oxaprozin, that is repeated daily use as once daily or in divided doses, and the PK of Oxaprozin Capsule will be bioequivalent to Daypro after repeated once daily doses.

Typically, the formulation differences are deciphered precisely with a single dose PK/BE study. Therefore, the Cmax difference between Oxaprozin Capsule and Daypro may be reduced at steady state after repeated once daily dosing or after divided daily dosing.

Study SBX-P0-750 demonstrated similar PK profiles between Oxaprozin Capsule and Daypro. The terminal slope of the elimination phase of Oxaprozin Capsule was comparable to that of Daypro. The differences were observed only in the absorption phase. Considering the 95% bioavailability of Daypro, the comparable AUC and comparable terminal slope between Oxaprozin Capsule and Daypro, the accumulation of Oxaprozin Capsule is expected to be similar to Daypro. Therefore, the Cmax differences is expected to be reduced after repeated dosing. Nevertheless, the immediate release nature of this formulation and the fact that the inactive ingredients (b) (4), the reasonable expectation is that after multiple doses (once daily or divided daily doses), the systemic exposure between Oxaprozin Capsule and Daypro may not be clinically significantly different.

For adult OA, and RA patients, the recommended standard dose for Daypro is 1200 mg once daily. The Daypro label also allows a one-time loading dose of 1800 mg (not to exceed 26 mg/kg) in adults. The systemic exposure of one-time loading dose of 1800 mg Daypro may be able to cover the systemic exposure of 1200 mg Oxaprozin Capsule. Excluding the option of one-time loading dose of 1800 mg and limiting the maximum daily dose to 1200 mg for Oxaprozin Capsule will adequately mitigate the safety concerns due to 34% higher Cmax observed in the single dose study.

Therefore, the applicant proposed 1200 mg once daily dose for OA and RA patients is considered acceptable.

For JRA patients aged 6 to 16 years, the proposed dose and dosing regimen are the same as Daypro, and is bodyweight based into three broad strata (22 to 31 kg; 32 to 54 kg; and 55 kg and greater). The efficacy for JRA patients can be extrapolated from adult efficacy, the potential safety risk due to higher Cmax at first dose can be mitigated as the nature of the expected acute adverse events (AEs), primarily nonserious GI AEs, is age-related in adults, and the overdose level to cause symptoms is much higher. Therefore, the applicant's proposed dose and dosing regimen for JRA patients aged 6 to 16 years are acceptable.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The quantification of oxaprozin in plasma samples from Study SBX-P0-750 and SBX-P0-194 was carried out via high performance liquid chromatography with tandem mass spectrometry detection (HPLC-MS/MS). The plasma samples with K_2EDTA as anticoagulant were prepared using protein precipitation method with oxaprozin-D5 as the internal standard (IS). The analytical method was validated for the

Reference ID: 5249158

concentration range of 0.75 to 250 µg/mL with QC levels of 2.25, 20, 125, and 187.5 µg/mL. The specificity of the analytical method was tested in the presence of possible concomitant medications (acetaminophen, acetylsalicylic acid, caffeine, ibuprofen, nicotine, cotinine, dextromethorphan, pseudoephedrine, cyproterone acetate, drospirenone, ethinyl estradiol, 3-keto desogestrel, levonorgestrel, norelgestromin, norethindrone, dimenhydrinate, diphenhydramine, estradiol, medroxyprogesterone acetate, progesterone, tetrahydrocannabinol, and cannabidiol). No interference was observed. The validated long term storage stability of 79 days at -80°C was able to cover the sample storage periods of Study #SBX-P0-750 (47 days) and #SBX-P0-194 (43 days).

Additional QC of 30 µg/mL was added in the sample analysis of Studies # SBX-P0-750 and # SBX-P0-194. The detected oxaprozin concentrations ranged from < LLOQ to 108.879 µg/mL in Study SBX-P0-750 and from < LLOQ to 109.416 µg/mL in Study SBX-P0-194.

Reference ID: 5249158

Table 4: Summary of Method Validation for Oxaprozin in Plasma

Analytical Validation Report	OAI-V3-329	
Short description of method	Protein precipitation Reversed-phase HPLC with MS/MS detection	
Biological matrix	Human plasma	
Anticoagulant	K2 EDTA	
Analyte	Oxaprozin	
Internal standard (IS)	Oxaprozin-D5	
Calibration concentrations	0.750 µg/mL to 250.000 µg/mL.	
Quality Control (QC) concentrations	0.750 µg/mL, 2.250 µg/mL, 125.000 µg/mL and 187.500 µg/mL.	
Specificity	No significant interference observed in the 10 regular blank matrix lots screened as well as in lipemic and hemolyzed matrix lots.	
Specificity in the presence of concomitantly administered compounds	No significant interference observed.	
Carryover	No significant carryover observed.	
Lower limit of quantification	0.750 µg/mL Between-run accuracy (%Bias): -9.3% Between-run precision (%CV):14.1% Within-run accuracy (%Bias): -17.6% - 4.0% Within-run precision (%CV): 5.9% - 12.3%	
Between-run accuracy (%Bias)	-9.3% - 3.4%	
Between-run precision (%CV)	3.3% - 14.1%	
Within-run accuracy (%Bias)	-17.6% - 4.6%	
Within-run precision (%CV)	1.6% - 12.3%	
Largest run size	285 injections	
Matrix Effect (Calculation of Matrix Factor (MF)) Mean Analyte MF Mean IS MF IS Normalized MF CV% of IS Normalized MF	Low QC Mean Analyte MF: 1.0015 Mean IS MF: 0.9848 Mean IS-Normalized: 1.0173 %CV: 2.2	High QC Mean Analyte MF: 1.0035 Mean IS MF: 0.9858 Mean IS-Normalized: 1.0182 %CV: 1.5
Dilution integrity / Dilution factor	187.500 µg/mL diluted 2-fold. Accuracy (%Bias): -0.9% Precision (%CV): 2.6% 500.000 µg/mL diluted 5-fold. Accuracy (%Bias): -0.5% Precision (%CV): 6.3% 500.000 µg/mL diluted 10-fold. Accuracy (%Bias): -1.0% Precision (%CV): 4.0%	
Recovery of analyte	83.4 % - 93.7 %	
Recovery of IS	81.5 %	

Reference ID: 5249158

Short-term stability of the stock solution and working solutions	Confirmed up to 26.7 hours for Oxaprozin in MeOH:DMSO 50:50% v/v at 25.00 mg/mL at 22°C nominal. % deviation: -3.9%. Confirmed up to 26.7 hours for Oxaprozin in MeOH:DMSO 50:50% v/v at 0.25 mg/mL at 22°C nominal. % deviation: -1.7%. Confirmed up to 26.7 hours for Oxaprozin-D5 in MeOH:DMSO 50:50% v/v at 1.00 mg/mL at 22°C nominal. % deviation: 1.7%.
Long-term stability of the stock solution and working solutions	Confirmed up to 81 days for Oxaprozin in MeOH:DMSO 50:50% v/v at 25.00 mg/mL at 4°C nominal. % deviation: 0.9%. Confirmed up to 81 days for Oxaprozin in MeOH:DMSO 50:50% v/v at 0.25 mg/mL at 4°C nominal. % deviation: 1.5%. Confirmed up to 81 days for Oxaprozin-D5 in MeOH:DMSO 50:50% v/v at 1.00 mg/mL at 4°C nominal. % deviation: -3.5%. Confirmed up to 81 days for Oxaprozin-D5 in ACN at 5.00 µg/mL at 4°C nominal. % deviation: 0.3%.
Short-term stability in biological matrix	Confirmed up to 28.3 hours at 4°C nominal. Accuracy (%Bias): 2.4% for Low Stability QC and -0.6% for High Stability QC.
Stability in whole blood	Confirmed up to 2.0 hours in an Ice/Water Bath. % deviation: -1.3% for Low QCs and 0.9% for High QCs.
Freeze and thaw stability	4 cycles. Accuracy (%Bias): -0.4% for Low Stability QC and -1.4% for High Stability QC.
Autosampler storage stability (referred to as Processed Reconstituted Stability)	Confirmed up to 216.3 hours at 4°C nominal. Accuracy (%Bias): -1.5% for Low Stability QC and -0.1% for High Stability QC.
Long-term stability in biological matrix	Confirmed up to 79 days at -80°C nominal. Accuracy (%Bias): -0.7% for Low Stability QC and -1.9% for High Stability QC. Confirmed up to 14 days at -20°C nominal. Accuracy (%Bias): 1.5% for Low Stability QC and -0.2% for High Stability QC.
Partial validation	NA
Cross validation(s)	NA

Reference ID: 5249158

4.2 Clinical PK Assessments

4.2.1 Synopsis of Study SBX-P0-750

Study SBX-P0-750 is a single-dose comparative bioavailability study under fasting conditions, aiming to assess whether the proposed Oxaprozin Capsule (2 x 300 mg) is bioequivalent to the Daypro® (oxaprozin) caplet, 600 mg, and to support a scientific bridge to the Agency's previous findings of safety and efficacy for Daypro. The study used two-way cross-over design in healthy volunteers, with a washout period of 28 days. Thirty healthy subjects were enrolled in the study. Four subjects withdrew from the study due to COVID-19 positive. The remaining twenty-six subjects (13 males and 13 females ranged from 28 to 60 years old) completed the study and were included in the PK and statistical analysis. A total of 5 adverse events (AEs) were reported including 4 COVID-19 positive after administration of Oxaprozin Capsules and 1 headache after administration of Daypro. All AEs were mild and were resolved without any treatment at the end of the study.

Blood samples were collected for PK analysis at pre-dose, and 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 48, and 72 hours in each period. Oxaprozin concentrations were measured using the validated LC-MS/MS method. One subject (b) (6) had measurable concentration at pre-dose in period 2. Because the pre-dose concentration was 1.7% of the corresponding Cmax, this subject was included in the PK and statistical analysis. A non-compartmental analysis with a log-linear terminal phase assumption was used to calculate PK parameters. Statistical analysis was performed using a mixed-effect analysis of variance (ANOVA) of the PK parameters and the two one-sided t-tests procedure at the α =0.05 level of significance. The model included sequence, treatment, and period as fixed factors and subject nested within sequence as the random factor.

The mean oxaprozin plasma concentration-time profiles are shown in Figure 3. The PK results and statistical analysis results including Cmax, AUC0-72h are presented in Tables 5 and 6 below. Based on the results, the 90% confidence interval of ln transformed AUC0-72h ratio for oxaprozin is within the acceptable limits of 80.00-125.00%. However, the 90% confidence interval of ln transformed Cmax ratio is outside the acceptable limits of 80.00-125.00%. The Cmax of Oxaprozin Capsule was about 34% higher than that of Daypro.

Table 5: Summary of Plasma Oxaprozin Pharmacokinetic Parameters

Parameter	Test (n=26)		Reference (n=26)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (µg/mL)	85.144	15.3	64.367	19.5
T_{max} (hours)[a]	3.00	1.50 – 5.00	4.00	3.00 – 6.00
AUC_{0-72} (µg·h/mL)	2939.697	18.2	2604.245	20.2
T_{lag} (hours)[a]	0.00	N/AP	0.00	0.00 – 0.50

Abbreviation: CV = coefficient of variation.
a. Median and range are presented.

Source: Study report SBX-P0-750, Table 11-1 (Test refers to Solubiomix's Oxaprozin Capsule, and reference refers to Daypro)

Reference ID: 5249158

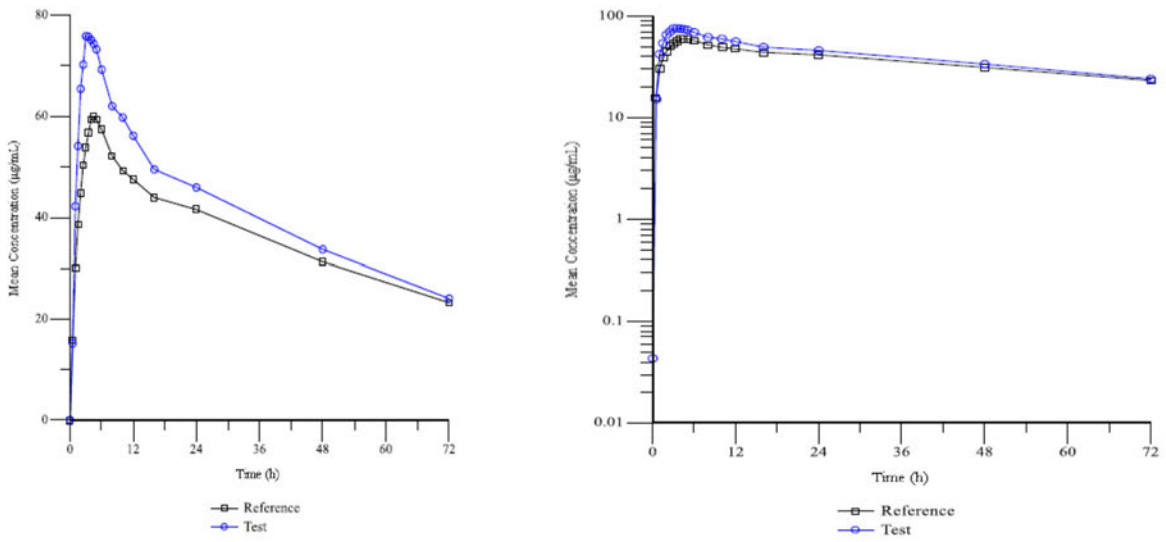
Table 6: Summary of the Statistical Analysis of Oxaprozin

Parameter	Intra-subject CV (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Test (n=26)	Reference (n=26)		Lower	Upper
C_{max}	6.2	84.673	63.379	133.60	129.68	137.63
AUC_{0-72}	6.0	2890.332	2544.812	113.58	110.33	116.92

Abbreviations: CV = coefficient of variation; LSmeans = least-square means.
a. units are µg/mL for C_{max} and µg·h/mL for AUC_{0-72}

Source: Study report SBX-P0-750, Table 11-2 (Test refers to Solubiomix's Oxaprozin Capsule, and reference refers to Daypro)

Figure 3: Mean oxaprozin concentration-time profiles after single-dose administration- linear and semi-logarithmic scale



Source: Study report SBX-P0-750, Figure 11-1

4.2.2 Synopsis of Study SBX-P0-194

Study SBX-P0-194 is a single-dose comparative bioavailability study, studying the oxaprozin pharmacokinetics under fasting and fed conditions to assess the food effect of Oxaprozin Capsule (2 x 300 mg). The study used two-way cross-over design in healthy volunteers, with a washout period of 28 days. Thirty healthy subjects were enrolled in the study. Four subjects withdrew from the study due to

Reference ID: 5249158

COVID-19 positive, one subject withdrew due to personal reason and one subject did not show up for PCR test. The remaining 24 subjects (11 males and 13 females, ranged from 22 to 60 years old) completed the study and were included in the PK and statistical analysis. A total of 7 AEs were reported including 4 COVID-19 positive (2 subjects received Oxaprozin Capsule and 2 subjects received Daypro), 2 injection site haematoma and 1 headache after receiving Daypro. All AEs were mild and were resolved without any treatment at the end of the study.

Blood samples were collected for PK analysis at pre-dose, and 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 48, and 72 hours in each period. Oxaprozin concentrations were measured using the validated LC-MS/MS method. Two subjects (b) (6) had measurable concentration at pre-dose in period 2. Because the pre-dose concentrations were less than 5% of the corresponding Cmax values (0.7% and 3.5% for Subjects (b) (6), respectively), both subjects were included in the PK and statistical analysis. A non-compartmental analysis with a log-linear terminal phase assumption was used to calculate PK parameters. The applicant also conducted statistical analysis using a mixed-effect analysis of variance (ANOVA) of the PK parameters and the two one-sided t-tests procedure at the α =0.05 level of significance. The model included sequence, treatment, and period as fixed factors and subject nested within sequence as the random factor.

The mean oxaprozin plasma concentration-time profiles are shown in Figure 4. The PK results and statistical analysis results including Cmax, Tmax, AUC0-72h are presented in Tables 7 and 8 below. Comparing to the fasting conditions, food (high-fat, high-calorie meal) delayed the absorption of oxaprozin. The geometric mean of Cmax of oxaprozin under fed conditions was 16.8% lower than the Cmax under fasting conditions, and the median Tmax under fed conditions was 3 hours later than the Tmax under fasting conditions. The presence of food did not impact the AUC0-72 of oxaprozin. The statistical results showed that the 90% CI of AUC geometric mean ratio were within the acceptance range of 80.00 to 125.00%.

Based on the study results, high-fat, high-calorie meal reduced the rate of absorption of oxaprozin, but the extent of absorption was not changed. This result is consistent with the food impact of Daypro.

Reference ID: 5249158

Table 7: Summary of Plasma Oxaprozin Pharmacokinetic Parameters

Parameter (Units)	Treatment-1 Fed Conditions (n=24)		Treatment-2 Fasting Conditions (n=24)	
	Mean	CV (%)	Mean	CV (%)
C_{max} (µg/mL)	72.746	16.9	87.024	13.0
T_{max} (hours)[a]	6.00	4.00-24.00	3.00	1.00-4.63
AUC_{0-72} (µg·h/mL)	3072.818	16.6	3170.410	15.9
T_{lag} (hours)[a]	0.50	0.00-2.00	0.00	N/AP

Abbreviations: CV = coefficient of variation.
a. Median and range are presented.

Source: Study report SBX-P0-194, Table 11-1

Table 8: Summary of Statistical Analysis of Oxaprozin

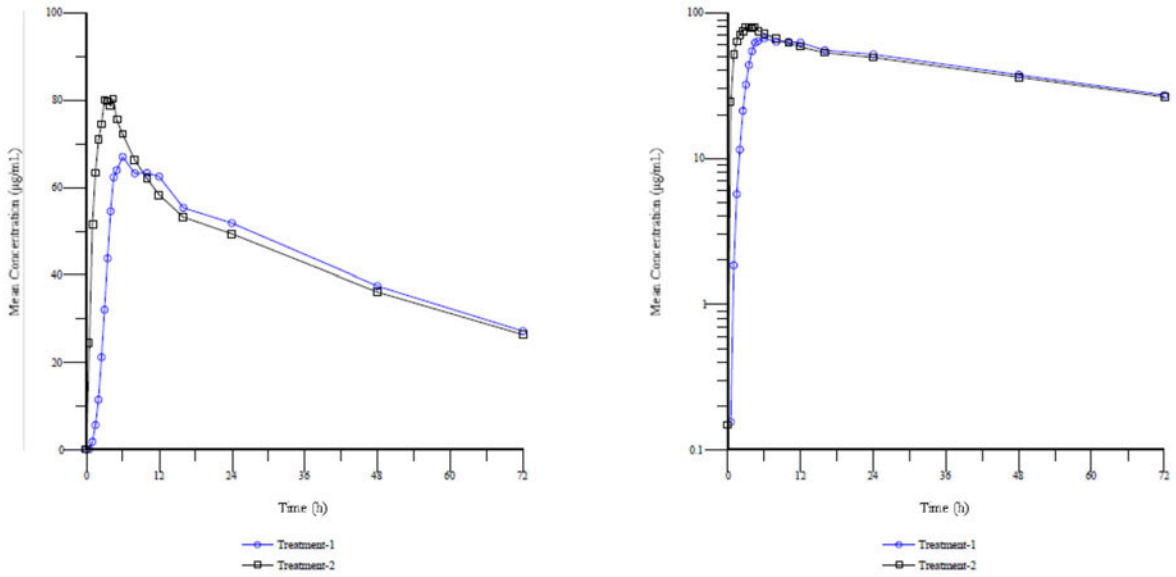
Parameter	Intra-subject CV (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Treatment-1 Fed Conditions (n=24)	Treatment-2 Fasting Conditions (n=24)		Lower	Upper
C_{max}	12.0	71.851	86.389	83.17	78.37	88.27
AUC_{0-72}	3.3	3044.228	3142.331	96.88	95.30	98.48

Abbreviations: CV = coefficient of variation; LSmeans = least-square means.
a. Units are µg/mL for C_{max} and µg·h/mL for AUC_{0-72}.

Source: Study report SBX-P0-194, Table 11-2

Reference ID: 5249158

Figure 4: Mean oxaprozin concentration-time profiles after single-dose administration of Oxaprozin Capsule under fasting (Treatment-2) or fed (Treatment-1) conditions



Source: Study report SBX-P0-194, Figure 11-1 (Treatment-1: fed conditions; Treatment-2: fasting conditions)

Reference ID: 5249158

4.3 Population PK Analyses

Sponsor submitted report *5335-oxaprozin-capsule-steady-state-be.pdf* in module 5335 of sequence 0001. This report describes PPK modeling and simulations. as part of the filing communication of OCP potential review issue regarding use of a linear PPK model for simulations when oxaprozin is known to follow non-linear PK. The Applicant responded by submitting an updated version of *5335-oxaprozin-capsule-steady-state-be.pdf* in sequence 0006. The report in 0006 contains new PK simulations generated after applying a non-linear protein binding correction factor to the CL terms and V terms from the model in the 0001 sequence. All modeling and simulation analyses were conducted using Phoenix™ NLME version 8.3.2.

4.3.1 Population PK Modeling

The final PPK models are located in report *5335-oxaprozin-capsule-steady-state-be.pdf*, titled "*Modeling and Simulations to Support Bioequivalence and Oxaprozin Following Repeated Administrations of a Novel Capsule and Daypro® Caplet Formulations in Health Adult Subjects*", submitted to module 5335 of sequence 0006. The objectives of the PPK analyses are:

1) to develop a population PK model to characterize the concentration-time profiles of oxaprozin following a single oral dose administered as a capsule formulation (2 x 300 mg) under fed and fasting conditions, and as the caplet formulation (Daypro®, 600 mg) and ultimately
2) to perform simulations to assess bioequivalence between the capsule and caplet formulations

[*Reviewer comment: The Applicant's report contains a separate population PK model for 600 mg oxaprozin administered in the fed condition from food effect study SBX-P0-750. However, as the Applicant did not utilize the fed state PPK model to support approval or any label statements, the fed state PPK model was not reviewed.*]

PK data for these population PK analyses came from two studies.

Study SBX-P0-750 is an open-label, randomized, two treatment, two period, two sequence, crossover, single oral dose comparative bioavailability study of oxaprozin 300 mg capsules and Daypro® (oxaprozin) 600 mg caplets following single administrations of 600 mg in n=52 healthy adult subjects (n=26 per arm) under fasting conditions. Details on Study SBX-P0-750 can be found in section **4.2.1 Synopsis of Study SBX-P0-750**.

Study SBX-P0-194 is an open-label, randomized, two-period, two-sequence, single oral dose crossover food effect comparative bioavailability study of oxaprozin 300 mg capsules following a 600 mg dose in n=48 healthy adult subjects (n=24 per arm). Details on Study SBX-P0-194 can be found in section **4.2.2 Synopsis of Study SBX-P0-194**.

A summary of the PK data provided from these two studies is presented in **Table 9**.

Reference ID: 5249158

Table 9: Summary of PK Data Available for PPK Analyses

Study Number, Phase, Type	Subject Population	Number of Subjects Included in the Analysis	Drug Dose and Regimen	PK Sampling
SBX-P0-750	HV	26	Single dose of 600 mg capsule or single dose of 600 mg caplet under fasting conditions	Pre-dose, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 4.5h, 5h, 6h, 8h, 10h, 12h, 16h, 24h, 48h, and 72h
SBX-P0-194	HV	24	Single dose of 600 mg capsule, under fasting or fed conditions	Pre-dose, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 4.5h, 5h, 6h, 8h, 10h, 12h, 16h, 24h, 48h, and 72h

Abbreviations: HV=healthy volunteer; PK=pharmacokinetics; N=number of subjects with available information.

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 12

The population PK models for oxaprozin capsules administered in a fasted state and oxaprozin caplets (Daypro®) administered in a fasted state are presented below.

4.3.1.1 Capsules in a Fasted State

The final model consisted of a two-compartment model with linear elimination parameterized in terms of first-order absorption rate constant (ka), apparent clearance (CL/F), apparent volume of distribution of the central compartment (V/F), apparent intercompartmental clearance (CL2/F), apparent volume of distribution of the peripheral compartment (V2/F), and absorption lag time (Tlag). Interindividual variability was estimated for all six structural PK parameters. An additive model was used to describe residual error. The final model code is in the file capfacor.txt in module 5335 of sequence 0004. The parameter estimates for the final model are presented in **Table 10**.

Reference ID: 5249158

Table 10: Population PK Estimates for Final Model for Capsule Under Fasting Conditions

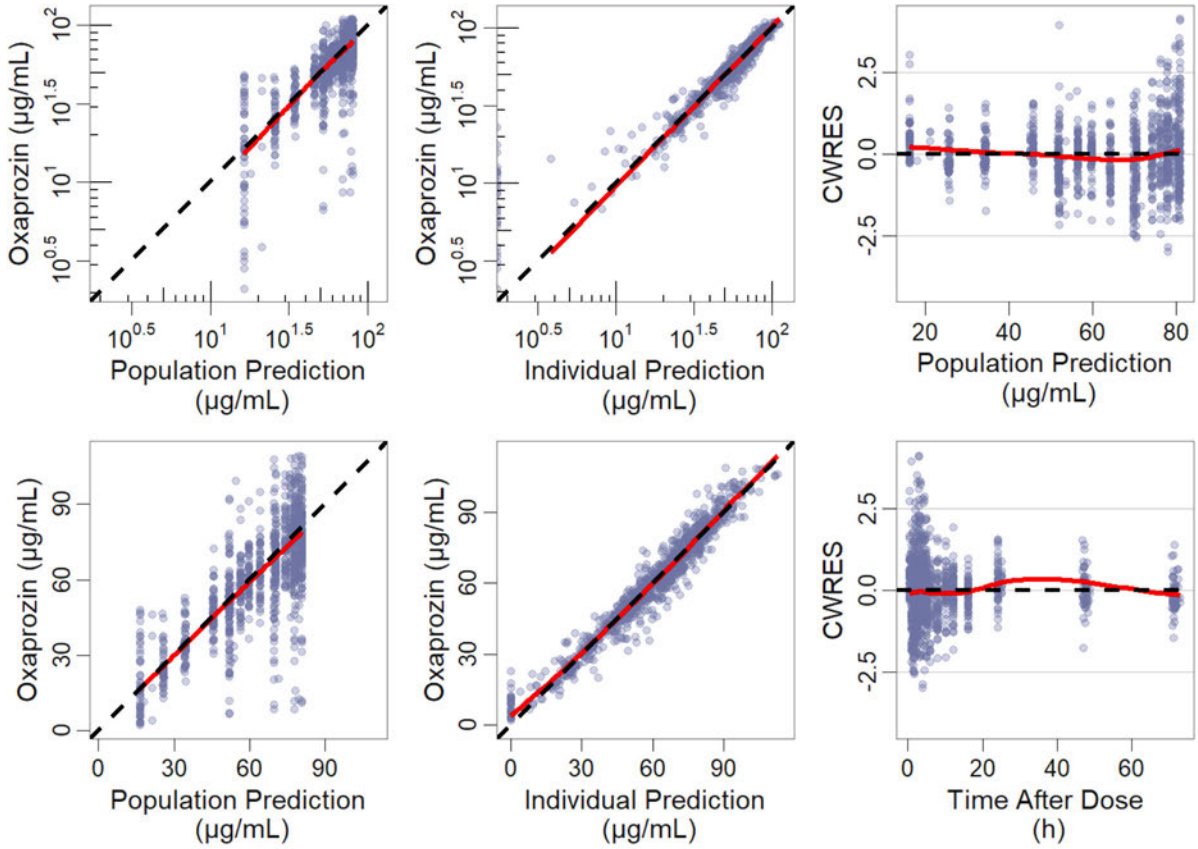
Parameters	Estimates	%RSE	95% CI
Ka (1/h)	1.20	11.7	0.928 – 1.48
CL/F (mL/h)	116	3.92	108 - 125
V/F (mL)	6070	3.52	5650 - 6490
CL2/F (mL/h)	446	9.56	363 - 530
V2/F (mL)	3260	4.73	2960 - 3570
Tlag (h)	0.348	12.8	0.261 - 0.436
Random effects	**BSV%**	**%RSE**	**Shrinkage (%)**
IIV on Ka	76.9	9.03	11.9
IIV on CL/F	20.8	11.9	20.3
IIV on V/F	19.5	9.72	15.0
IIV on CL2/F	28.2	30.7	60.2
IIV on V2/F	18.3	22.2	21.1
IIV on Tlag	102	13.7	18.2
Residual error	**Estimates**	**%RSE**	
Additive Error (µg/mL)	5.82	5.10	NA

Abbreviations: BSV = between subject variability; CI=confidence interval; CL/F=apparent clearance; CV=coefficient of variation; IIV=inter-individual variability; Ka = absorption rate constant; RSE=relative standard error; Tlag = absorption lag time; V=apparent central volume of distribution; V2=peripheral volume of distribution

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 21

Key diagnostic plots are presented in the figures below.

Figure 5: Goodness-of-Fit Diagnostic Plots for Final Model for Capsule Under Fasting Conditions

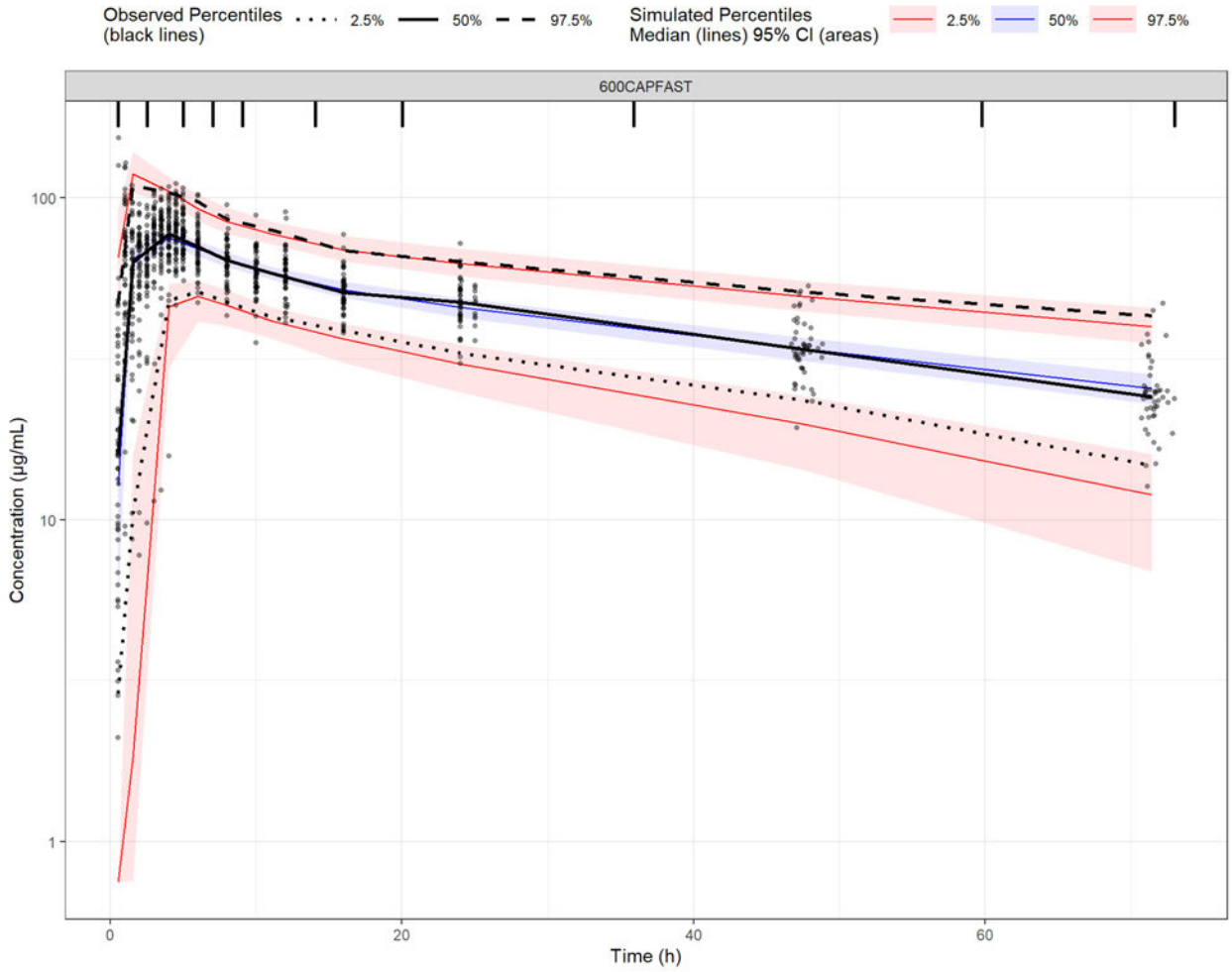


Circles are individual data points, and solid lines are smoothed LOESS lines. In the plots in the left and middle column, dashed lines are lines of identity. CWRES=conditional weighted residuals; GOF = goodness-of-fit; LOESS = locally weighted scatterplot smoothing.

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 22

Reference ID: 5249158

Figure 6: Prediction Corrected Visual Prediction Check for Final Model for Capsule Under Fasting Conditions



Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 23

[*Reviewer comment: Eta-shrinkage is highest for CL2/F with a value of 60.2%.*

No apparent signs of systemic bias with respect to time after administration nor magnitude of concentration prediction. Most CWRES values are within +/- 2 standard deviations. The prediction-corrected visual predictive check (pcVPC) demonstrates that the model can describe the central tendency and variability reasonably well over the observed time frame. The residual squared error values are acceptable for fixed effects as well as random effects.

A linear disposition model was utilized yet oxaprozin is known to have non-linear PK from 600 mg to 1800 mg. ***This model is most reliable for single administrations of 600 mg oxaprozin capsules in a fasted state.***]

4.3.1.2 Caplets (Daypro®) in a Fasted State

The final PPK model includes two-compartments with linear elimination, parameterized with first-order absorption rate constant (ka), apparent clearance (CL/F), apparent volume of distribution of the central compartment (V/F), apparent intercompartmental clearance (CL2/F), apparent volume of distribution of the peripheral compartment (V2/F), and absorption lag time (Tlag). Interindividual variability was estimated for all six of the structural PK parameters except CL2/F. An additive model was used to describe residual error. The final model code is in the file tabfacor.txt in module 5335 of sequence 0004. The final parameter estimates are displayed in

Table 11: Population PK Estimates for Final Model for Caplet (Daypro) Under Fasting Conditions

Parameters	**Estimates**	**%RSE**	**95% CI**
Ka (1/h)	0.881	8.25	0.738 - 1.02
CL/F (mL/h)	125	6.67	109 – 142
V/F (mL)	8180	4.19	7510 – 8860
CL2 (mL/h)	527	7.54	449 – 605
V2 (mL)	3180	10.4	2530 – 3830
Tlag (h)	0.221	10.9	0.173 – 0.268
Random effects	**BSV%**	**%RSE**	**Shrinkage (%)**
IIV on Ka	38.8	13.5	10.5
IIV on CL/F	31.1	9.08	18.0
IIV on V/F	22.4	9.62	3.75
IIV on V2/F	39.1	13.2	34.6
IIV on Tlag	477.5	8.06	22.2
Residual error	**Estimates**	**%RSE**	
Additive Error (µg/mL)	4.77	6.95	NA

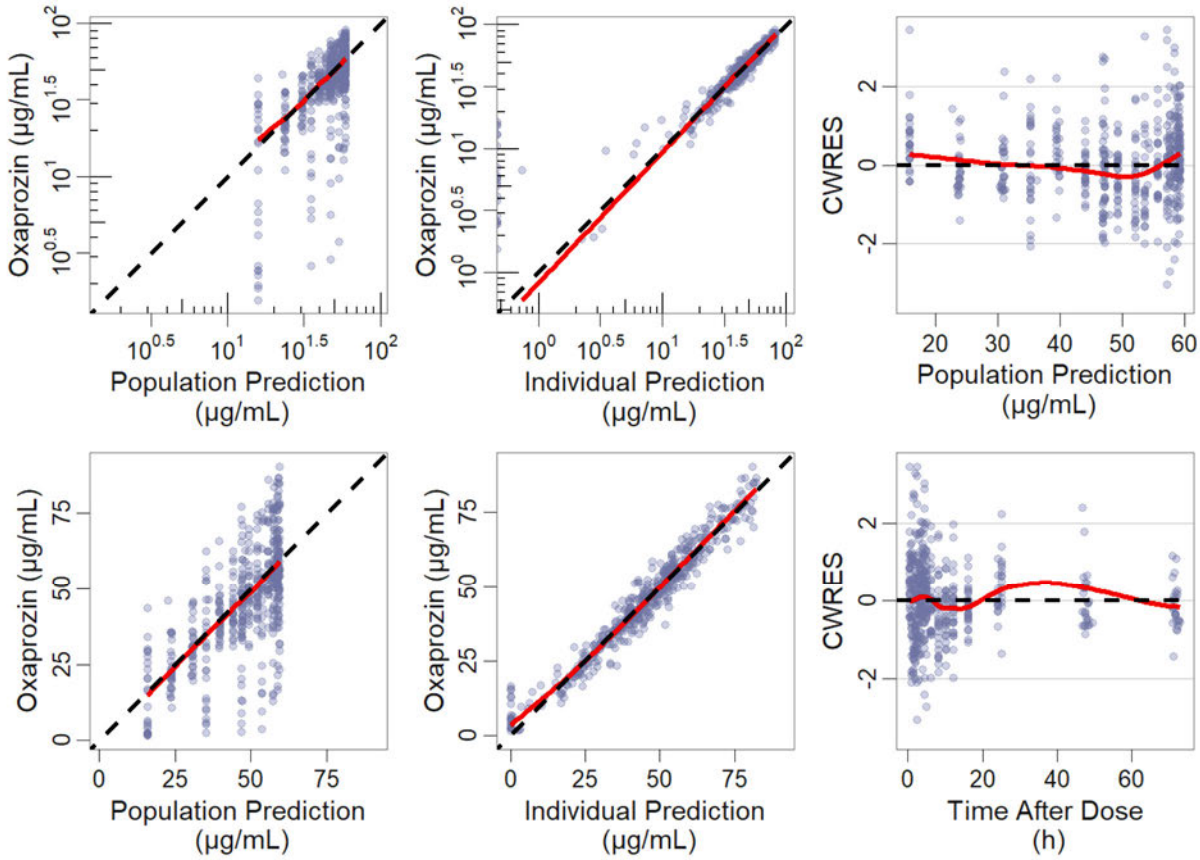
Abbreviations: BSV = between subject variability; CI=confidence interval; CL/F=apparent clearance; CV=coefficient of variation; IIV=inter-individual variability; Ka = absorption rate constant; RSE=relative standard error; Tlag = absorption lag time; V=apparent central volume of distribution; V2=peripheral volume of distribution

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 25

Key diagnostic plots shown below.

Reference ID: 5249158

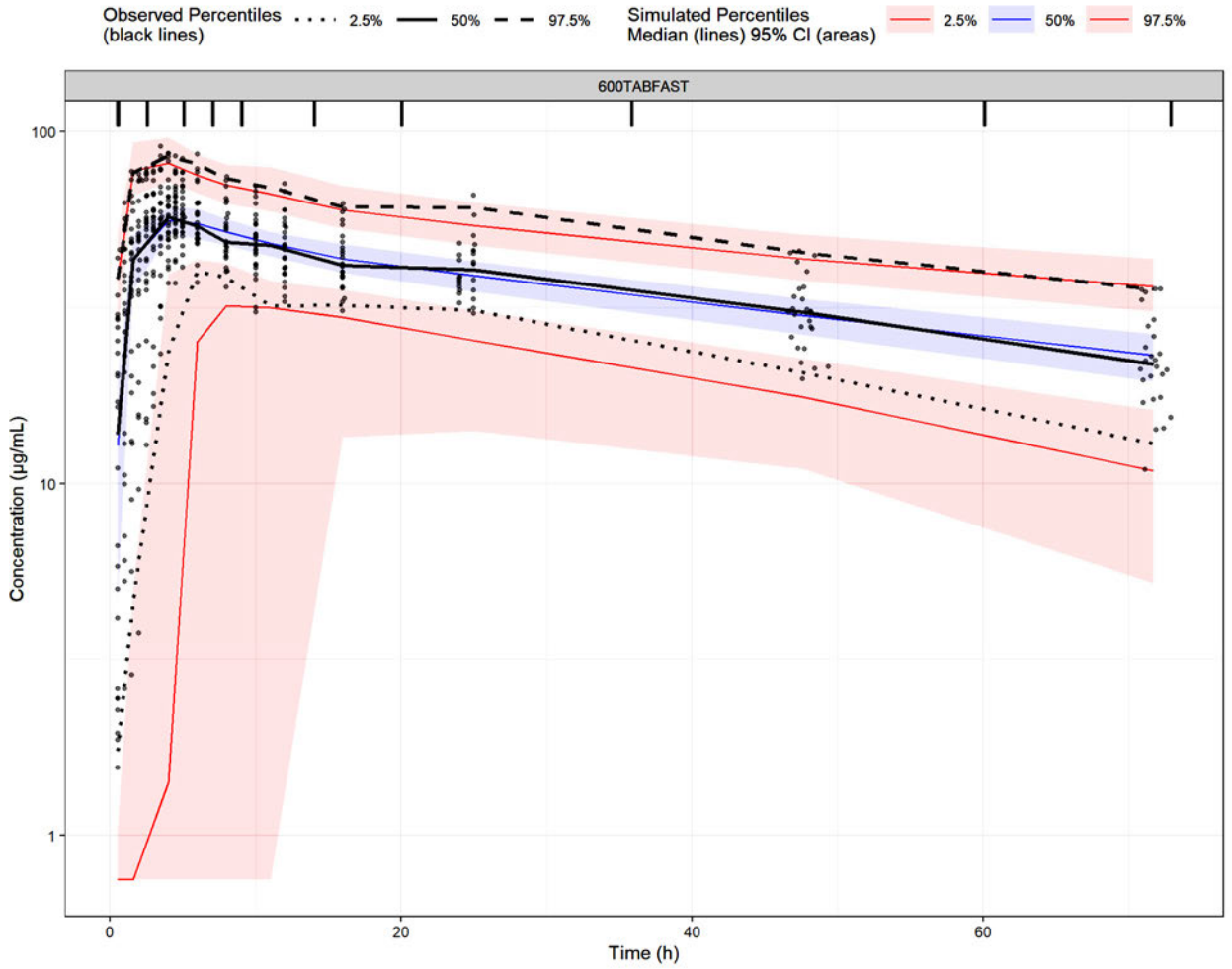
Figure 7: Goodness-of-Fit Diagnostic Plots for Final Model for Caplet Under Fasting Conditions



Circles are individual data points, and solid lines are smoothed LOESS lines. In the plots in the left and middle column, dashed lines are lines of identity. CWRES=conditional weighted residuals; GOF = goodness-of-fit; LOESS = locally weighted scatterplot smoothing.

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 26

Figure 8: Prediction Corrected Visual Prediction Check for Final Model for Caplet Under Fasting Conditions



Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 27

[*Reviewer comment: Eta shrinkage is highest for V2/F which is 34.6%.*

The diagnostic plots do not suggest the presence of bias with respect to magnitude of concentration nor time. The majority of the CWRES values are within +/- 2 standard deviations. The pcVPC indicates that the model can describe the mean and variability of the observed data over the observation time frame.

This PPK model used a linear elimination model to describe PK data representing a single administration at a single dose level (600 mg Daypro). ***This model is most reliable for describing the PK of a single administration of 600 mg Daypro® caplet in a fasted state***.]

4.3.2 Population PK Simulation

Report *5335-oxaprozin-capsule-steady-state-be.pdf* , titled "*Modeling and Simulations to Support Bioequivalence and Oxaprozin Following Repeated Administrations of a Novel Capsule and Daypro® Caplet Formulations in Health Adult Subjects*", was submitted to module 5335 of sequence 0001. This report contains results of population pharmacokinetic (PPK) modeling and simulation. In the filing review communication (archived on 2023/03/03), OCP communicated concerns regarding potential review issues. Some of the issues raised by OCP in the filing communication relate to the PPK model simulations described in report *5335-oxaprozin-capsule-steady-state-be.pdf* from sequence 0001:

i. Though the Applicant acknowledged that oxaprozin is known to display non-linear pharmacokinetics, a 2-compartment PPK model with linear elimination was used to assess oxaprozin pharmacokinetics.
ii. Steady state exposures were simulated yet the model was built using PK data following a single oxaprozin administration.
iii. it is not clear whether the simulations accounted for non-linear PK of oxaprozin when deriving the steady-state exposures.

Sponsor submitted their response addressing the concerns above on 2023/04/06 in sequence 0006. The sequence 0006 submission included an amended modeling and simulation report *5335-oxaprozin-capsule-steady-state-be.pdf*. The version of report *5335-oxaprozin-capsule-steady-state-be.pdf* submitted to sequence 0006 is the final version and thus the version in sequence 0001 will not be further discussed.

The updated modeling and simulation report in sequence 0006 did not include additional modeling (that is, no new parameter estimates were generated). Instead, the Applicant derived a non-linear correction factor for clearance terms (CL and Q) and volume of distribution terms (Vc and Vp). The Applicant's approach involves comparing their PK parameters estimates derived from a single administration of 600 mg oxaprozin capsules to literature oxaprozin PK parameters for single administration, multiple administration, and at various dose levels. The PK data from the Sponsor's program as well as the literature PK data are described below.

The PK data in the Applicant's program consists of PK collected after a single administration of 600 mg (2 x 300 mg) capsule or 600 mg Daypro caplet in studies SBX-P0-750 or SBX-P0-194 (see **Table 9** for details).

The Applicant located literature that describes oxaprozin PK parameter estimates following single administrations and multiple administrations at various dose levels. Oxaprozin PK parameters from two articles, Karim 1996[3], and Karim et al. 1997[4], were included in these analyses. A Summary of the PK parameters from the two articles is found in the tables below.

[3] Karim A, 1996 J Clin Pharmacol 1997;37:267-278
[4] Karim A, Noveck R, McMahon FG, Smith M, Crosby S, Adams M, Wilton J. J. Clin. Pharmacol 1997; 37: 267-278.

Reference ID: 5249158

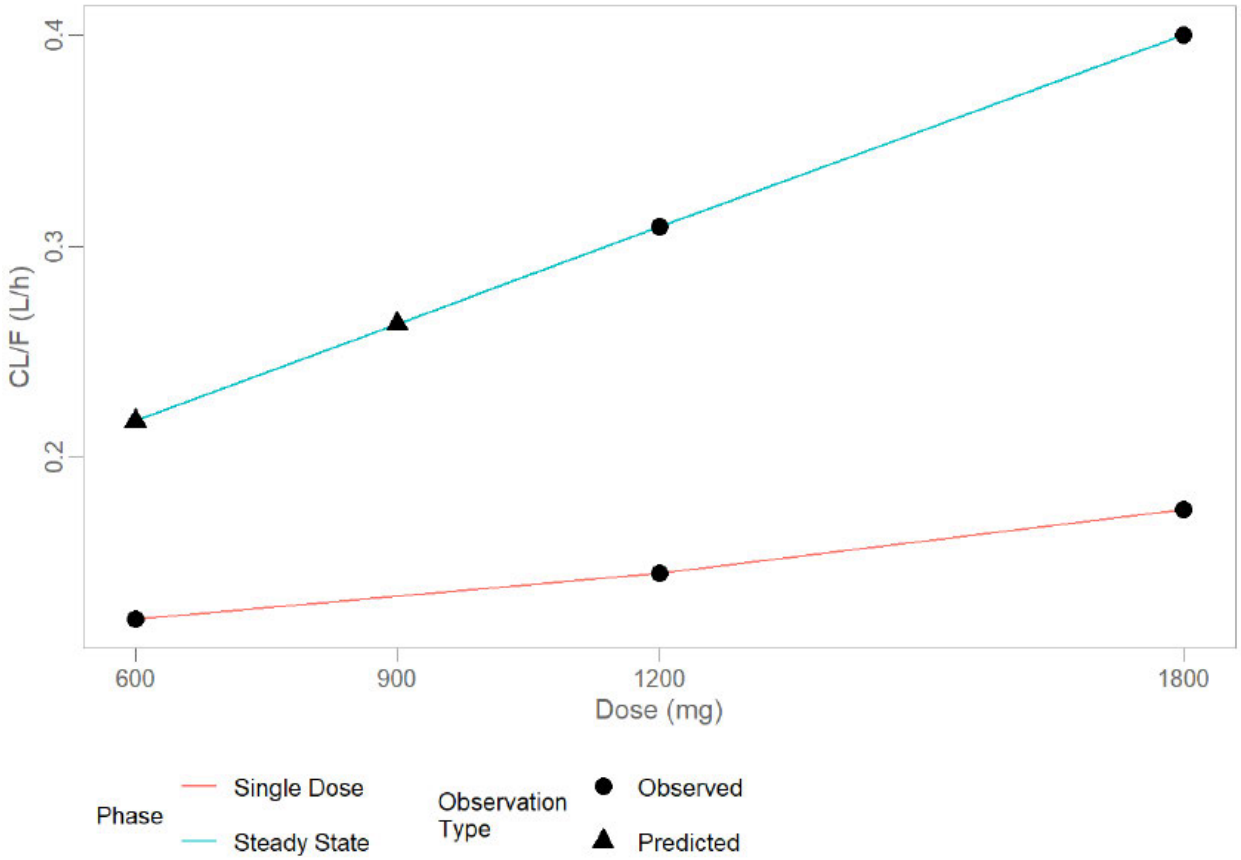
Table 12: Oxaprozin CL/F for Single Administrations and at Steady-State

Experimental Conditions	Dose	CL/F (L/h)	Nonlinear CL/F Factor (SS vs 600 SD)
Single Dose	600	0.123 (observed)[5]	Not Applicable
	900	Not Available	Not Applicable
	1200	0.145 (observed, averaged)[5-6]	Not Applicable
	1800	0.175 (observed)[5]	Not Applicable
Steady State	600	0.217 (extrapolated)	**1.76**
	900	0.263 (extrapolated)	**2.14**
	1200	0.309 (observed, averaged)[5-6]	**2.51**
	1800	0.400 (observed)[5]	Not Applicable

Reference 5 in this figure refers to Karim 1996. Reference 6 refers to Karim et al., 1997. The term "observed" means the CL/F value was reported in one of the two articles. The CL/F value for a single dose 1200 mg is the mean of the values reported in the two articles (CL/F after a singe 1200 mg dose reported as 0.150 L/h for Karim 1996, 0.139 L/h for Karim et al., 1997; mean of these two values is 0.145 L/h). The CL/F value for steady-state 1200 mg is also the mean of the values reported in the two articles (CL/F for steady-state at 1200 mg reported as 0.301 L/h for Karim 1996 and reported as 0.316 L/h for Karim et al., 1997; mean of these two values is 0.309 L/h). The term "extrapolated" refers to a CL/F value that was inferred based on the Sponsor's extrapolation of the data from the two articles. The Sponsor's extrapolation process is described in the next section.

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 14

Figure 9: Oxaprozin CL/F for Single Administrations and at Steady -State



Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 14

Reference ID: 5249158

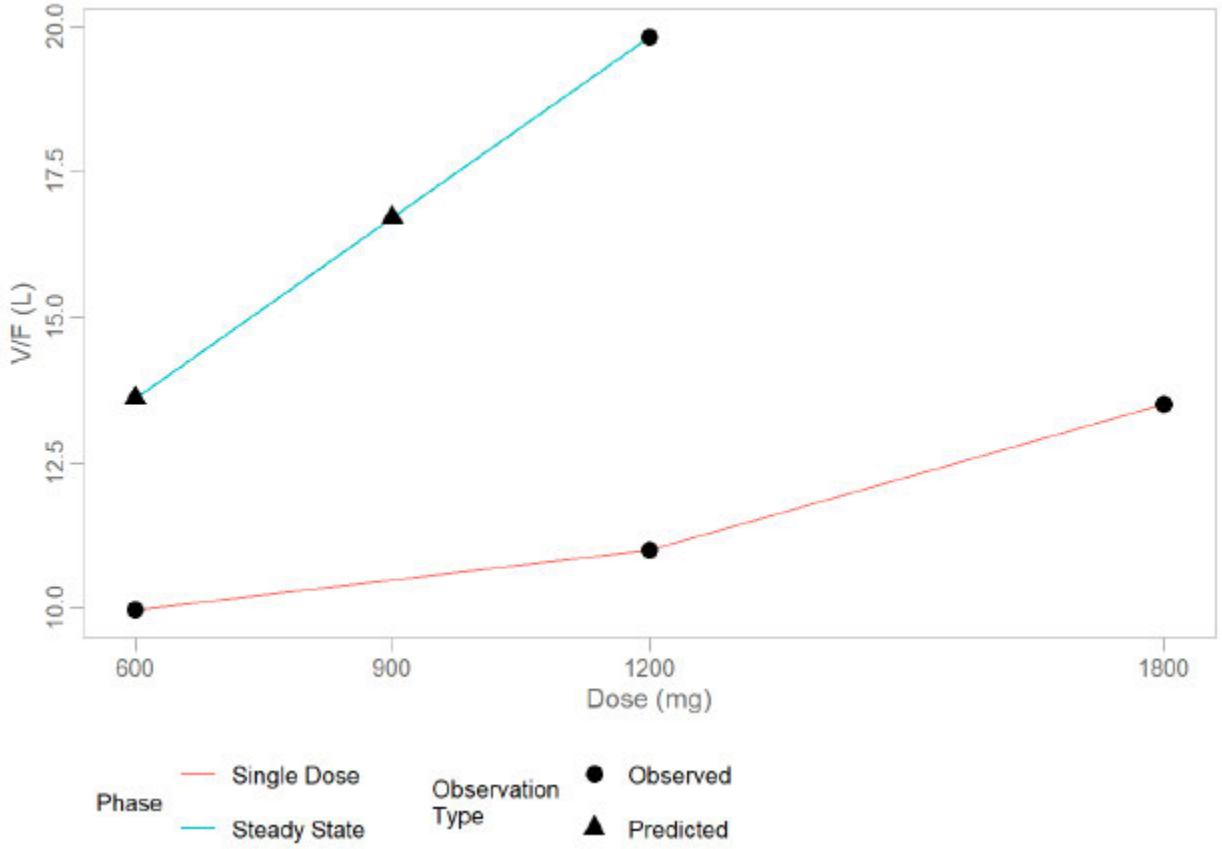
Table 13: Oxaprozin V/F for Single Administrations and at Steady-State

Experimental Conditions	Dose	V/F (L)	Nonlinear V/F Factor (SS vs 600 SD)
Single Dose	600	9.97 (observed)[5]	Not Applicable
	900	Not Available	Not Applicable
	1200	11.0 (observed, averaged)[5-6]	Not Applicable
	1800	13.5 (observed)[5]	Not Applicable
Steady State	600	13.6 (extrapolated)	**1.36**
	900	16.7 (extrapolated)	**1.68**
	1200	19.8 (observed, averaged)[5-6]	**1.99**
	1800	Not Available	Not Applicable

Reference 5 in this figure refers to Karim 1996. Reference 6 refers to Karim et al., 1997. The term "observed" means the V/F value was reported in one of the two articles. The V/F value for a single dose 1200 mg is the mean of the values reported in the two articles (V/F after a singe 1200 mg dose reported as 11.7 L for Karim 1996, 10.2 L for Karim et al., 1997; mean of these two values is 11.0 L). The V/F value for steady-state 1200 mg is also the mean of the values reported in the two articles (V/F for steady-state at 1200 mg reported as 16.7 L for Karim 1996 and reported as 22.8 L for Karim et al., 1997; mean of these two values is 19.8 L). The term "extrapolated" refers to a V/F value that was inferred based on the Sponsor's extrapolation of the data from the two articles. The Sponsor's extrapolation process is described in the next section.

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 15

Figure 10: Oxaprozin V/F for Single Administrations and at Steady -State



Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 15

[*Reviewer comment: In Figure 9, the top series, colored blue, representing steady-state, the CL/F values for 600 mg and 900 mg were extrapolated by a linear fit relating dose to CL/F for 1200 mg and 1800 mg. In contrast, Figure 10 shows a single observed steady-state V/F (at 1200 mg), with a line relating dose to V/F, and two V/F values (600 mg and 900 mg) that were extrapolated.*

On 2023/05/17, OCP sent an information request seeking clarification on the Applicant's process described in the sequence 0006 report 5335-oxaprozin-capsule-steady-state-be.pdf for extrapolating steady-state CL/F and V/F for 600 mg and 900 mg. In this information request, OCP asked Sponsor to clarify how they extrapolated steady-state V/F values for 600 mg and 900 mg based on a linear relationship that appears to be fit with only a single observed point (observed steady-state V/F of 19.8 L for 1200 mg). The Applicant's response detailing their extrapolation process was received on 2023/05/25 in sequence 0010. The Applicant's explanation for their extrapolation process is in the next section.]

Sponsor's Extrapolation of Non-linear PK Parameters: The Applicant fit a linear model to relate the steady-state CL/F values for 1200 mg (0.309 L/h) and 1800 mg (0.400 L/h) to dose. The resulting model was used to extrapolate to obtain steady-state CL/F values for 600 mg (0.217 L/h) and 900 mg (0.263 L/h).

Reference ID: 5249158

As a steady-state V/F value is available for only one dose level (19.8 L for 1200 mg), Applicant applied the following steps to extrapolate values of steady-state V/F and steady state CL/F for the 600 mg and 900 mg dose levels:

Step 1: A linear model was fit to relate CL/F to dose for the single dose scenario and a separate linear model was fit to relate Cl/F to dose for the steady-state scenario. The slopes of CL/F for the single dose and steady state conditions were 0.000152 and 0.0000433 L/h/mg, respectively. The ratio of slopes of CL/F between the single dose and steady state conditions is therefore 3.51 (0.000152 / 0.0000433).

Step 2: The slopes of V/F for the single dose condition is 0.00294 L/mg. The slopes of V/F for the multiple dose condition were derived by applying the above CL/F ratio (single/multiple) to 0.00294 L/mg, which gives a slope of 0.01032 L/mg.

Step 3: The V/F under steady state conditions for the 600 mg and 900 mg were, therefore, derived based on the observed 1200 mg dose and the above slope steady state conditions (0.01032 L/mg).

•The predicted V/F for the 600 mg dose is therefore: 19.8 L - (600 mg x 0.01032 L/mg) = 13.6 L

•The predicted V/F for the 900 mg dose is therefore: 19.8 L - (300 mg x 0.01032 L/mg) = 16.7 L

Step 4: A ratio non-linear correction factor for Cl/F and V/F was calculated for each steady-state dose level normalized to 600 mg single dose. For example, in **Table 12**, the observed single dose CL/F for 600 mg is 0.123 L/h and steady-state Cl/F for 600 mg is extrapolated to be 0.217 L/h, resulting in a non-linear correction factor for CL/F of 0.217/0.123 = 1.76. In order to adjust an individual subjects Cl/F value to represent steady-state 600 mg, the Applicant multiplies each subject's individual Cl/F value by 1.76. In **Table 13**, the observed single dose V/F for 600 mg is 9.97 L/h and steady-state V/F for 600 mg is extrapolated to be 13.6 L, resulting in a non-linear correction factor for V/F of 13.6/9.97 = 1.36. In order to adjust an individual subjects V/F value to represent steady-state 600 mg, the Applicant multiplies each subject's individual V/F value by 1.36.

The Applicant simulated PK for each individual subject in bioequivalence study SBX-P0-750 on Day 1, 7, 14, 21, and 28. The non-linear correction factors to individual subject PK parameters starting at Day 7 and onward. The results of the simulated bioequivalence assessment over time are show in **Tablet 14**.

Reference ID: 5249158

Table 14: Simulated Steady-State Bioequivalence Estimate for 600 mg (2x300 mg) Capsule versus 600 mg Daypro® Caplet Under Fasted Conditions

Comparison	Day	Parameters	Ratio (%) Test/Reference	90% Confidence Interval (%)
Capsule (Test) Fasting Conditions vs. Daypro® Caplet (Reference) Fasting Conditions	1	$Ln(AUC_{0-24})$	124.03	116.33 – 132.23
		$Ln(C_{max})$	135.02	126.36 - 144.28
	7	$Ln(AUC_{0-24})$	111.47	103.45 - 120.11
		$Ln(C_{max})$	117.9	110.2 - 126.14
	14	$Ln(AUC_{0-24})$	108.82	100.25 - 118.13
		$Ln(C_{max})$	114.95	106.81 - 123.72
	21	$Ln(AUC_{0-24})$	108.26	99.57 - 117.71
		$Ln(C_{max})$	114.36	106.11 - 123.25
	28	$Ln(AUC_{0-24})$	108.15	99.44 - 117.62
		$Ln(C_{max})$	114.25	105.98 - 123.16

Abbreviations: AUC_{0-24}=area under the curve from 0 to 24h; C_{max} = maximum plasma concentration;

Source: sequence 0006, module 5335, 5335-oxaprozin-capsule-steady-state-be.pdf, page 15

Sponsor concludes the following:

- Computer modeling demonstrates that Oxaprozin Capsules (300 mg) is bioequivalent to DAYPRO at steady state, which is applicable to the real-world use of oxaprozin given its indication for relief of long-term pain.
- The characteristic nonlinear pharmacokinetics of oxaprozin effectively mitigate any risk the elevated single-dose fasting Cmax.

[*Reviewer comment: The Applicant's results are plausible as the geometric mean ratio of test/reference for Cmax and AUC0-24 is expected to be closer to 1 at steady state versus after a single dose. However, comparison of simulated PK at steady state does not necessarily alleviate the safety concerns for the 34% higher Cmax after a single dose.*

The Clinical team is currently considering the available safety data as adequate support the approval of this submission provided an agreement is reached regarding labeling language. Please refer to the Clinical review for details.]

Reference ID: 5249158

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HONGWU SHEN
09/22/2023 10:58:13 AM

MICHAEL A BEWERNITZ
09/22/2023 04:06:08 PM

VENKATESH A BHATTARAM
09/22/2023 04:07:22 PM

SRIKANTH C NALLANI
09/22/2023 04:10:23 PM