CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217927Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE
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Primary Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary

Date	See electronically signed dates
From	Elizabeth Kilgore, MD; Medical Officer, DAAP Robert Shibuya, MD; Clinical Team Leader, DAAP Rigoberto Roca, MD; Division Director, DAAP
NDA #	217927
Applicant	Solubiomix, LLC
Date of Submission	December 22, 2022 (electronic submission)
PDUFA Goal Date	October 22, 2023
Proprietary Name	Coxanto
Established or Proper Name	Oxaprozin
Dosage Form	300 mg capsule
Applicant Proposed Indications/Populations	Oxaprozin capsule is a non-steroidal anti-inflammatory drug indicated for: 1) Relief of signs and symptoms of Osteoarthritis (OA); 2) Relief of signs and symptoms of Rheumatoid Arthritis (RA); and 3) Relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)
Applicant Proposed Dosing Regimens	1) Osteoarthritis:1200 mg (four 300 mg capsules) given orally once a day 2) Rheumatoid Arthritis:1200 mg (four 300 mg capsules) given orally once a day 3) Juvenile Rheumatoid Arthritis:600 mg once daily in patients 22-31 kg. 900 mg once daily in patients 32-54 kg. 1200 mg once daily in patients ≥55 kg
Regulatory Action	Approval
Indications/Populations	1) Adult patients with OA or RA 2) Pediatric patients aged 6-16 years with JRA
Dosing Regimens	Use the lowest effective dosage for shortest duration consistent with individual patent treatment goals 1) OA: 1200 mg (four 300 mg capsules) given orally once a day 2) RA: 1200 mg (four 300 mg capsules) given orally once a day 3) JRA: 600 mg once daily in patients 22-31 kg. 900 mg once daily in patients 32-54 kg. 1200 mg once daily in patients ≥55 kg

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The subject of this NDA is oxaprozin capsules, 300 mg. The proprietary name of "Coxanto" was granted on March 21, 2023. Therefore, the oxaprozin 300 mg capsules will be referenced as Coxanto henceforth. The oxaprozin molecule is an orally administered nonsteroidal anti-inflammatory drug (NSAID), approved in 1992 under NDA 018841 as a 600 mg caplet for the indications of relief of signs and symptoms of osteoarthritis (OA), relief of signs and symptoms of rheumatoid arthritis (RA), and relief of signs and symptoms of juvenile rheumatoid arthritis (JRA). The innovator product (Listed Drug [LD]) is a 600 mg caplet tradenamed, Daypro. Oxaprozin 600 mg caplets/tablets are also available as generics. Oxaprozin potassium, tradename Daypro Alta, was approved under NDA 20776 in 2002 for the indications of relief of signs and symptoms of OA and RA in adults but has been discontinued.

Risks: The key risks of NSAIDs are cardiovascular thrombotic events, including myocardial infarction (MI) and graft stenosis after coronary artery bypass graft surgery, GI-related adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, and renovascular adverse effects including heart failure and negative effects on blood pressure. The product label will include the Boxed Warnings required for NSAID medications (b) (4)

Benefits: NSAIDs have long been a first or second-line treatment for the conditions of OA, RA, and JRA, with numerous NSAIDs approved based on clinical trials supporting efficacy in these conditions. The efficacy of Daypro was based on clinical trials in patients with OA and RA. The efficacy of Daypro for JRA was based on an extrapolation of the efficacy of Daypro in adults with rheumatoid arthritis and the similarity in the course of the disease and the drug's mechanism of effect between these two patient populations.

Specific to this NDA, given that NSAIDs are to be used at the lowest dose, hypothetically, a 300 mg capsule provides opportunity to use less oxaprozin for an acceptable clinical effect. The availability of a 300 mg strength also increases the precision of dosing for patients who require 900 mg per weight-based dosing requirements. A 900 mg dose would require splitting a 600 mg dosage form. The Applicant has neither generated any data nor proposed labeling related to this theoretical advantage.

The Applicant submitted this 505(b)(2) application for Coxanto for the same indications as Daypro. The Applicant relies upon the Agency's previous findings of safety and effectiveness for Daypro to support this NDA. The regulatory strategy was to demonstrate that two 300 mg capsules of Coxanto would be bioequivalent to one 600 mg Daypro caplet.

Pertinent Pharmacokinetic Data: Consistent with the Applicant's regulatory strategy, the clinical package submitted in this NDA consists of one Phase 1 comparative bioavailability (BA) study (Study SBX-P0-750) and one Phase 1 food effect study (Study SBX-P0-190). Both studies are discussed in more detail below.

Study SBX-P0-750 is the key comparative bioavailability (BA) study to establish the scientific bridge of Coxanto to Daypro. Study SBX-P0-750 was an open-label, randomized, two-period, crossover, single-dose PK study, conducted in 30 healthy adults. The Agency's clinical pharmacology reviewers determined that the study demonstrated that Coxanto had similar AUC compared to Daypro, However, the Cmax for Coxanto was 34% higher than that of Daypro. The study otherwise demonstrated similar PK profiles between Coxanto and Daypro. The differences between formulations were observed only in the absorption phase. Considering the 95% bioavailability of Daypro, the comparable AUC and comparable terminal slope between Coxanto and Daypro, the accumulation of Coxanto is expected to be similar to Daypro. In addition, the formulation differences are deciphered precisely with a single dose BE study.

Study SBX-P0-194 was an open-label, randomized, two-period, single-dose comparative food effect bioavailability study of two 300 mg Coxanto capsules compared to one 600 mg Daypro caplet in 30 healthy adults. The results showed that food exerts a small effect on Coxanto by reducing the rate of absorption without affecting the extent of absorption. This is reflected in the Daypro label.

Pertinent Clinical Data: To assess the clinical risks of elevated levels of oxaprozin when dosed as Coxanto, we issued an Information Request asking the Applicant to assess available data for oxaprozin products when administered in doses exceeding the maximum labeled dose (i.e., overdosage) and to conduct a benefit-risk assessment of the safety implications related to the higher Cmax finding, especially in special populations such as pediatrics. In response to the IR, the Applicant reported that there were no cases pertinent to a transient 34% elevation in plasma concentration and the number of cases of overdose identified overall was low.

Safety findings in the two bioavailability studies reveal that there were no deaths, serious adverse events, or discontinuations due to AEs that were causally related to Coxanto. Overall, the safety profile of Coxanto was comparable to that of the LD, Daypro. The submission also included the Applicant's analysis of oxaprozin based on literature, Daypro and Daypro Alta labels, Daypro postmarketing data, and FAERS (FDA Adverse Events Reporting System) data which revealed no new information that changes the current benefit-risk assessment of this product. The lack of clinical significance of the increased Cmax is further supported by the following factors: a) No increased incidence of oxaprozin-related AEs in healthy subjects in the Coxanto arm compared to the Daypro treatment arm and b) no serious AEs reported in the bioavailability studies.

Risk Mitigation for finding of elevated Cmax: The Agency's clinical pharmacology reviewers determined that the Cmax difference between Coxanto and Daypro may be reduced at steady state after repeated once daily dosing rendering the higher Cmax a first-dose phenomenon. The Daypro label allows for a one-time loading dose of 1800 mg (not to exceed 26 mg/kg) in adults in which the Cmax finding could have a substantive effect. The review team mitigated the first-dose Cmax issue by excluding the option for the 1800 mg loading dose and limiting the maximum daily dose to 1200 mg for Coxanto.

Conclusions: After consideration of the implications of the elevated Cmax in the comparative bioavailability study, the benefit-risk profile for this product appears favorable. The issue of the elevated Cmax is a first-dose phenomenon and has been mitigated by elimination of the option for a loading dose and limiting daily dose to 1200 mg. Oxaprozin 300 mg capsules to be taken as labeled is considered safe and effective for relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. While there is a theoretical advantage to the smaller dosing increment, the Applicant did not provide any data to support any theoretical advantage.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoarthritis (OA): o Most common form of arthritis, affecting an estimated 30 million US adults[1] o Exact mechanism by which OA generates pain is not known but most theories include some component of inflammation and wear-and-tear o Risk factors include age, female gender, lifestyle factors, and certain occupations • Rheumatoid arthritis (RA): o Most commonly diagnosed systemic inflammatory arthritis[2] o Etiology is multifactorial o Risk factors include age (peaks between 30 and 50 years), family history of the disease, and female sex • Juvenile rheumatoid arthritis (JRA): o May be referred to as Juvenile Idiopathic Arthritis o Most common chronic rheumatological condition in children o During 2017-2021, an estimated 220,000 US children and adolescents aged <18 years had arthritis[3]	Pain is the most common reason people seek medical care, and is frequently the major presenting complaint in OA, RA, and JRA as discussed below: • OA: Clinical presentation includes pain, stiffness, loss of flexibility, crepitus, and joint instability of the affected joint(s). • RA: Clinical presentation includes pain, aching, stiffness, and swelling in multiple joints, especially the hands in a symmetrical fashion. • JRA: Signs and symptoms may include pain, synovitis, joint effusion, soft tissue swelling, osteopenia, bone edema, and erosions. OA, RA, and JRA are serious medical conditions. Due to the aging population, demographic changes, and increasing obesity, the prevalence of OA in particular is expected to rise. Untreated pain has a significant impact on quality of life with physical, social, and economic consequences.
Current Treatment Options	The medications listed below may be available in a variety of formulations and can be administered through different routes, such as oral, intramuscular injection, intravenous injection, topical and transdermal systems, depending on the pharmacologic agent. • Osteoarthritis (OA): o Systemic NSAIDs o Topical NSAIDs	A multimodal approach to pain management, using a combination of non-pharmacologic and pharmacologic strategies is most frequently advised in the literature and Clinical Practice Guidelines for the treatment of pain due to OA, RA, and JRA. Nonpharmaceutical management such as exercise and physical therapy should be first line treatments and incorporated along with pharmaceutical interventions as

[1] United States Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States (BMUS). In. Fourth ed. Rosemont, IL. 2018.
[2] Wasserman AM, Diagnosis and management of rheumatoid arthritis. Am Fam Physician; 2011; 84 (11):1245-52.
[3] CDC Morbidity and Mortality Weekly Report (MMWR) Arthritis Among Children and Adolescents Aged <18 years United States, 2017-2021, July 21, 2023, 72(29); 788-792.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Topical capsaicin ○ Non-opioid analgesics (APAP) ○ Duloxetine ○ Corticosteroids ○ Intra-articular injections such as corticosteroids and hyaluronic acid ○ OTC dietary supplements such as glucosamine and chondroitin ○ Opioids (tramadol; other opioids) • Rheumatoid arthritis (RA): Disease modifying antirheumatic drugs (DMARDs), NSAIDs, and corticosteroids are the mainstays of therapy. • JRA: NSAIDs, DMARDs, and glucocorticoids (oral, IV, IA) are the mainstays of therapy.	warranted. The recommended treatment for OA may follow a staged approach. First-line treatments may include topical NSAIDs. Patients who do not respond adequately to the first-line treatments may receive Stage 2 treatments which typically include NSAIDs and corticosteroids. The final stage of non-surgical treatment, Stage 3 or later stages may include intra-articular hyaluronic acid or steroid injections, weak opioids and duloxetine. Treatments for RA and JRA primarily involve DMARDs. Current pharmacologic treatment options for OA, RA, and JRA all include oral NSAIDs.
Benefit	• The Applicant's listed drug, Daypro, is available only as a 600 mg caplet. The efficacy of Daypro was established through clinical trials which support the labeled indications. • At steady state, clinically relevant for chronic use, Coxanto is expected to have similar exposures as Daypro 600 mg caplet.	Coxanto provides the opportunity for flexibility and individualization in dosing and improves accuracy of weight-based dosing for patients when a 600 mg caplet would have to be split.
Risk and Risk Management	• NSAID use and the resulting inhibition of the cyclooxygenase enzymes has been linked to cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and graft stenosis after coronary artery bypass graft surgery, and GI-related adverse events, including bleeding, ulceration, and perforation of the stomach or intestines. • Because oxaprozin is an NSAID, oral administration can result in a CV thrombotic event, GI-related adverse events, and other adverse events currently identified in class-wide NSAID labeling. The proposed product label will include the boxed warnings and other safety language required for NSAID medications. • In single dose, the Cmax of two Coxanto capsules was 34% higher compared to a single Daypro 600 mg caplet. This poses a theoretical safety risk due to increased systemic exposure. This theoretical risk will be addressed	The anticipated risks of Coxanto are listed in the Daypro label. No new safety signals were identified in the healthy population studied in the two PK studies that would alter the currently proposed label. The increased AUC of a single dose is expected to be mitigated through the following labeling language: 1. Limitation of the maximum daily dose to 1200 mg. 2. Elimination of the option for a loading dose of 1800 mg.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	through labeling.	

2. Background

Coxanto is an orally administered product that belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs). The product will be referenced as Coxanto henceforth except in the detailed description of the clinical studies where the Applicant used the term “Oxaprozin 300 mg Capsules” and some of the language in those sections is verbatim from the NDA.

The Applicant (Solubiomix) has proposed three indications:

- 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)

The Applicant submitted a 505(b)(2) NDA referencing Daypro as the Listed Drug. The major difference between Daypro and Coxanto is that Daypro is available in a dosage strength of 600 mg caplets whereas Coxanto is a 300 mg capsule. The Applicant’s rationale for developing this dosage strength is to provide greater flexibility in dosing, especially in the pediatric population where the dosing is weight-based. For example, the labeled dosing for JRA in patients weighing 32-54 kg is 900 mg. To achieve this dose requires splitting the 600 mg caplet, which may result in dosing inaccuracy. The Applicant states that availability of a 300 mg capsule allows for more flexibility to individualize and administer the lowest dose for those patients who require doses other than multiples of 600 mg.

As per the Daypro label, oxaprozin has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of DAYPRO, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Dosing for Daypro is as follows:

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals
  - OA: 1200 mg (two 600 mg caplets) given orally once a day
  - RA: 1200 mg (two 600 mg caplets) given orally once a day
  - JRA: 600 mg once daily in patients 22-31 kg. 900 mg once daily in patients 32-54 kg. 1200 mg once daily in patients ≥55 kg

The proposed dosing for Coxanto is the same as that for Daypro except that dosing will be achieved with 300 mg capsules instead of 600 mg caplets.

- *Therapeutic context*:
  - Osteoarthritis: Osteoarthritis (OA) is the most common form of arthritis.[4] Risk factors for OA include age, female gender, lifestyle factors, and certain occupations. The prevalence of OA is expected to rise further with demographic change and increasing obesity. In OA, the primary patient complaint is usually pain, which is attributed to sensitized nociceptors in inflamed periarticular soft tissues, although the exact mechanism by which OA generates pain is not known. Most theories include some component of inflammation and wear-and-tear. Osteoarthritis is associated with a spectrum of disability severity from mild, when it may cause intermittent pain with only minimal difficulty in performing daily activities, to severe with chronic pain even at rest, progressive irreversible structural damage, and progressive loss of function, often associated with significant comorbidities and a decline in mental health, as well as an increase in mortality when a person is no longer able to walk or live independently.

  - Rheumatoid arthritis: Adult rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily involves the joints. RA causes damage mediated by cytokines, chemokines, and metalloproteases. Characteristically, peripheral joints (e.g., wrists, metacarpophalangeal joints) are symmetrically inflamed, leading to progressive destruction of articular structures, usually accompanied by systemic symptoms.

  - Juvenile rheumatoid arthritis: Juvenile Rheumatoid Arthritis (JRA), now referred to as Juvenile Idiopathic Arthritis (JIA), has presenting clinical signs and symptoms of persistent joint swelling, pain, and stiffness that is typically worse in the morning or after a nap. The pain may limit movement of the affected joint. Juvenile arthritis commonly affects the knees and the joints in the hands and feet. Besides joint symptoms, children with systemic juvenile arthritis have a transient high fever, skin rash, and lymphadenopathy. In some cases (fewer than half), internal organs including the heart and (very rarely) the lungs, may be Involved. Typically, there are periods of remissions and flares.

Treatments

- OA Treatments: Treatment for OA may depend, in part, on the joint(s) affected (e.g., hip, knee, hand). However,

[4] Vina, E, Epidemiology of osteoarthritis: literature update, Current Opinion in Rheumatology; March 2018, Vol 30(2); pages 160-167

regardless of the joint, oral NSAIDS are strongly recommended by the 2019 ACR (American College of Rheumatology)[5] as first or second-line treatments. There are numerous non-selective, semi-selective, and COX-2 or selective NSAIDs. Oxaprozin is classed as a non-selective NSAID. Other pharmacologic classes used to treat OA include corticosteroids and opioid or non-opioid analgesics. Acetaminophen, duloxetine, and tramadol are conditionally recommended by the ACR. Although non-tramadol opioids are conditionally recommended against, opioids have been used in clinical practice for pain management in some stages of OA. The routes of administration for these pharmacologic treatments may include oral, topicals (e.g.,NSAIDs and capsaicin), and intra-articular (e.g., glucocorticoid injections). Nonpharmacologic treatment examples may include weight-loss programs, physical therapy, muscle-strengthening, and graded exercise.

- Rheumatoid Arthritis Treatments: The 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis [6] relies upon a recommendations grading system based on certainty of evidence of literature. This guideline addresses treatment with disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic DMARDs, biologic DMARDs, targeted synthetic DMARDs, use of glucocorticoids; and use of DMARDs in certain high- risk populations (i.e., those with liver disease, heart failure, lymphoproliferative disorders, previous serious infections, and nontuberculous mycobacterial lung disease). The guideline includes 44 recommendations (7 strong and 37 conditional). In addition to DMARDs, the guideline also addresses the use of triple therapy (hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide) and biosimilars. Although not specifically listed in the 2021 RA Guideline, the use of NSAIDs is ubiquitous in rheumatology because of their effectiveness as anti-inflammatory and analgesic agents.

- JRA Treatments: The 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis[7] states that the pharmacologic classes of interventions include: a) NSAIDs ; b) Conventional synthetic DMARDs; c) Biologic DMARDs; and e) glucocorticoids (oral, IV, IA).

Possible adverse reactions which limit the use of the currently approved pharmacologic products are as follows: NSAIDS (cardiovascular or gastrointestinal); IA corticosteroids (increased degradation of joint tissue leading to the impairment of

[5] Kolasinski, et al, 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee Arthritis & Rheumatology Vol. 72, No. 2, February 2020, pp 220–233
[6] Fraenkel, L, et al, 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, Arthritis Care & Research, Vol 73(7), July 2021 pages 924-939
[7] Onel, et al, 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis, Arthritis & Rheumatology Vol.74,No.4,April 2022,pp 553–569

healing and cartilage volume loss); intra-articular hyaluronic acid (high variability of treatment effect); and opioids (numerous well-known risks such as GI, respiratory, abuse and misuse). DMARDs side effects may include increased risk of infections, leukopenia, thrombocytopenia, hepatic dysfunction, and GI complaints such as nausea, diarrhea, and abdominal pain.

Regulatory background and marketing history:

Coxanto is not currently marketed. The submission includes postmarketing data and literature for the oxaprozin moiety.

For use in adults, the current labeling of Daypro calls for doses that are multiples of 600 mg. The Daypro label provides for a maximum daily dose of 1800 mg. At half the unit strength of Daypro, Coxanto is intended to provide advantages in convenience, flexibility, and accuracy of dosing for patients who use oxaprozin in 300 mg increments, such as juveniles weighing 32-54 kg whose recommended dose is 900 mg.

Prescribing instructions also instruct the prescriber to use the lowest effective dose of Daypro and individualization of dosing. Coxanto provides a theoretical safety advantage that may contribute to the favorability of the benefit-risk balance of this new dosage form.

Regulatory History: This product was developed under IND 145336, which was originally submitted on December 22, 2021. Key regulatory history and milestones are summarized in the table below.

Table 1. Key Regulatory History of Drug Development of Oxaprozin 300 mg capsules

Date	Meeting	Relevant Key Comments and Summary
4/14/2020	Type B PIND WRO	■While the selection of a regulatory pathway for the submission of your application is at the Sponsor's discretion, the proposal to pursue a 505(b)(2) regulatory pathway for the NDA appeared reasonable. ■Daypro (oxaprozin) 600 mg caplets may be relied upon as a listed drug, providing that the Sponsor demonstrated that such reliance is scientifically appropriate. ■The proposed product involves a new dosage form compared to the proposed LD and therefore, PREA will be triggered. ■In addition to Cmax and AUC, the shapes of the PK profiles will also need to be compared. If the PK profiles are significantly different (e.g., much delayed Tmax) between the proposed product and the comparator under fasting condition, or for the proposed product with and without food, additional information or rationale will be needed to justify why it will not affect efficacy and safety for the proposed product.

6/10/2022	PeRC meeting with the Division	■The PeRC agreed with the Sponsor's plan for assessment in pediatric patients ages 6 years and older based on the existing information of Daypro for JRA. PeRC agreed that a plan for waiver in pediatric patients less than 2 years of age for JRA is appropriate because necessary studies are impossible or highly impracticable. ■The PeRC disagreed (b) (4) (b) (4) ■DAAP subsequently obtained consultation with DRTM and informed the Sponsor to provide use data for the marketed oxaprozin and NSAID products in pediatric patients with JRA. ■The Sponsor provided the information requested and on 12/21/2022, the Division issued the Agreed Initial Pediatric Study Plan letter to the Sponsor.

Table: reviewer; PIND=preIND; WRO=Written Response Only; PeRC=Pediatric Review Committee; DRTM=Division of Rheumatology and Transplant Medicine

3. Product Quality

The Chemistry/Manufacturing/Controls team conducted a complete review of the NDA. They have recommended "Approval with QPA(s). Their Action Letter Information reads, "Expiration Dating: An expiry of 24 months is acceptable when stored at controlled room temperature: 20°–25° (68°–77° F)."

4. Nonclinical Pharmacology/Toxicology

Excerpted from the Nonclinical Pharmacology/Toxicology Executive Summary

This NDA relies upon FDA's previous findings of safety and efficacy for Daypro, which is the listed drug (LD). The proposed drug product is a new dosage form of oxaprozin (300 mg), which is an orally active nonsteroidal antiinflammatory drug (NSAID) currently marketed as 600 mg tablets and caplets. The Applicant states that at half the unit strength of DAYPRO, the proposed drug product is intended to provide advantages in convenience and accuracy of dosing for patients who use oxaprozin in 300 mg increments, such as pediatric patients weighing 32-54 kg whose recommended dose is 900 mg.

The proposed indications are as the same as those for the LD. The originally proposed maximum recommended human dose (MRHD) was identical to the LD of 1800 mg/day. To establish a scientific bridge, the Applicant conducted Study SBX-P0-750, an open label randomized, two-period crossover study comparing single oral doses of two 300 mg Oxaprozin Capsules (test product) with a single 600 mg caplet of the LD DAYPRO. The proposed drug product met the bioequivalence (BE) criteria for AUC but failed to meet BE criteria for Cmax because the Cmax was 34% higher than that associated with the LD. The higher Cmax is deemed acceptable because the higher Cmax is considered a one-time initial dose event; at steady state, clinically relevant for chronic use, the products (proposed product and Daypro) are expected to have similar exposures; the Cmax elevation is not anticipated to result in doses that would result in clinically meaningful overdose symptoms and the theoretical safety risk is mitigated through labeling by limiting the MRHD to 1200 mg and eliminating a loading dose. The Applicant did not submit any new nonclinical studies to support the NDA, and none were requested given that an adequate scientific bridge to the LD was established. There were no nonclinical safety concerns with the drug substance impurities and drug product degradants or the container closure system.

5. Clinical Pharmacology

Excerpted from the Clinical Pharmacology 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.

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.

6. Clinical Microbiology

Not applicable.

7. Review Strategy

The Applicant seeks a 505(b)(2) regulatory pathway for approval with Daypro serving as the listed drug. In Pre-IND (PIND) minutes, the Agency advised the Applicant that such a regulatory pathway and proposed listed drug appeared reasonable. End-Of-Phase 2 and Pre-NDA meetings were not held as they were not requested by the Applicant.

We assessed the findings from the Applicant's bioavailability studies, literature, and post-marketing data, including FAERS (FDA Adverse Event Reporting System) data for the oxaprozin moiety.

8. Sources of Clinical Data

Since this application relies upon the Agency's previous findings of effectiveness and safety for Daypro, the Applicant did not conduct any additional clinical efficacy or safety studies. The Applicant also relied upon publicly available literature and postmarketing data for oxaprozin, Daypro, and Daypro Alta as supportive efficacy and safety for the proposed product. The clinical package submitted in the NDA consists of one comparative bioavailability study (fasted) and one food effect study in healthy adult subjects. Comparative bioavailability study SBX-PO-750 served as the key study that formed the scientific bridge. The table of clinical (bioavailability) studies is shown below.

Table 2. Table of Bioavailability Studies

Study Identifier/Title	Study Objectives	Study Design	Study Drugs	Population
SBX-PO-750/ An Open-Label, Randomized, Balanced, 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 a 600 mg Dose in Healthy Adult Subjects Under Fasting Conditions (Oxaprozin) 600 mg Caplets Following a 600 mg Dose in Healthy Adult Subjects Under Fasting Conditions	■Primary: To evaluate and compare the bioavailability of a new oxaprozin 300 mg capsule (Test) with the currently marketed Daypro® 600 mg caplet (Reference) after a single ■Secondary: To evaluate the safety and tolerability of the Test and Reference formulations in healthy subjects.	Phase 1, single-center, randomized, single-dose, laboratory-blinded, balanced, 2-period, 2-sequence, crossover study	■Test product: Oxaprozin (2x 300 mg) capsules ■Reference product: Daypro (Oxaprozin) 600 mg caplets ■Route: Oral administration	■N=30 healthy adult males and females included in safety analysis ■N=26 included in PK analysis
SBX-PO-194/Open-label, Randomized, Balanced, Two-Period, Two-Sequence Single Oral Dose Crossover Food Effect Comparative Bioavailability Study of Oxaprozin 300 mg Following a 600 mg Dose in Healthy Adult Subjects	■Primary: To evaluate the effect of food on the pharmacokinetics (PK) of oxaprozin 300 mg capsules after a single oral dose of 600 mg of oxaprozin in healthy subjects. ■Secondary: To evaluate the safety and tolerability of the Test formulation in healthy subjects.	Phase 1, single-center, balanced, randomized, single-dose, laboratory blinded, 2-period, 2 sequence, crossover design	■Formulation: capsule ■Dose: Single 600 mg dose (2x300 mg capsule) ■Route: Oral administration	■N=30 healthy adult males and females included in safety analysis ■N=24 included in PK analysis

Table; reviewer; modified from Applicant's table 5.1 Tabular Listing of Clinical Studies; Safety analysis includes all subjects who entered the study and received at least one dose of the investigational product under study; PK analysis includes subjects who are expected to provide evaluable PK data for both Treatment 1 and Treatment 2 based on viable PK samples. PK=pharmacokinetic

9. Clinical/Statistical- Efficacy

The Applicant showed that two 300 mg Coxanto capsules had comparable exposures to one 600 mg Daypro caplet. The Applicant also cited supportive efficacy by conducting a literature review and review of relevant sections of the Daypro Alta NDA. Findings from the key bioequivalence study bridging to the Daypro label, efficacy language in the Daypro label,

relevant efficacy findings in the Daypro Alta NDA, and findings from the Applicant's cited literature supporting oxaprozin efficacy are discussed and summarized below.

A) Comparative Bioavailability: The Applicant conducted two bioavailability studies to support the NDA. The key study to establish a scientific bridge was Study SBX-P0-750, a single-center, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence, crossover study conducted under fasting conditions to assess comparative bioavailability between one Daypro 600 mg caplet and two Coxanto capsules. For the Test versus Reference comparison, the resulting Test to Reference ratio of LS means for the Cmax, and AUC0-72, were 133.60% and 113.58%, respectively. Based on results obtained for oxaprozin, the ratio and corresponding 90% CI for AUC0-72 were within the 80.00 to 125.00% acceptance range for the Test formulation. The ratio and corresponding 90% CI were outside the protocol acceptance range for Cmax. The implications of these findings are discussed in other sections of this review.

B) Daypro label: Efficacy findings from the Daypro label are summarized below, taken verbatim from the label.

14 CLINICAL STUDIES

14.1 Osteoarthritis : DAYPRO was evaluated for the management of the signs and symptoms of osteoarthritis in a total of 616 patients in active controlled clinical trials against aspirin (N=464), piroxicam (N=102), and other NSAIDs. DAYPRO was given both in variable (600 to 1200mg/day) and in fixed (1200mg/day) dosing schedules in either single or divided doses. In these trials, oxaprozin was found to be comparable to 2600 to 3200 mg/day doses of aspirin or 20 mg/day doses of piroxicam. Oxaprozin was effective both in once daily and in divided dosing schedules. In controlled clinical trials several days of oxaprozin therapy were needed for the drug to reach its full effects [*see Dosage and Administration (2.5)*].

14.2 Rheumatoid Arthritis : DAYPRO was evaluated for managing the signs and symptoms of rheumatoid arthritis in placebo and active controlled clinical trials in a total of 646 patients. DAYPRO was given in single or divided daily doses of 600 to 1800 mg/day and was found to be comparable to 2600 to 3900 mg/day of aspirin. At these doses there was a trend (over all trials) for oxaprozin to be more effective and cause fewer gastrointestinal side effects than aspirin. DAYPRO was given as a once-a-day dose of 1200 mg in most of the clinical trials, but larger doses (up to 26 mg/kg or 1800 mg/day) were used in selected patients. In some patients, DAYPRO may be better tolerated in divided doses. Due to its long half-life, several days of DAYPRO therapy were needed for the drug to reach its full effect [*see Dosage and Administration (2.5)*].

8.4 Pediatric Use: Safety and effectiveness of DAYPRO in pediatric patients below the age of 6years of age have not been established. The effectiveness of DAYPRO for the treatment of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in

pediatric patients aged 6 to 16 years is supported by evidence from adequate and well controlled studies in adult rheumatoid arthritis patients and is based on an extrapolation of the demonstrated efficacy of DAYPRO in adults with rheumatoid arthritis and the similarity in the course of the disease and the drug's mechanism of effect between these two patient populations. Use of DAYPRO in JRA patients 6 to 16 years of age is also supported by the following pediatric studies.

The pharmacokinetic profile and tolerability of oxaprozin were assessed in JRA patients relative to adult rheumatoid arthritis patients in a 14-day multiple dose pharmacokinetic study. Apparent clearance of unbound oxaprozin in JRA patients was reduced compared to adult rheumatoid arthritis patients, but this reduction could be accounted for by differences in body weight [*see Clinical Pharmacology (12.3)*]. No pharmacokinetic data are available for pediatric patients under 6 years. Adverse events were reported by approximately 45% of JRA patients versus an approximate 30% incidence of adverse events in the adult rheumatoid arthritis patient cohort. Most of the adverse events were related to the gastrointestinal tract and were mild to moderate.

In a 3-month open label study, 10 to 20 mg/kg/day of oxaprozin were administered to 59 JRA patients. Adverse events were reported by 58% of JRA patients. Most of those reported were generally mild to moderate, tolerated by the patients, and did not interfere with continuing treatment. Gastrointestinal symptoms were the most frequently reported adverse effects and occurred at a higher incidence than those historically seen in controlled studies in adults. Fifty-two patients completed 3 months of treatment with a mean daily dose of 20 mg/kg. Of 30 patients who continued treatment (19 to 48 week range total treatment duration), nine (30%) experienced rash on sun-exposed areas of the skin and 5 of those discontinued treatment. Controlled clinical trials with oxaprozin in pediatric patients have not been conducted.

C) Daypro Alta NDA: Daypro Alta is the potassium salt of Daypro. The Medical Review in the Daypro ALTA NDA includes descriptions of comparative efficacy studies of oxaprozin potassium and other analgesic drugs including oxycodone hydrochloride, acetaminophen, and etodolac. Oxaprozin free acid was not included as a comparator in any of these studies. The Medical Review in the Daypro ALTA NDA also includes data tables from efficacy studies that compared oxaprozin potassium to oxaprozin free acid. There was no statistically significant difference in efficacy between oxaprozin potassium and oxaprozin.

D) Literature: The Applicant's submission cited literature to support the efficacy of the oxaprozin moiety. The literature tables in the initial submission had some minor discrepancies. In response to a clinical IR, the Applicant submitted corrected tables on May 2, 2023. The Applicant's findings from the cited literature are summarized below.

The Applicant stated that they conducted a literature search in PubMed and ScienceDirect using the search term, "Oxaprozin" to identify and analyze clinical efficacy information not already captured in the approved Daypro label. No

time limits were included on the data. The Applicant identified a total of 723 abstracts with the key criterion that the papers contained clinical efficacy data through a period pre-Daypro approval to post approval. After eliminating non-relevant review papers, case studies, duplicates, and papers published before Daypro' s approval in 1992, the Applicant identified a total of 16 publicly available citations that met criteria as containing relevant efficacy data. Of these, five were published after 1992 and were used by the Applicant to analyze efficacy data for oxaprozin after approval of Daypro. Those papers were further divided into those that provide information about arthritis indications (i.e., osteoarthritis and rheumatoid arthritis) versus other uses reported in the literature (i.e., Alzheimer's disease, Neurodegeneration, and Cancer).

For the purposes of this review, we focused on the articles pertaining to arthritic indications published after 1992. See Appendix A for a list of the Applicant's key cited materials supporting efficacy. The Applicant found that overall, literature on efficacy data published after Daypro approval provided no new information relevant to the labeling of Daypro or the proposed labeling of Coxanto. The Applicant's analysis of published information on oxaprozin efficacy did not reveal any information that would justify a change to the approved labeling of Daypro or the proposed labeling of Coxanto.

Agency's Conclusions on the Substantial Evidence of Effectiveness: Findings from the key comparative BA study demonstrate that Coxanto is comparable to Daypro excepting an elevated Cmax. Review of the five publications providing supportive efficacy cited by the Applicant and the Applicant's summary of key findings for the cited literature reveal that no new findings were identified in the literature that refute the efficacy of the oxaprozin moiety for the proposed indications.

10. Safety

The Applicant relies upon findings from their bioavailability studies, the Daypro label, Daypro postmarketing data, FAERS reports, and literature relevant to the oxaprozin moiety. A description of the bioavailability studies and study findings are discussed below:

l) Study SBX-PO-750

Title: An Open-Label, Randomized, Balanced, 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 a 600 mg Dose in Healthy Adults Subjects Under Fasting Conditions

Treatments: The study treatments were taken as a single 600 mg dose (i.e., two 300 mg oxaprozin capsules or a single 600 mg Daypro caplet) on two occasions, separated by a washout of 28 days. Subjects received each of the following treatments on one occasion according to the randomization list:

- Test: 2 x oxaprozin 300 mg capsules
- Reference: 1 x Daypro (oxaprozin) 600 mg caplets

Subject Disposition: A total of 30 subjects were randomized into the study, with all 30 subjects (100.0%) receiving the Test treatment and 26 subjects (86.7%) receiving the Reference treatment. The majority of randomized subjects (86.7%) completed the study according to the protocol. A total of 4 subjects (13.3%) were prematurely discontinued for the following reason: a) Subjects (b) (6) were withdrawn prior to dosing of Period 2 after testing positive for COVID-19 at check-in (categorized under withdrawal for physician decision). A TEAE of COVID-19 was reported for these subjects. There were no major protocol deviations. Minor protocol deviations included 12 subjects did not consume the full content of their critical meals within 45 minutes as indicated in the protocol. The Applicant considered that these deviations were deemed to have no impact on the PK profile of oxaprozin as the drug's absorption was deemed to be completed before the state of the meals and enterohepatic recycling was determined to be insignificant.

Table 3. Subject Disposition Study SBX-PO-750

Category		Overall
Subjects included (N)		30
Subjects discontinued before end of study (n[%])	Yes	4 (13.3)
	No	26 (86.7)
If yes, reason of study discontinuation (n[%])	Adverse event	0
	Withdrawal by subject	0
	Study terminated by Sponsor	0
	Physician decision	4 (13.3)
	Protocol deviation	0
	Death	0
	Lost to follow-up	0
	Other	0
	Other, protocol withdrawal criteria	0

Applicant's Table 10-1, CSR, p. 30

Demographics: The mean age of the subjects was approximately 44 years and the sex distribution was balanced. There was a high predominance of White race (>95%).

Table 4. Summary of Demographic Characteristics Study SBX-P0-750 Safety Population

		Test (N=30)	Reference (N=26)	Overall (N=30)
Age (years)	N	30	26	30
	Mean (SD)	45 (11)	44 (11)	45 (11)
	Median	45	41	45
	Min, Max	28, 60	28, 60	28, 60
Sex [n(%)]	MALE	16 (53.3)	13 (50.0)	16 (53.3)
	FEMALE	14 (46.7)	13 (50.0)	14 (46.7)
Ethnicity [n(%)]	HISPANIC OR LATINO	11 (36.7)	9 (34.6)	11 (36.7)
	NOT HISPANIC OR LATINO	19 (63.3)	17 (65.4)	19 (63.3)
Race [n(%)]	ASIAN	1 (3.3)	1 (3.8)	1 (3.3)
	WHITE	29 (96.7)	25 (96.2)	29 (96.7)
Weight (kg)	N	30	26	30
	Mean (SD)	74.2 (14.8)	73.8 (15.2)	74.2 (14.8)
	Median	75.7	72.9	75.7
	Min, Max	46.3, 95.7	46.3, 95.7	46.3, 95.7
Height (cm)	N	30	26	30
	Mean (SD)	167.6 (10.3)	167.0 (10.0)	167.6 (10.3)
	Median	166.4	165.8	166.4
	Min, Max	146.4, 184.5	146.4, 184.5	146.4, 184.5
Body Mass Index (kg/m^2)	N	30	26	30
	Mean (SD)	26.2 (3.1)	26.2 (3.2)	26.2 (3.1)
	Median	27.2	27.4	27.2
	Min, Max	19.4, 29.9	19.4, 29.9	19.4, 29.9

Applicant's Table 14.1.2.2, CSR 750, p. 44

Safety Results: Safety assessments included physical examination, vital signs, clinical laboratory tests, and AE monitoring. For the purpose of the study, the monitoring period for AEs extended from the pretrial evaluation until 12 days after collection of the last blood sample of the study. Descriptive statistics were used to summarize AEs, safety results, and demographic variables (age, height, weight, and body mass index). The safety population includes all subjects who entered the study and received at least one of the investigational products under study (Subjects (b) (6)).

No deaths or SAEs were reported. A total of 5 TEAEs were experienced by 5 of the 30 subjects (16.7%) who participated in this study. Of these TEAEs, four occurred after administration of the Test and one occurred after administration of the Reference. Most of the TEAEs experienced during the study were considered not drug-related (4/5; 80.0%). All TEAEs

were deemed Grade 1 in intensity and were resolved at the end of the study. Four of the 30 subjects (13.3%) who received the Test each reported a TEAE of COVID-19. The 4 TEAEs of COVID-19 were all deemed not related to drug administration. One of the 26 subjects (3.8%) who received the Reference reported a TEAE of headache that was deemed related to drug administration.

Table 5. Study SBX-PO-750 TEAEs by SOC and MedDRA Preferred Terms

SOC, n(%) MedDRA PT, n(%)	Test (N=30)	Reference (N=26)
Infections and infestations	4 (13.3)	0
COVID-19	4 (13.3)	0
Nervous system disorders	0	1 (3.8)
Headache	0	1 (3.8)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE =treatment-emergent adverse event.
Note: Each TEAE was counted only once for each subject within each SOC and MedDRA PT.

Applicant's Table 12-2, CSR 750 p. 38

No clinically significant abnormal findings in laboratory parameters, vital signs, ECGs, and physical examinations were noted during the study.

Applicant's conclusions: Study SBX-P0-750, is a single-center, randomized, balanced, single-dose, laboratory-blinded, 2-treatment, 2-period, 2-sequence, crossover study conducted under fasting conditions to assess comparative bioavailability between 2 formulations (test and reference). The Applicant found that for the Test versus Reference comparison, the resulting Test to Reference ratio of LS means for the Cmax, and AUC0-72, were 133.60% and 113.58%, respectively. Based on results obtained for oxaprozin, the ratio and corresponding 90% CI for AUC0-72 were within the 80.00 to 125.00% acceptance range for the Test formulation. However, the ratio and corresponding 90% CI were outside the protocol acceptance range for Cmax. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Agency's conclusion Study SBX-P0-750: Overall, there is no new safety information from this study that alters the benefit-risk assessment of this product.

II) Study SBX-PO-194

Title of Study: An Open-Label, Randomized, Balanced, Two-Period, Two-Sequence, Single Oral Dose Crossover Food Effect Comparative Bioavailability Study of Oxaprozin 300 mg Following a 600 mg Dose in Healthy Adult Subjects

Overview: The study treatments were taken as a single 600 mg dose on 2 occasions (fed and fasted), separated by a washout of 28 days.

Subject Disposition: A total of 30 subjects were randomized into the study, with 28 subjects (93.3%) receiving Treatment-1 (fed) and 26 subjects (86.7%) receiving Treatment-2 (fasting). The reasons for discontinuation are as follows: a) Subjects (b) (6) were withdrawn prior to dosing of Period 2 after testing positive for COVID-19 at check-in (categorized under physician decision) and a TEAE of COVID-19 was reported for these subjects; b) Subject (b) (6) withdrew consent after the last blood draw of Period 1 (categorized under withdrawal by subject) and c) Subject (b) (6) did not show-up for the PCR test (categorized under physician decision). There were no major protocol deviations during the study.

Table 6. Subject Disposition Study SBX-PO-194

Category		Overall
Subjects included (N)		30
Subjects discontinued before end of study (n[%])	Yes	6 (20.0)
	No	24 (80.0)
If yes, reason of study discontinuation (n[%])	Adverse event	0
	Withdrawal by subject	1 (3.3)
	Study terminated by Sponsor	0
	Physician decision	5 (16.7)
	Protocol deviation	0
	Death	0
	Lost to follow-up	0
	Other	0
	Other, protocol withdrawal criteria	0

Applicant's Table 10-1, CSR, p. 31

Demographics: The demographics in the food effect study were similar to the comparative BA study except that the mean age was slightly higher ~47 compared to ~45 years.

Table 7. Summary of Demographic Characteristics Study SBX-P0-194 Safety Population

		Treatment-1 (N=28)	Treatment-2 (N=26)	Overall (N=30)
Age (years)	N	28	26	30
	Mean (SD)	47 (10)	48 (11)	48 (10)
	Median	52	52	52
	Min, Max	22, 60	22, 60	22, 60
Sex [n(%)]	MALE	13 (46.4)	12 (46.2)	14 (46.7)
	FEMALE	15 (53.6)	14 (53.8)	16 (53.3)
Ethnicity [n(%)]	HISPANIC OR LATINO	6 (21.4)	7 (26.9)	7 (23.3)
	NOT HISPANIC OR LATINO	22 (78.6)	19 (73.1)	23 (76.7)
Race [n(%)]	ASIAN	1 (3.6)	0	1 (3.3)
	BLACK OR AFRICAN AMERICAN	1 (3.6)	1 (3.8)	1 (3.3)
	WHITE	26 (92.9)	25 (96.2)	28 (93.3)
Weight (kg)	N	28	26	30
	Mean (SD)	69.1 (10.6)	71.6 (12.8)	70.9 (12.7)
	Median	70.5	73.5	72.2
	Min, Max	50.0, 86.3	50.0, 109.0	50.0, 109.0
Height (cm)	N	28	26	30
	Mean (SD)	166.4 (7.8)	167.2 (9.0)	167.3 (8.8)
	Median	165.1	166.7	166.7
	Min, Max	155.3, 180.5	155.3, 191.5	155.3, 191.5
Body Mass Index (kg/m^2)	N	28	26	30
	Mean (SD)	24.9 (3.0)	25.5 (3.0)	25.2 (3.1)
	Median	24.6	25.5	25.1
	Min, Max	19.9, 30.0	19.9, 30.0	19.9, 30.0

Applicant's table 14.1.2.1, CSR p. 45

Safety Results: Safety assessments included physical examination, vital signs, clinical laboratory tests, and AE monitoring.

No deaths or serious AEs were reported for any of the subjects dosed in this study. No subject was withdrawn by the Investigator due to a safety-related, treatment-emergent adverse event (TEAE). The incidence of TEAEs was 7.1% % following administration of the Treatment-1 (fed) and 15.4% following administration of Treatment-2 (fasting). None of the subjects reported drug-related TEAEs following administration of the Treatment-1, while 3 TEAEs (two subjects who experienced injection site hematoma and one subject who experienced headache) following administration of Treatment-2 were considered treatment related.

A total of 7 TEAEs were experienced by 6 of the 30 subjects (20%) who participated in this study. Of these TEAEs, two occurred after administration of Treatment-1 and five occurred after administration of Treatment-2. Most of the TEAEs experienced during the study were considered not drug-related. All TEAEs experienced during the study were resolved at the end of the study. The TEAE experienced most commonly in this study was COVID-19, reported by 2 subjects (7.1%) after administration of Treatment-1 and 2 subjects (7.7%) after administration of Treatment-2. Other TEAEs experienced less frequently included injection site hematoma, reported by 2 subjects (7.7%) and headache, reported by 1 subject (3.8%) after administration of the Treatment-2. All TEAEs experienced during the study were deemed Grade 1 in intensity. None of the subjects experienced a severe TEAE during the study.

Table 8. Study SBX-PO-194 TEAEs by SOC and MedDRA Preferred Terms

SOC, n(%) MedDRA PT, n(%)	Treatment-1 Fed Conditions (N=28)	Treatment-2 Fasting Conditions (N=26)
Infections and infestations	**2 (7.1)**	**2 (7.7)**
COVID-19	2 (7.1)	2 (7.7)
General disorders and administration site conditions	**0**	**2 (7.7)**
Injection site haematoma	0	2 (7.7)
Nervous system disorders	**0**	**1 (3.8)**
Headache	0	1 (3.8)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE =treatment-emergent adverse event
Note: Each TEAE was counted only once for each subject within each SOC and MedDRA PT.

Applicant's table 12-2, CSR, p. 39

Blood samples for PK measurements were collected prior to and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 48.00, and 72.00 hours following drug administration.

No clinically significant abnormal findings in laboratory parameters, vital signs, ECGs, and physical examinations were noted during the study.

Applicant's conclusions: Study SBX-P0-194 was a single-center, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence, crossover study performed under fed and fasting conditions to assess the effect of food on the PK of oxaprozin. The statistical results of this study indicate that oxaprozin Treatment-1 (Test under fed conditions)/Treatment-2 (Test under fasting conditions) ratio of geometric LS means for Cmax was within the acceptance range of 80.00-125.00 but the lower limit of the 90% CI was outside the 80.00% boundary. The AUC0-72 ratio of geometric LS means and 90% CI were within the acceptance range (80.00 – 125.00%). Based on results obtained for oxaprozin, food exerts a small effect on oxaprozin 300 mg capsules by reducing the rate of absorption without affecting the extent of absorption. Overall, the drug tested was generally safe and well-tolerated.

Agency's conclusions Study SBX-P0-194: From the clinical standpoint, we determined that the oxaprozin 300 mg capsule appears generally well tolerated in the healthy population studied and no new or unexpected safety signals were identified. See the clinical pharmacology review for full discussion of the PK results and the acceptability of the Applicant's interpretation of the PK findings.

11. Other Sources of Safety Data

The Applicant relies upon the following sources to support safety of Coxanto: a) Bioavailability studies included in the NDA; b) Daypro label; c) Literature; and d) Postmarketing information from the Daypro label, Daypro Alta NDA review, and FAERS database.

The Applicant's Summary of Clinical Safety included analyses from each of these sources based on extent of exposure, demographic and other characteristics of the study populations, adverse events (deaths, serious adverse events, significant adverse events, adverse events by organ system or syndrome, common adverse events), narratives, clinical

laboratory findings, vital signs, physical examinations, and safety in special groups and situations (e.g., overdose, pregnancy) and compared these findings from the various sources to currently approved Daypro to put the results in context to determine if there were any new safety signals not currently labeled. Key safety findings from each of these sources are discussed below.

I) *Bioavailability studies included in the submission to support the NDA:* There were no deaths, serious adverse events, dropouts and/or discontinuations due to adverse events or significant adverse events definitely causally related to Coxanto in the Phase 1 bioavailability studies included in this submission to support the NDA. Since there were no deaths, serious adverse events, or other significant adverse events reported, there were no narratives in the clinical study reports for the BA studies in healthy subjects. Across both studies, the only treatment-related adverse reaction possibly related to Coxanto was headache, which occurred in one subject in Study SBX-PO-194. COVID 19 and injection site hematoma were reported AEs but are not directly causally related to Coxanto.

II) *Daypro label:* The Daypro label states that the adverse reaction data were derived from patients who received Daypro in multidose, controlled, and open-label clinical trials. Rates for events from clinical trial experience are based on 2253 patients who took 1200 mg to 1800 mg Daypro per day in clinical trials. Of these, 1721 patients were treated for at least 1 month, 971 patients for at least 3 months, and 366 patients for more than 1 year. Most common adverse reactions (>3%) are constipation, diarrhea, dyspepsia, nausea, and rash. Serious adverse events for Daypro are listed in the Warnings and Precautions and Adverse Reactions sections of the label. There were no deaths reported in the clinical trials section of the Daypro label.

III) *Literature:* The Applicant's submission cited published literature to support safety of the oxaprozin moiety. The tables in the initial submission had some minor discrepancies. In response to a clinical IR, the Applicant submitted corrected tables on May 2, 2023. As per the submission, the Applicant conducted literature searches in PubMed and ScienceDirect using the search term "oxaprozin" and identified a total of 723 abstracts based on these searches. The key criterion for inclusion was that the papers contained clinical safety data. After excluding duplicates, case reports and review papers without clinical data, the Applicant identified a total of 16 papers as meeting the key criterion of containing relevant safety data. Of the 16 papers, three were published before 1992 and were excluded by the Applicant because their content was presumably taken into account as part of the approval process of the original Daypro NDA. The remaining 13 papers were summarized and discussed by the Applicant. See Appendix B of this review for a list of Applicant's key cited literature supporting safety.

The Applicant also reviewed the literature for the AE term of death and identified no reports of deaths in the cited literature, acknowledging that some papers did not provide information. The Applicant analyzed the literature for serious adverse events and common adverse event terms and compared to the currently approved Daypro label. The Applicant concluded that their literature review identified no safety information that identifies a new safety signal or alters the benefit-risk profile of the proposed product.

IV) *Postmarketing Safety Data:* The Applicant obtained post-marketing data on oxaprozin from the following three sources: a) the current version of the Daypro label; b) the Daypro Alta NDA which contains analysis of oxaprozin safety relevant to the safety of the oxaprozin potassium moiety; and c) FDA Adverse Events Reporting System (FAERS) which contain post-marketing safety data on oxaprozin. The Applicant's conclusions and findings from each of these sources are discussed below:

a. Daypro label postmarketing data: The Daypro label states that the following adverse reactions have been identified during post approval use of Daypro: Serum sickness; Hepatitis; Pancreatitis; Agranulocytosis; Pancytopenia; Pseudo-porphyria; Exfoliative dermatitis, Erythema multiforme, Steven's Johnson syndrome; Toxic epidermal necrolysis (Lyell's syndrome); Acute interstitial nephritis; Nephrotic syndrome; and Acute renal failure.
b. Daypro Alta NDA review: The Daypro Alta NDA review includes post-marketing experience with Daypro. According to a Daypro Alta Annual Report covering the period of 2004-2005, the Daypro Alta product has not been marketed in the US at least since 2004. The NDA submission includes the Applicant's analysis of the Daypro Alta NDA review of post-marketing data and analysis of the literature. Overall, the Applicant determined there were no new findings in the Daypro Alta post-marketing analysis that would require labeling changes for the proposed Oxaprozin label.
c. FAERS data: The Applicant stated that they searched the FAERs database using the search terms "Oxaprozin" and "Daypro" for the period of 1992 (when Daypro was initially approved) through September 2022 (date of most recent FAERS update at the time of the NDA submission). The Applicant identified 2,767 cases, of which 1,115 were serious with 57 deaths. Overall, most of the reports occurred between 1992 and 1994, then dropped abruptly in 1995. Since 1995, the number of yearly cases has remained below 100 with some years reporting less than 20 reports. The Applicant analyzed the FAERs reports by categories of reaction, demographics, and deaths and compared those findings against the safety profile of literature and the Daypro label to determine if there were any common reactions to oxaprozin not reflected in the current Daypro label. They determined that the FAERs database demonstrated that the established safety profile of Daypro is applicable to recent experience and no new relevant safety findings were identified. The Applicant searched the FAERs data for reports with the outcome of death and identified a total of 58 cases for an overall rate of 2.1% (58 of 2,767). The most frequent cause of death was GI hemorrhage (4 cases) and 3 cases each of Aplastic anemia; Completed suicide; Hemorrhage; and Death

(no causality identified). Of these cases identified, 31 of 58 involved co-suspect drugs and in 42 of 58 cases, causality was determined to be multifactorial with no definite causality to oxaprozin identified.

V) Narratives: The Applicant identified the following narratives for serious adverse events reported in the literature for cases in which patients were taking oxaprozin or other NSAIDs: a) Case report of a 36-year-old man with hypertension who experienced severe peripheral edema[8] and b) Reports of six patients diagnosed with pseudo-porphyria[9]. The terms, edema and pseudo-porphyria are included in the Daypro label.

VI) Laboratory Findings: Laboratory measurements from the bioavailability studies revealed no clinically significant abnormal laboratory values. The Applicant's review of literature provided no new information related to clinical laboratory evaluations.

VII) Vital Signs and Physical Findings: Vital sign measurements and physical examinations from the bioavailability studies revealed no clinically significant abnormal findings. The Applicant's review of literature provided no new information related to these parameters.

VIII) Assessment of Clinical Significance of Increased Cmax: As previously noted, the 34% higher Cmax for Coxanto vs. Daypro presents a theoretical safety concern. As such, the Agency required the Applicant to conduct additional analyses and provide additional information regarding this potential safety concern. In a clinical Information Request, we advised the Applicant to address the following:

a. Provide a summary table of literature by dose and duration of studies and/or analysis of other publicly available information including FAERs data in which oxaprozin was administered in single dose or repeat dose >1800 mg per day;
b. Provide additional information regarding any cases of overdose in post-marketing data;
c. Conduct a benefit-risk assessment including implications in special populations; and
d. Propose measures to address the increased Cmax finding.

Applicant's conclusions: The Applicant's response to the Information Request is summarized as follows:

[8] Ogawa M, et al, Membranous nephropathy associated with Oxaprozin treatment. Nephron, 1996 74(2):439-40.
[9] LaDuca JR. Nonsteroidal anti-inflammatory drug-induced pseudo porphyria: A Case Series. Journal of Cutaneous Medicine and Surgery July 2002 6(4):320-6.

- There was no additional information on dosing >1800 mg that is clinically relevant. Specifically, in the FAERs reports there was one case of a dose of 10,800 mg and one case of 18,000 mg. These cases are so far in excess of 1800 mg that they are not relevant to the question of potential sides effects of a dose exceeding 1800 mg.
- Overall, there is limited information on overdosage of oxaprozin. What information is available is consistent with the Daypro label.
- Increased Cmax does not require additional labeling for special populations.
- The benefit-risk profile is favorable and potential risk due to increased Cmax can be mitigated through labeling.

Applicant's Overall Benefit-Risk Assessment: The Applicant asserts that the benefits of Coxanto outweigh the risks for patients experiencing OA, RA, and JRA, just as the benefits of approved dosage forms of oxaprozin outweigh the risks. The Applicant asserted that the benefit-risk profile of Coxanto is further enhanced by its 300 mg dose for patients weighing 32-45 kg and for patients requiring individualization of dosing in increments smaller than 600 mg. Specifically, with regard to pediatric populations the maximum dose limits the potential safety concerns expressed by FDA with the 1800 mg dose, and the results of computer modeling indicate that at the maximum pediatric dose of 1200 mg Coxanto is bioequivalent to Daypro. With regards to special populations, no change in the risk-benefit assessment of Coxanto is warranted as currently detailed in the Daypro label

Agency's Conclusions: The data submitted in this NDA support that Coxanto, dosed identically to Daypro, will have a similar safety profile. While the ability to titrate to lower doses without splitting a solid oral dosage form is a theoretical advantage, Solubiomix has presented no data to support any advantage. The clinical pharmacology data submitted show a Cmax that is 34% higher than the Listed Drug. We have mitigated this first-dose risk by eliminating an option for an 1800 mg loading dose in the Daypro package insert and limiting the dose to 1200 mg. The safety of Coxanto is expected to be similar to that of Daypro and its generics.

12. Advisory Committee Meeting

The NDA was not taken to an Advisory Committee (AC) as the review team determined that there were no issues which needed to be discussed requiring AC input.

13. Pediatrics

No pediatric studies were conducted. Efficacy and safety in adults are to be extrapolated to the pediatric population ages 6 to 16 years for the Coxanto capsules.

On August 5, 2022, the Division of Rheumatology and Transplant Medicine (DRTM) provided a consult review to DAAP in which DRTM: a) agreed with the Sponsor for a planned full waiver in OA and partial waiver for pediatric studies in JRA patients aged <6 years because these studies would be impossible or highly impracticable and b) agreed that, if bioequivalence (comparable exposure) of the proposed product to the listed drug is established, then the proposed product could be considered fully assessed in JRA patients ages 6 to 16 years.

Accordingly, the regulatory history includes an Agreed Pediatric Study Plan (PSP) (12/21/2022) for a full waiver of OA studies in pediatric patients based on the absence of OA in pediatric populations, a partial waiver of JRA <6 years, and a pediatric assessment of bioequivalence based on the current approval for oxaprozin for use in JRA patients from 6 to 16 years of age.

On August 29, 2023, DAAP met with the PeRC and discussed the following:

- Pediatric information in the Daypro NDA (18841) included a steady-state PK study in 44 JRA patients versus 40 adult RA patients and an open-label study in 59 patients with JRA. The findings from these studies are reflected in Sections 8.4 and 12.3 of the Daypro label.
- The Daypro label states that a population pharmacokinetic study indicated no clinically important age dependent changes in the apparent clearance of unbound oxaprozin between adult rheumatoid arthritis patients (N=40) and juvenile rheumatoid arthritis (JRA) patients (≥6 years, N=44) when adjustments were made for differences in body weight between these patient groups. Pharmacokinetic model-based estimates of daily exposure (AUC0-24) to unbound oxaprozin in JRA patients relative to adult rheumatoid arthritis patients suggest dose to body weight range relationships.
- Pediatric dosing for Daypro and for the 300 mg capsules is weight-based into three rather broad strata (22 to 31 kg; 32 to 54 kg; and ≥55 kg). The concern would be the elevated Cmax in pediatric patients at the low end of the weight stratum. It is important to assess the magnitude of the elevation in Cmax in the context of the level of overdose

accepted to cause symptoms in adults and pediatric patients. Available literature[10,11] suggests a floor ingestion of 100 mg/kg to result in symptoms. For a 22 kg pediatric patient, this equates to 2200 mg to result in nonserious symptoms. The 34% overage would approximate a dose of 804 mg.

- The risks of an initial high exposure to oxaprozin are also mitigated by the nature of the expected acute adverse reactions for NSAIDs. The clinical manifestations of a high Cmax are primarily nonserious GI adverse events. The NSAID Boxed Warning indicates that the GI risk is age-related in adults thus, the likelihood of a transient elevation in oxaprozin is unlikely to result in a GI SAE.

DAAP and PeRC agreed that the pediatric labeling from Daypro would suffice for this product. The appropriate sections will be updated in the package insert for Coxanto.

14. Other Relevant Regulatory Issues

- Exclusivity or patent issues of concern: No issues were identified. On 9/26/2023, the Agency's 505(b)(2) committee confirmed that the NDA was cleared from a 505(b)(2) perspective.

- Financial disclosures: The submission included financial disclosure Form 3454 for both BA studies which stated that no investigators had financial interests or arrangements to disclose.

- Other Good Clinical Practice (GCP) issues: Both BA studies SBX-P0-750 and SBX-P0-194 include the following statement: "This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents."

- Office of Scientific Investigations (OSI) audits:
  - An OSI audit was not requested or conducted because the review teams determined that there were no specific efficacy or safety concerns identified based on site-specific data. Additionally, no new clinical efficacy or safety trials were conducted because the Applicant does not plan to rely on data from new clinical trials to support efficacy or safety, but instead plans to rely on the determination of the establishment of bioequivalence to the listed drug, Daypro.

[10] Hall, A, et al, Ibuprofen Overdose:126 Cases, Rocky Mountain Poison and Drug Center, University of Colorado Health Sciences Center, Presented in part at AACT/AAPCC/ABMT/CAPCC Annual Scientific Meeting 1985, received for publication 1986

[11] Su, M, etal, Nonsteroidal anti-inflammatory drug (NSAID) poisoning, UpToDate; Literature review current through September 2023

- An OSIS (Office of Study Integrity and Surveillance) clinical inspection was conducted for the key bridging Study SBX-P0-750. As per the reviewer's 8/31/2023 report, there were no identified concerns regarding reliability of the data and human subject protection for the inspected study. A remote regulatory assessment of the analytical portion of Study SBX-P0-750 found that the data from the audited study was reliable.

15. Labeling

The labeling is currently being negotiated with the Applicant and is not finalized. Proposed relevant labeling recommendations are summarized and discussed below.

Prescribing Information

- INDICATIONS AND USAGE: The Applicant's proposed indications are appropriate and consistent with the currently approved listed drug.

1 INDICATIONS AND USAGE COXANTO is indicated:

- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis
- For relief of the signs and symptoms of juvenile rheumatoid arthritis

DOSAGE AND ADMINISTRATION: Because of the theoretical risk of increased systemic exposure, the following dosing language will be included in the label:

Highlights Dosage and Administration

DAYPRO Label	Proposed Coxanto Label
Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	Use the lowest effective dosage for shortest duration consistent with individual patent treatment goals.
OA: 1200 mg (two 600 mg caplets) given orally once a day	OA: 1,200 mg (four 300 mg capsules) given orally once a day
RA: 1200 mg (two 600 mg caplets) 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 22-31 kg. 900 mg once daily in patients 32-54 kg. 1200 mg once daily in patients ≥55 kg	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

2.5 Individualization of Dosage

DAYPRO Label	Proposed COXANTO Label
After observing the response to initial therapy with DAYPRO, 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 DAYPRO to minimize adverse effects. The maximum recommended total daily dose of DAYPRO in adults is 1800 mg (26 mg/kg, whichever is *lower*) in divided doses. In children, doses greater than 1200 mg have not been studied.	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 and pediatric patients is 1,200 mg.
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).	~~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 1,200 mg. to 1800 mg (not to exceed 26 mg/kg).~~

8.2 Lactation

DAYPRO Label	Proposed COXANTO Label
Risk Summary Lactation studies have not been conducted with DAYPRO. It is not known whether DAYPRO is excreted in human milk. DAYPRO should be administered to lactating women only if clearly indicated. The developmental and health benefits of breastfeeding should be considered along with the	Risk Summary There are no data on the presence of oxaprozin in human milk, the effects on the breastfed infant, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COXANTO and any potential

mother's clinical need for DAYPRO and any potential adverse effects on the breastfed infant from the DAYPRO or from the underlying maternal condition.	adverse effects on the breastfed infant from the COXANTO or from the underlying maternal condition.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS: The proposed label will include the same Boxed Warnings, Contraindications, and Warnings and Precautions as the listed drug and class-wide NSAIDs.
- Section 6 Adverse Reactions: No substantive changes will be made.
- Section 14 Clinical Studies: No new clinical studies were conducted. No substantive changes will be made.

Other Labeling

- Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use): No substantive changes.
- Carton and container labeling: No substantive changes.

16. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS): A REMS will not be required for this product.

Postmarketing Requirements (PMRs) and Commitments (PMCs): The Division of Pediatric and Maternal Health determined that a Post Marketing Requirement (PMR) for a milk only lactation study would be required for this product. On 9/27/2023, the Division sent a PMR Communication to the Applicant as follows:

PMR 4503-2: Perform a lactation study (milk only) in lactating women who have received Oxaprozin to assess concentrations of Oxaprozin in breast milk using a validated assay and to assess the effects on the breastfed infant.

Draft Protocol Submission: 04/2024 (6 months post approval)
Final Protocol Submission: 10/2024
Study/Trial Completion: 10/2026
Final Report Submission: 04/2027

On 10/3/2023, the Applicant replied that they commit to performing the lactation study with agreement to the proposed timelines.

17. Recommended Comments to the Applicant: None

Appendix A. Applicant's Cited Key Literature Supporting Efficacy

1. Weaver A, Rubin B, Caldwell J, McMahon FG, Lee D, Makarowski W, et al. Comparison of the efficacy and safety of oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the knee. Clin Ther. 1995;17(4):735–45.
2. Makarowski W, Weaver A, Rubin B, Caldwell J, McMahon FG, Noveck RJ, et al. The efficacy, tolerability, and safety of 1200 mg/d of oxaprozin and 1500 mg/d of nabumetone in the treatment of patients with osteoarthritis of the knee. Clin Ther. 1996;18(1):114–24.
3. Zhao SZ, Dedhiya SD, Bocanegra TS, Fort JG, Kuss ME, Rush SM. Health-related quality-of-life effects of oxaprozin and nabumetone in patients with osteoarthritis of the knee. Clin Ther. 1999 Jan;21(1):205–17.
4. Heller B, Tarricone R. Oxaprozin versus diclofenac in NSAID-refractory periarthritis pain of the shoulder. Curr Med Res Opin. 2004 Aug 30;20(8):1279–90.
5. ben Mrid R, Bouchmaa N, Ainani H, el Fatimy R, Malka G, Mazini L. Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. Biomed Pharmacother [Internet]. 2022 Jul 1 [cited 2022 Sep 22];151:113126. Available from: https://pubmed.ncbi.nlm.nih.gov/35643074

Appendix B. Applicant's Cited Key Literature Supporting Safety

1. Weaver A, Rubin B, Caldwell J, McMahon FG, Lee D, Makarowski W, et al. Comparison of the efficacy and safety of oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the knee. Clin Ther. 1995;17(4):735–45.
2. Makarowski W, Weaver A, Rubin B, Caldwell J, McMahon FG, Noveck RJ, et al. The efficacy, tolerability, and safety of 1200 mg/d of oxaprozin and 1500 mg/d of nabumetone in the treatment of patients with osteoarthritis of the knee. Clin Ther. 1996;18(1):114–24.
3. Ogawa M, Ueda S, Mainano Y, Ito K, Saisho H, Akikusa B. Membranous nephropathy associated with oxaprozin treatment. Nephron [Internet]. 1996 [cited 2022 Sep 2];74(2):439–40.
4. LaDuca JR, Bouman PH, Gaspari AA. Nonsteroidal antiinflammatory drug-induced pseudoporphyria: a case series. J Cutan Med Surg [Internet]. 2002 Jul [cited 2022 Sep 10];6(4):320–6.
5. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. Lancet

6. Mockenhaupt M, Kelly JP, Kaufman D, Stern RS, SCAR Study Group. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. J Rheumatol. 2003 Oct;30(10):2234–40.
7. Brinker A, Goldkind L, Bonnel R, Beitz J. Spontaneous Reports of Hypertension Leading to Hospitalisation in Association with Rofecoxib, Celecoxib, Nabumetone and Oxaprozin. Drugs Aging. 2004;21(7):479–84.
8. Heller B, Tarricone R. Oxaprozin versus diclofenac in NSAID-refractory periarthritis pain of the shoulder. Curr Med Res Opin. 2004 Aug 30;20(8):1279–90.
9. LactMed. Oxaprozin - Drugs and Lactation Database (LactMed) - NCBI Bookshelf [Internet]. 2022 [cited 2022 Sep 8].
10. Fowke JH, Motley SS, Smith JA, Cookson MS, Concepcion R, Chang SS, et al. Association of nonsteroidal anti-inflammatory drugs, prostate specific antigen and prostate volume. J Urol [Internet]. 2009 May [cited 2022 Sep 22];181(5):2064–70.
11. LiverTox. Oxaprozin - LiverTox - NCBI Bookshelf [Internet]. 2022 [cited 2022 Sep 8].
12. Heyer GL, Idris SA. Does analgesic overuse contribute to chronic post-traumatic headaches in adolescent concussion patients? Pediatr Neurol [Internet]. 2014 [cited 2022 Sep 22];50(5):464–8.
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/s/

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10/13/2023 12:00:40 PM

ROBERT B SHIBUYA
10/13/2023 12:42:40 PM

RIGOBERTO A ROCA
10/13/2023 01:11:49 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 217927
Supporting document/s:	1
Applicant's letter date:	12/22/2022
CDER stamp date:	12/22/2022
Product:	Oxaprozin Capsules
Indication:	Relief of Signs and Symptoms of Osteoarthritis, Rheumatoid Arthritis and Juvenile Rheumatoid Arthritis
Applicant:	Solubiomix, LLC
Review Division:	Division of Pharm/Tox for Neuroscience (DPT-N)
Reviewer:	Min Zhang, PhD
Supervisor:	Newton Woo, PhD
Deputy Division Director:	R. Daniel Mellon, PhD
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Clinical Division Director:	Rigoberto Roca, MD
Project Manager:	Jane Mun, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 217927 are owned by Solubiomix, LLC or are data for which Solubiomix, LLC has obtained a written right of reference.

Any information or data necessary for approval of NDA 217927 that Solubiomix, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 217927.

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1 Executive Summary

1.1 Introduction

Solubiomix, LLC submitted a New Drug Application (NDA), via a 505 (b)(2) regulatory pathway, for Oxaprozin Capsules (300 mg) and proposes the following indication: for relief of signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA) and juvenile rheumatoid arthritis (JRA). The NDA relies upon FDA's previous findings of safety and efficacy for Daypro, which is the listed drug (LD). The proposed drug product is a new dosage form of oxaprozin (300 mg), which is an orally active nonsteroidal anti-inflammatory drug (NSAID) currently marketed as 600 mg tablets and caplets. The Applicant states that at half the unit strength of DAYPRO, the proposed drug product is intended to provide advantages in convenience and accuracy of dosing for patients who use oxaprozin in 300 mg increments, such as pediatric patients weighing 32-54 kg whose recommended dose is 900 mg.

1.2 Brief Discussion of Nonclinical Findings

The proposed indications are as the same as those for the LD. The originally proposed maximum recommended human dose (MRHD) was identical to the LD of 1800 mg/day. To establish a scientific bridge, the Applicant conducted Study SBX-P0-750, an open-label, randomized, two-period crossover study comparing single oral doses of two 300 mg Oxaprozil Capsules (test product) with a single 600 mg caplet of the LD DAYPRO. The proposed drug product met the bioequivalence (BE) criteria for AUC but failed to meet BE criteria for C_{max} because the C_{max} was 34% higher than that associated with the LD. The higher C_{max} is deemed acceptable because the higher C_{max} is considered a one-time initial dose event; at steady state, clinically relevant for chronic use, the products (proposed product and Daypro) are expected to have similar exposures; the C_{max} elevation is not anticipated to result in doses that would result in clinically meaningful overdose symptoms and the theoretical safety risk is mitigated through labeling by limiting the MRHD to 1200 mg and eliminating a loading dose.

The Applicant did not submit any new nonclinical studies to support the NDA, and none were requested given that an adequate scientific bridge to the LD was established.

There were no nonclinical safety concerns with the drug substance impurities and drug product degradants or the container closure system.

1.3 Recommendations

1.3.1 Approvability

From a pharmacology and toxicology perspective, NDA 217927 may be approved.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The following changes to the Applicant's proposed labeling are recommended in the table below. Refer to the action letter for final drug product labeling.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
(b) (4)		

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(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)
21256-18-8

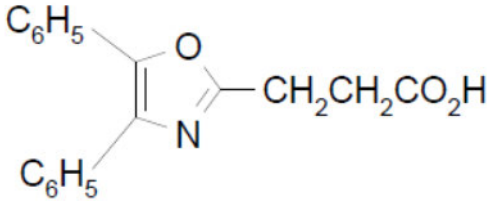
Generic Name
Oxaprozin

Code Name
None

Chemical Name
3-(4,5-Diphenyl-2-oxazolyl)propionic acid

Molecular Formula/Molecular Weight
$C_{18}H_{15}NO_3$
293.33 g/mol

Structure



Pharmacologic Class
Nonsteroidal anti-inflammatory drug (NSAID)

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application	Drug Product	Indication	Company
DMF (b) (4)	Oxaprozin drug substance		(b) (4)
NDA 18841	Daypro	Relief of signs and symptoms of osteoarthritis, rheumatoid arthritis and juvenile rheumatoid arthritis	Pfizer

2.3 Drug Formulation

The proposed drug product is an immediate-release hard gelatin capsule containing 300 mg oxaprozin. The components and composition of the final drug product are as follows.

Table 1: Quantitative Composition of the Drug Product

Ingredients	Pharmaceutical Function	Quantity (% w/w)	Quantity per Capsule
Oxaprozin	Active	(b) (4)	300 mg
Microcrystalline Cellulose			(b) (4)
Pregelatinized Corn Starch			
Hypromellose 2910			
Sodium Starch Glycolate			
Stearic Acid			
Silicon Dioxide			
(b) (4)			
Total			

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product. The excipients in the drug product and their total daily exposure based on the proposed MRHD of 1200 mg (4 capsules) in comparison to the maximum potency data from the FDA Inactive Ingredients Database (IID), and the acceptability are presented in the table below. There are no safety concerns with the excipients from a pharmacology toxicology perspective.

Table 2: Acceptability of Excipients in the Drug Product

Excipient	**Amount per capsule**	**Maximum Daily Exposure (4 capsules)**	**Maximum Daily Level in IID for Oral Products Intended for Chronic Use**	**Acceptability and Rationale**
Microcrystalline Cellulose	(b) (4)		3780 mg	Yes; within IID levels
Pregelatinized Corn Starch			4160 mg	

Hypromellose 2910	(b) (4)	880 mg	
Sodium Starch Glycolate		900 mg	
Stearic Acid		1.9 g	
Silicon Dioxide		672 mg	
(b) (4)			Yes

2.5 Comments on Impurities/Degradants of Concern

Drug Substance (DS) Impurities and Drug Product (DP) Degradants

A list of drug substance (DS) and drug product (DP) impurity specifications, including comparisons to ICH Q3A(R2) and ICH Q3B(R2) qualification or identification thresholds and safety determination, are summarized in the tables below.

As shown in the table below, the proposed specification for each DS impurity, NMT (b) (4)%, is in line with the ICH Q3A-recommended qualification threshold, NMT 0.15%, for total daily dose ≤ 2g; (b) (4) All the impurities, except (b) (4), are listed at NMT 0.1% in the USP monograph for oxaprozin DS, (b) (4) according to the manufacturer's DMF for the DS, which has been deemed adequate by CMC (confirmed by the CMC reviewer Dr. Zhixing Shan) and is utilized in other approved oxaprozin drug products. Taken together, the proposed specifications are deemed acceptable from the pharmacology toxicology perspective.

Table 3: Impurities in Drug Substance

Impurity	Proposed Spec.	Maximum TDL* (mg/ day)	Comparison to ICH Thresholds Qualification Threshold Q3A(R2) 0.15% or 1.0 mg/per day whichever is lower	Acceptability
Oxaprozin imidazole analog[1]	NMT 0.1%	(b) (4) mg	(b) (4)	Yes (see discussion above)
Benzoin				
Oxaprozin amide				
Benzoin succinate				
Benzil				
Oxaprozin bisoxazole analog				
Tetraphenylpyrazine[2]				
(b) (4)				
Individual Unspecified Impurities	NMT 0.06%	(b) (4) mg	Complies	Yes

1 (b) (4)

2 2,3,5,6-Tetraphenylpyrazine

As shown in the table below for the DP degradants, the specifications for drug product degradants are acceptable given that they are in line with the ICH Q3B-recommended thresholds.

Table 4: Impurities in Drug Product

Impurity	Proposed Specification	Maximum TDI* (mg/day)	Comparison to ICH Thresholds		Acceptability
			Qualification Threshold Q3B(R2)	Identification Thresholds Q3B(R2)	
(b) (4)	NMT (b) (4) %	(b) (4)	(b) (4)		Yes
	NMT (b) (4) %	(b) (4)			

Residual Solvents

As shown in the table below, only one (b) (4) residual solvent, (b) (4), is controlled in the drug substance specification with a limit set at NMT (b) (4) ppm according to DMF (b) (4), which is in compliance with ICH Q3C(R7) recommended limit for (b) (4) residual solvents.

Table 5: Residual Solvents in the Drug Substance

Residual Solvent	Solvent Class	Proposed Specification	Acceptance Criteria as per ICH Q3C (R7)	Acceptability
(b) (4)	(b) (4)	NMT (b) (4) ppm (release testing)	(b) (4) ppm	Yes

(b) (4)

Elemental Impurities

As shown in the table below, only (b) (4) elemental impurity is controlled in the drug substance specification with a limit set at NMT (b) (4) ppm according to DMF (b) (4), which is in compliance with ICH Q3D recommended limit for (b) (4) elemental impurity.

It is indicated in the drug product specification that the limits of elemental impurities are in compliance with ICH Q3D, Option 2b. The Applicant states that "A risk assessment was performed to evaluate the potential for elemental impurities in the finished drug product. Based on the assessment, it is determined that Oxaprozin Capsules complies with the requirements established in the ICH Q3D guideline because the levels of elemental impurities are below their PDE." The acceptability of this justification is deferred to the CMC reviewer.

Table 6: Elemental Impurities in the Drug Substance

Element	Class	Proposed Specification	MaximumTotal Daily Exposure at MRHD	Acceptable Oral PDE Q3D	Acceptability
(b) (4)	(b) (4)	(b) (4) ppm (b) (4) mcg/g)	(b) (4) mcg/day	(b) (4) mcg/day	Yes

(b) (4) The acceptability of this justification is deferred to the CMC reviewer.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population (adult and pediatric patients, see below) and dosing regimen are the same as those indicated for the LD, except that the maximum recommended human dose (MRHD) has been lowered to 1200 mg.

- 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 to 16 years of age, the recommended dosage given orally once per day should be based on body weight of the patient as given in the table below:

Table 1. Recommended Daily Dose of OXAPROZIN CAPSULES by Body Weight in Pediatric Patients

Body Weight Range (kg)	Dose (mg)
22–31	600
32–54	900
≥55	1200

2.7 Regulatory Background

In a PIND written-response-only communication dated 4/14/2020, the Division agreed that nonclinical studies would not be required to support the safety of the API if the BE study demonstrates that the systemic exposures (both in AUC and C_{max}) from the product do not exceed those of the listed drug and that the proposed product does not contain novel excipients.

In August 2023, the Agency agreed to the pediatric study plan, which did not propose any nonclinical juvenile studies.

3 Studies Submitted

No new nonclinical studies have been submitted.

3.1 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

There were no new primary pharmacology studies conducted with oxaprozin for this 505(b)(2) application. The labeling reflects the language contained in the referenced product label.

4.2 Secondary Pharmacology

There were no new secondary pharmacology studies with oxaprozin submitted in this 505(b)(2) application.

4.3 Safety Pharmacology

There were no new safety pharmacology studies with oxaprozin submitted in this this 505(b)(2) application.

5 Pharmacokinetics/ADME/Toxicokinetics

There were no new nonclinical studies in pharmacokinetics or ADME or toxicokinetics with oxaprozin submitted in this this 505(b)(2) application.

6 General Toxicology

There were no general toxicology studies with oxaprozin submitted in this 505 (b)(2) application.

7 Genetic Toxicology

There were no genetic toxicology studies with oxaprozin submitted in this 505 (b)(2) application. The labeling reflects the language contained in the referenced product label.

8 Carcinogenicity

There were no carcinogenicity studies with oxaprozin submitted in this 505(b)(2) application. The labeling reflects the language contained in the referenced product label.

9 Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies with oxaprozin submitted in this 505(b)(2) application. The labeling reflects the language contained in the LD label with revised exposure margins corresponding to the MRHD of 1200 mg/day.

10 Special Toxicology Studies

There were no special toxicology studies with oxaprozin submitted in this 505(b)(2) application.

11 Integrated Summary and Safety Evaluation

There were no new nonclinical studies, which include primary and secondary pharmacology, safety pharmacology, ADME, toxicokinetics, general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology, and special toxicology studies, submitted to this 505(b)(2) application for Oxaprozin Capsules (300 mg).

There were no nonclinical safety concerns identified with the drug substance and drug product specifications as well as the container closure system given that the proposed drug product is formulated as solid oral capsules.

12 Appendix/Attachments

None

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/

MIN ZHANG
09/28/2023 11:14:57 AM

NEWTON H WOO
09/28/2023 11:20:33 AM

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)

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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)	

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.

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.

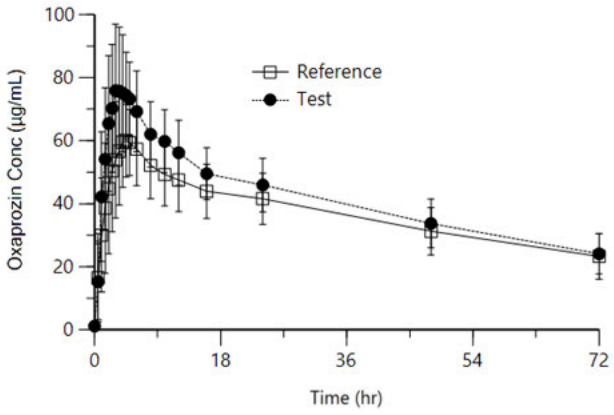


Table 1: Summary of PK parameters of oxaprozin from Oxaprozin Capsule (Test) versus Daypro (Reference) under fasting conditions in Study #SBX-P0-750.

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.

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

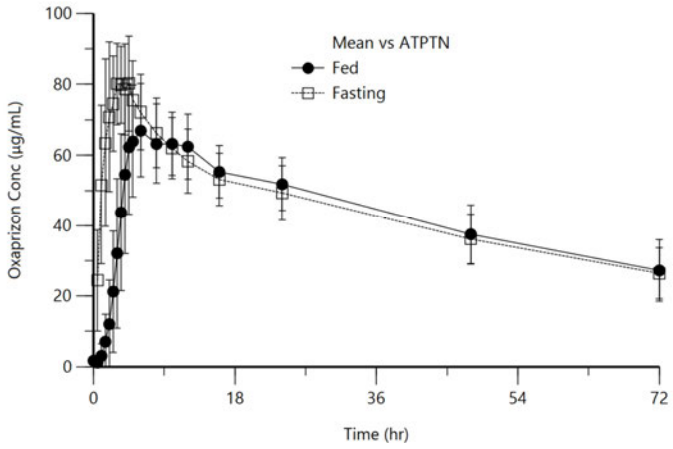


Table 3: Summary of PK parameters of oxaprozin under fasting and fed conditions in Study #SBX-P0-194

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.

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)

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

	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

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.

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 %	

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

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)

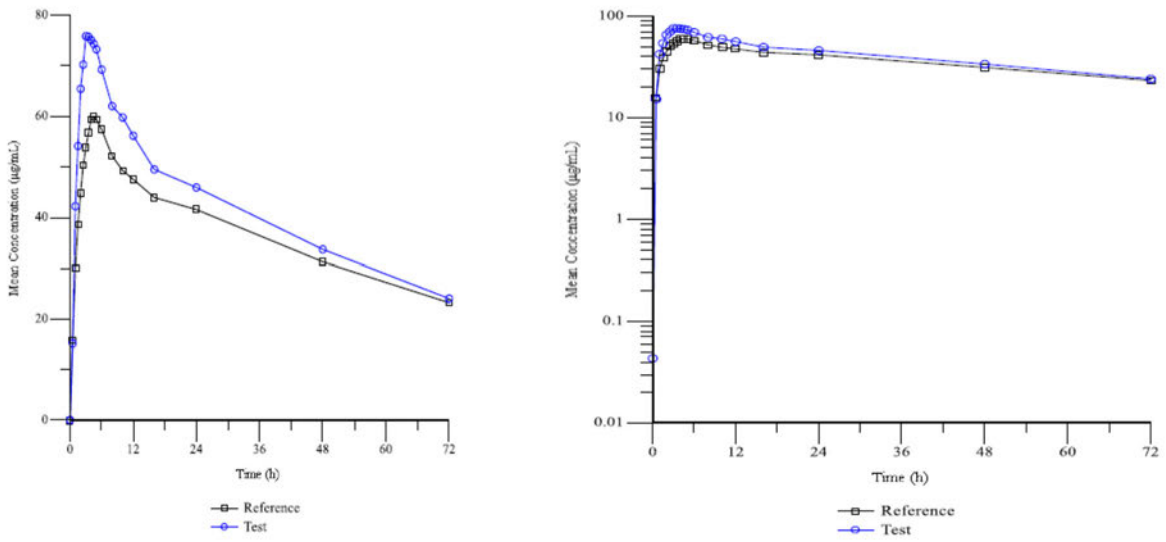
Table 6: Summary of the Statistical Analysis of Oxaprozin

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

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.

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

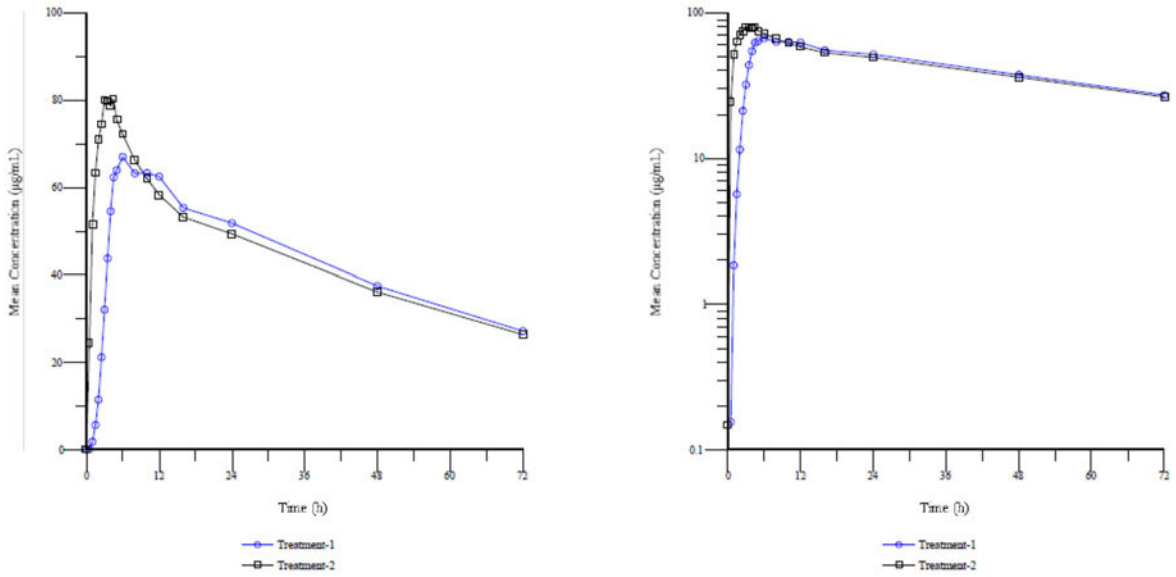
Table 8: Summary of Statistical Analysis of Oxaprozin

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

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)

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**.

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**.

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

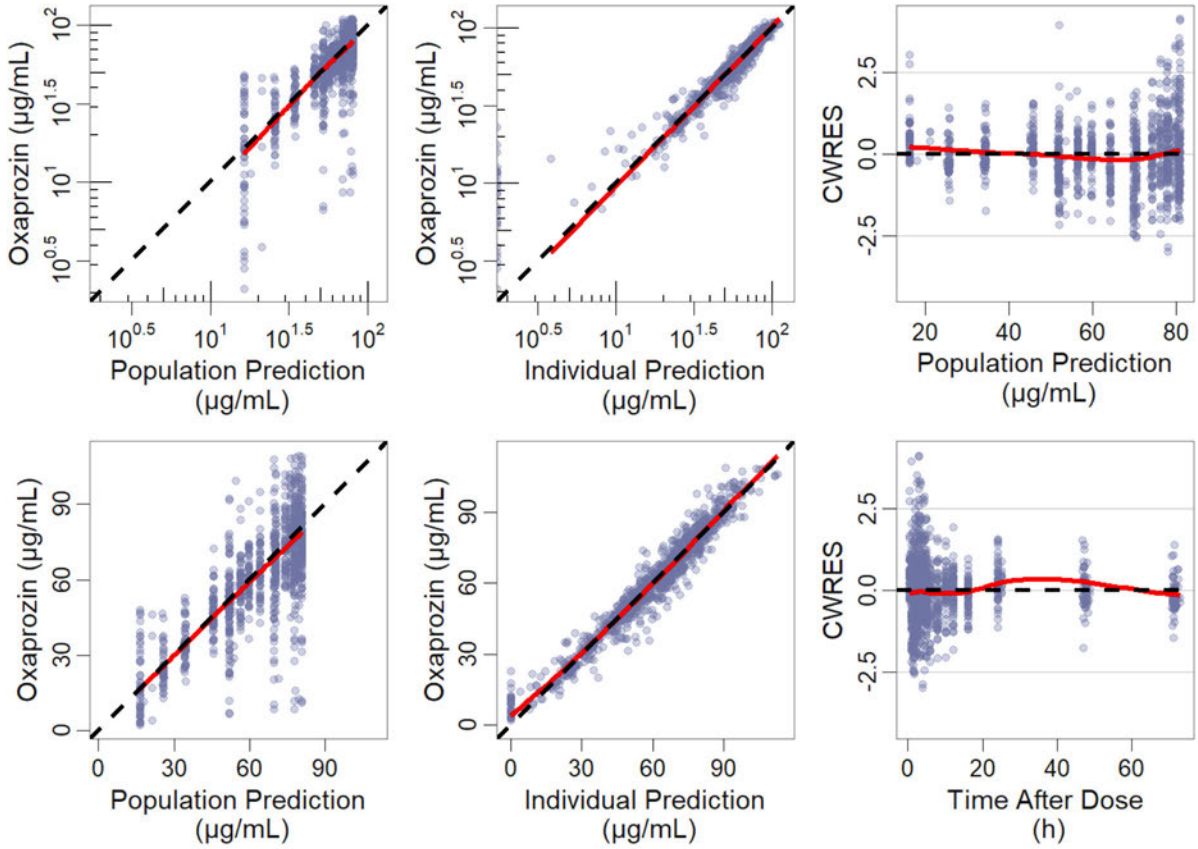
Parameters	Estimates	%RSE	95% CI
Ka (1/h)	1.20	11.7	0.928 – 1.48
CL/F (mL/h)	116	3.92	108 - 125
V/F (mL)	6070	3.52	5650 - 6490
CL2/F (mL/h)	446	9.56	363 - 530
V2/F (mL)	3260	4.73	2960 - 3570
Tlag (h)	0.348	12.8	0.261 - 0.436
Random effects	**BSV%**	**%RSE**	**Shrinkage (%)**
IIV on Ka	76.9	9.03	11.9
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.

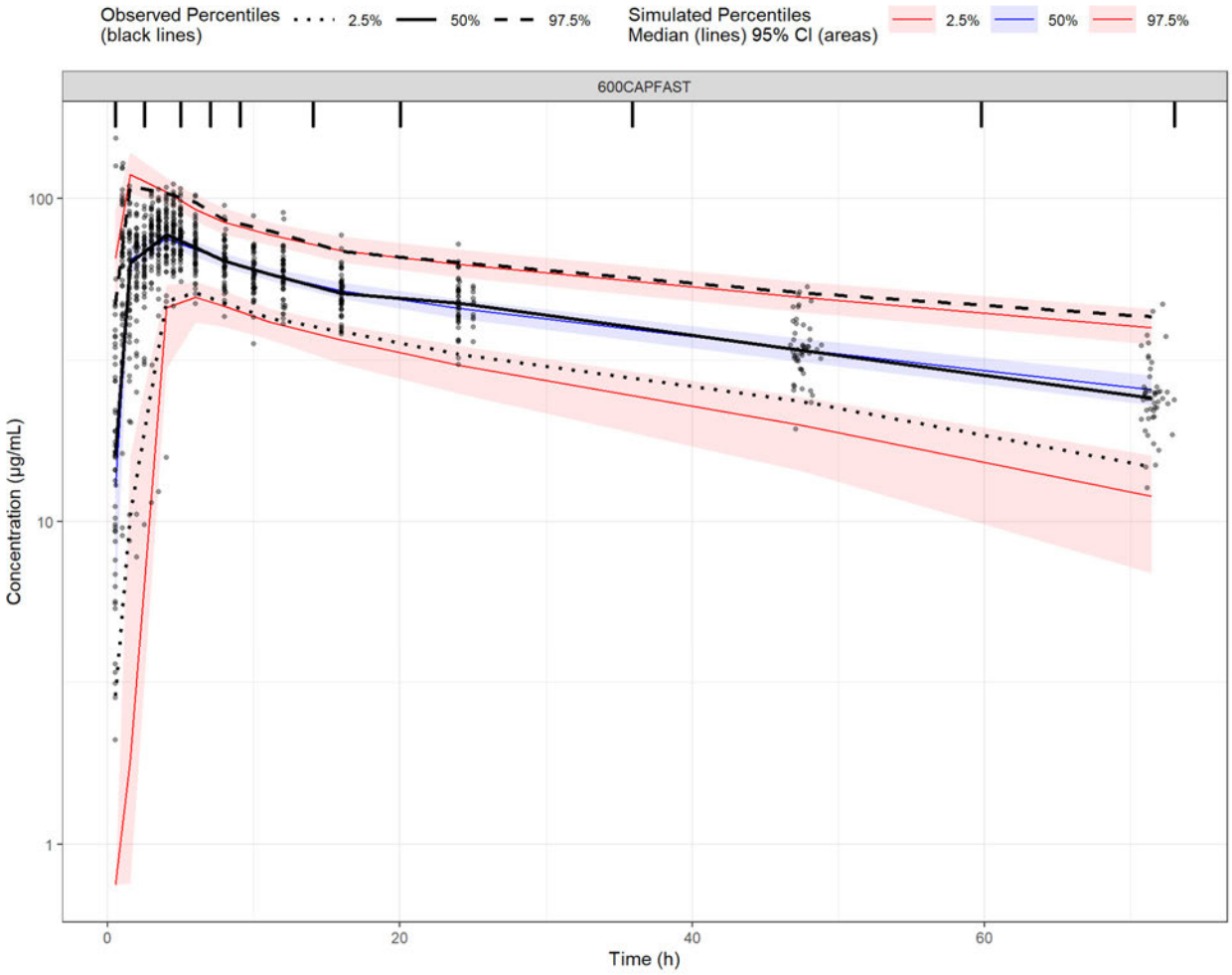
Figure 5: Goodness-of-Fit Diagnostic Plots for Final Model for Capsule Under Fasting Conditions



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

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

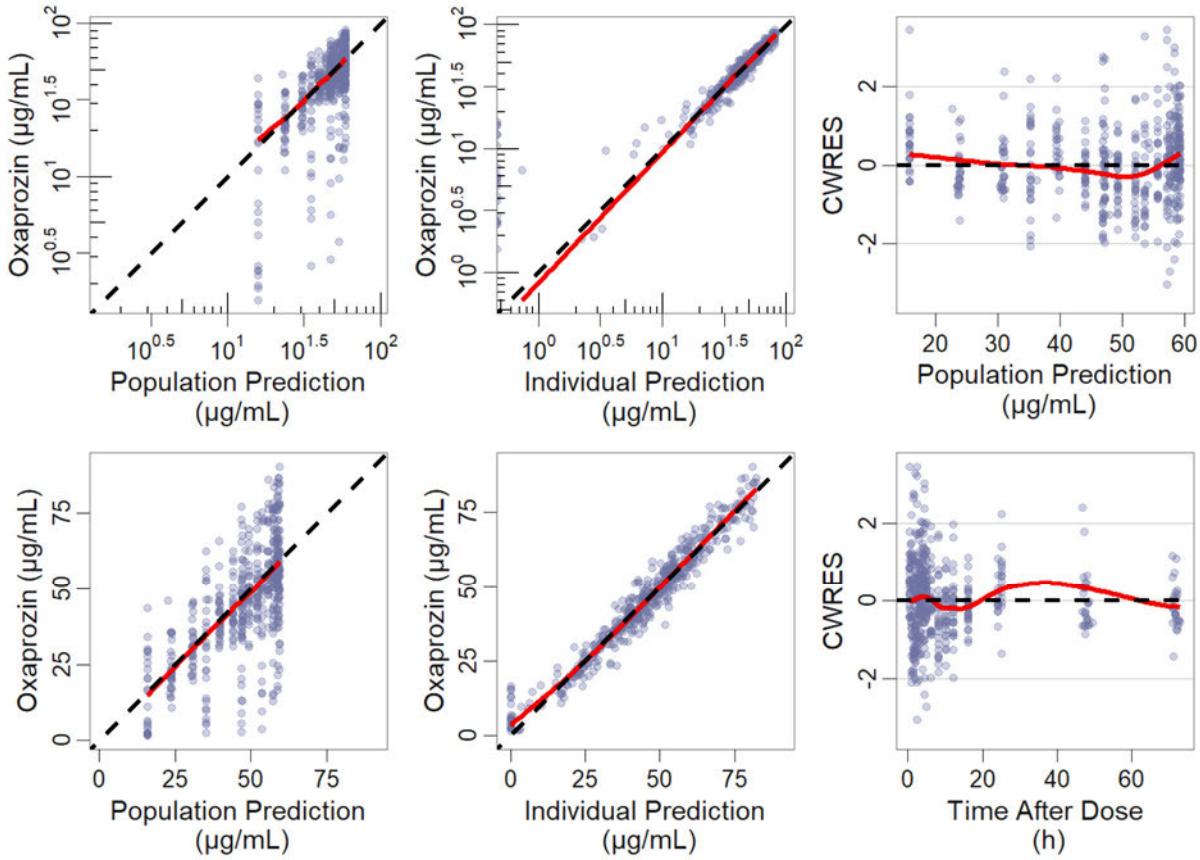
Parameters	**Estimates**	**%RSE**	**95% CI**
Ka (1/h)	0.881	8.25	0.738 - 1.02
CL/F (mL/h)	125	6.67	109 – 142
V/F (mL)	8180	4.19	7510 – 8860
CL2 (mL/h)	527	7.54	449 – 605
V2 (mL)	3180	10.4	2530 – 3830
Tlag (h)	0.221	10.9	0.173 – 0.268
Random effects	**BSV%**	**%RSE**	**Shrinkage (%)**
IIV on Ka	38.8	13.5	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.

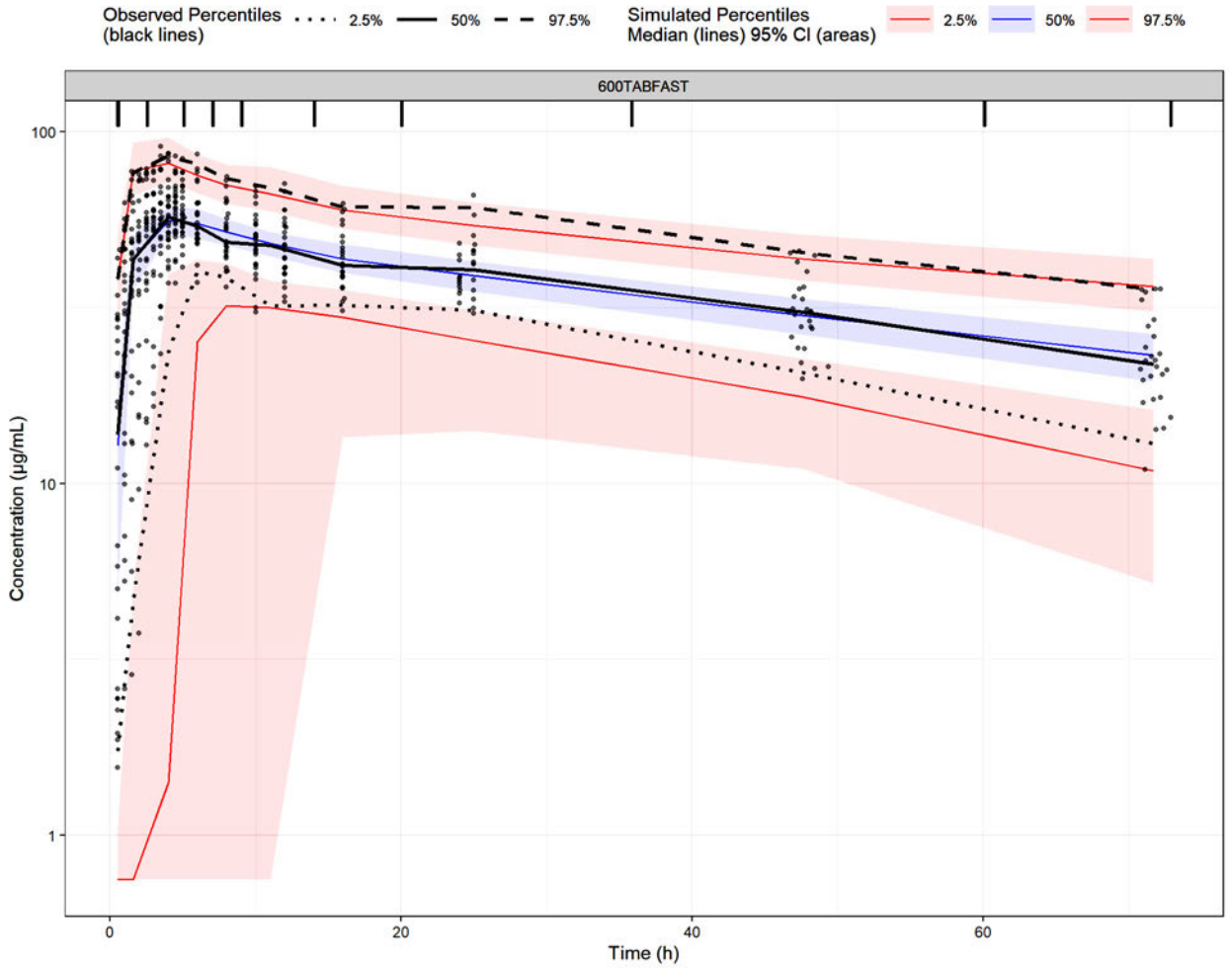
Figure 7: Goodness-of-Fit Diagnostic Plots for Final Model for Caplet Under Fasting Conditions



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.

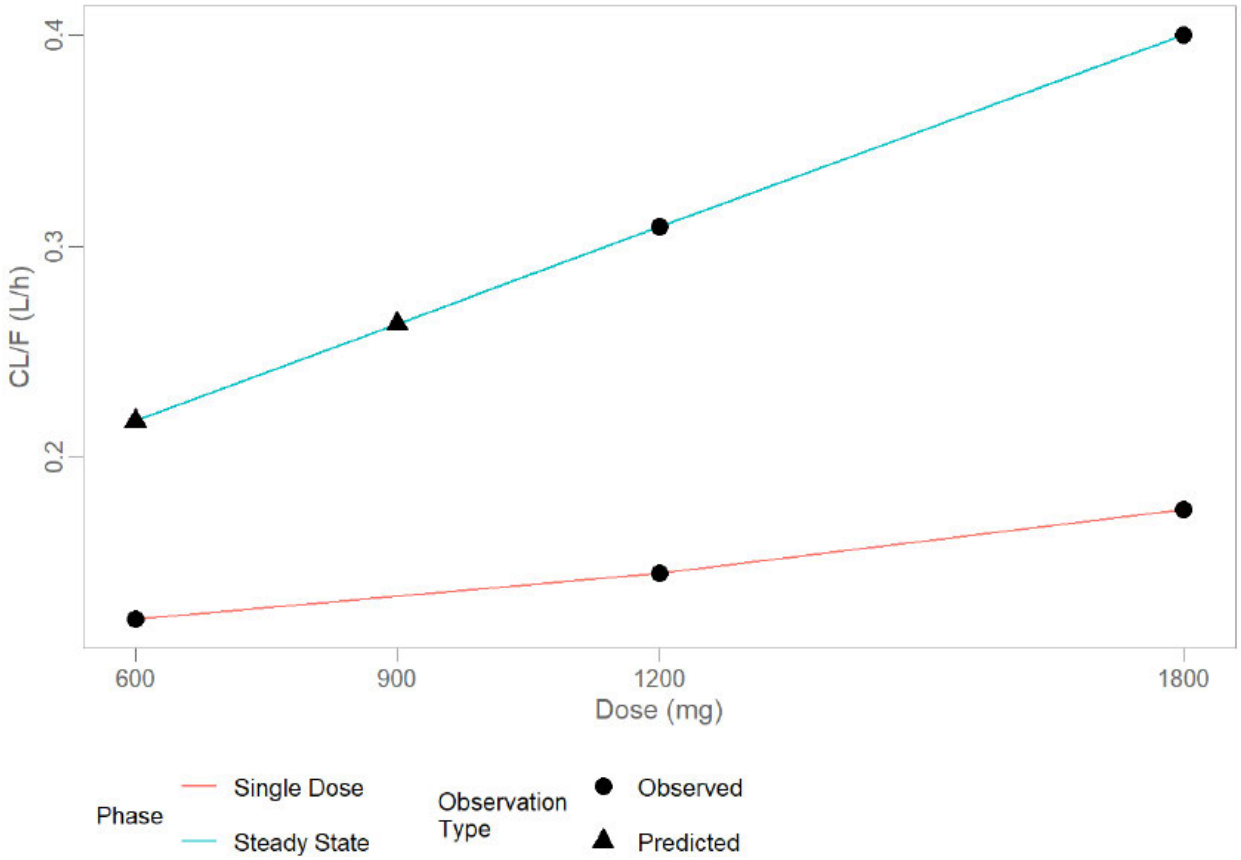
Table 12: Oxaprozin CL/F for Single Administrations and at Steady-State

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

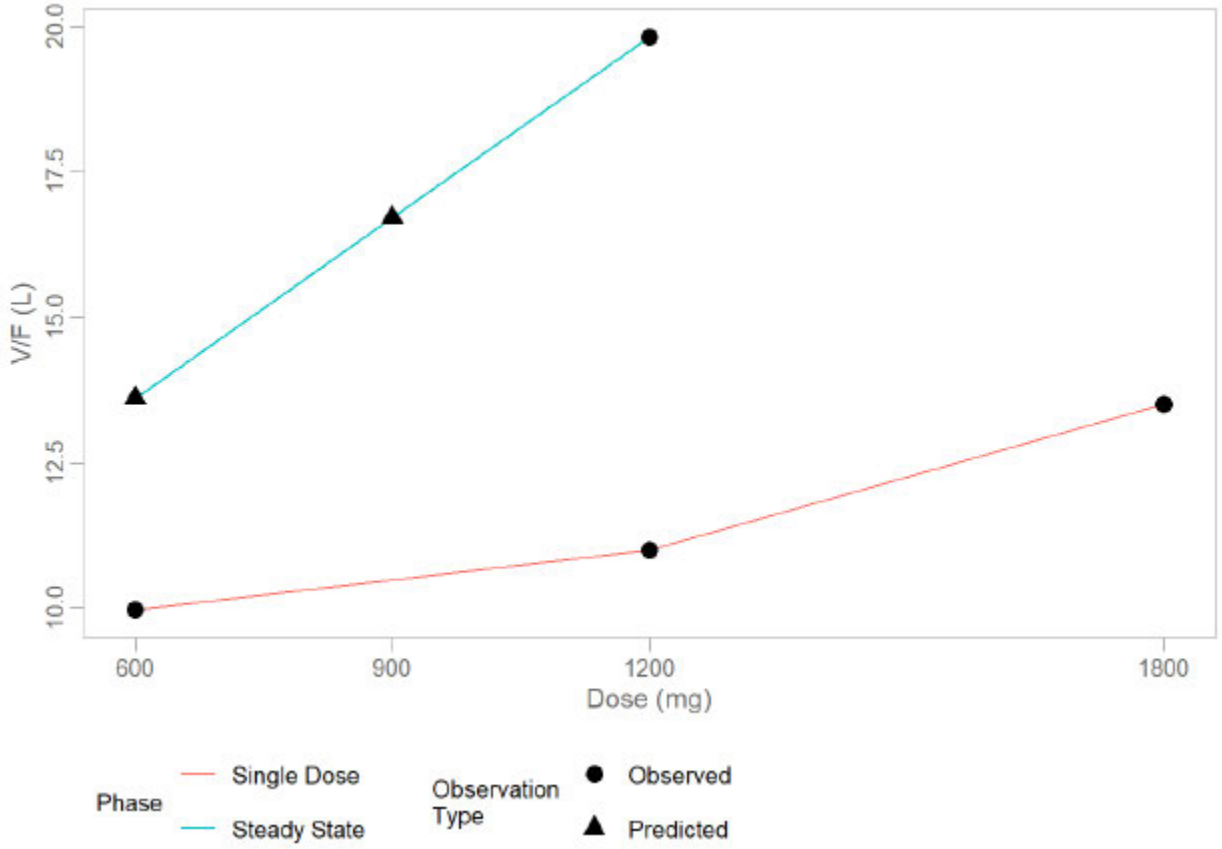
Table 13: Oxaprozin V/F for Single Administrations and at Steady-State

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).

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**.

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.]

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/s/

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