Office of Clinical Pharmacology Review

NDA or BLA Number	211759 Resubmission
Link to EDR	\\CDSESUB1\evsprod\211759\0006
Submission Date	9/30/2024; PDUFA date: 7/30/2025
Submission Type	Standard; 505(b)(2); Listed Drug product: Celebrex (celecoxib) capsules (NDA 020998)
Brand Name	VYSCOXA
Generic Name	Celecoxib oral suspension
Dosage Form and Strength	Oral suspension; 10 mg/mL
Route of Administration	Oral
Proposed Indication	The Listed Drug product Celebrex capsule was approved for chronic indications including Osteoarthritis (OA), Rheumatoid Arthritis (RA), Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older, Ankylosing Spondylitis (AS) and acute indications including Acute Pain (AP) and Primary Dysmenorrhea (PD). The Applicant seeks only chronic indications including OA, RA, JRA in patients 2 years and older, and AS.
Proposed Dosage and Administration	Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (b) (4) (b) (4) • OA: 200 mg (20 mL) once daily (QD) or 100 mg (10 mL) twice daily (BID). • RA: 100 mg (10 mL) to 200 mg (20 mL) BID. • JRA: 50 mg (5 mL) BID in patients 10 kg to 25 kg. 100 mg (10 mL) BID in patients more than 25 kg. • AS: 200 mg (20 mL) QD single dose or 100 mg (10 mL) BID. If no effect is observed after 6 weeks, a trial of 200 mg (20 mL) BID may be of benefit. Important: VYSCOXA is not recommended at a single dose greater than 200 mg (20 mL). Single doses of the oral suspension greater than 200 mg (20 mL) may result in celecoxib concentrations higher than expected. For patients who require a single dose over 200 mg (20 mL), use a different celecoxib formulation. (b) (4) Hepatic Impairment: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B).

	Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers.
Applicant	codaDose
Associated IND	IND 122698
OCP Reviewer	Wei Qiu, Ph.D.
OCP Team leader	Deep Kwatra, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the information submitted in the current application, NDA 211759 resubmission, for celecoxib oral suspension, submitted on 9/30/2024. In this resubmission, the Applicant submitted a comparative bioavailability and food effect study 915/22. From a clinical pharmacology perspective, the information submitted in the NDA resubmission is acceptable (though significant

labeling changes are needed) pending OSIS inspection and assessment on the comparative bioavailability study 915/22.
CDER Medical Policy and Program Review Council (MPPRC) meeting was held on 5/7/2025 for this application to discuss the significant food effect with the sponsor's formulation and if labeling is a feasible option to prevent potential adverse events due to potential increased exposure. Based on the recommendations from the MPPRC the review team has decided to approve this product to be taken on empty stomach. The new labeling language would propose that the proposed oral suspension must be taken on an empty stomach at least 2 hours before or 1 hour after food because of the significant food effect.

Review Issue	**Recommendations and Comments**
Pivotal or supportive evidence of effectiveness	In the single dose comparative bioavailability and food effect study 915/22 conducted in 52 healthy subjects, the proposed celecoxib oral suspension 200 mg showed equivalent AUC_{0-t} and AUC_{0-inf} values to 200 mg Celebrex capsules under fasting condition because the 90% Confidence Intervals (CIs) for the AUC_{0-t} and AUC_{0-inf} ratios between the proposed celecoxib oral suspension and the Listed Drug (LD) product Celebrex capsules fell within the bioequivalence acceptance range of 80-125%. The proposed celecoxib oral suspension did not meet BE criteria for C_{max} and the mean C_{max} for proposed celecoxib oral suspension was 22% lower. Median T_{max} of celecoxib was 1.5 hours (range 0.67 – 8.00 hours) and 2.5 hours (range 1.00 – 8.00 hours) for proposed oral suspension and Celebrex capsules, respectively. In addition, the PK modeling and simulation for 200 mg BID dosing showed that the simulated steady state AUC_{0-12} for the proposed celecoxib oral suspension under fasting condition are equivalent to Celebrex capsule under fasting condition, while the simulated steady state C_{max} values for celecoxib suspension are 19% lower than Celebrex capsule. The Applicant has decided to only seek the chronic pain indications, therefore, the difference in C_{max} (lower C_{max}) is not relevant as AUC values are more relevant to efficacy than C_{max}. Equivalent single dose AUC_{0-t} and AUC_{0-inf}, and equivalent simulated steady state AUC_{0-12} are expected to result in similar efficacy and safety between proposed oral suspension and Celebrex capsules when administered under fasting condition for chronic indications. According to Celebrex label, when Celebrex capsules are administered under fasting condition, both C_{max} and AUC are roughly dose-proportional up to 200 mg BID, at higher dose there are less than proportional increase in C_{max} and AUC which is thought to be due to the low solubility of the drug in aqueous media. The comparative bioavailability between the proposed oral suspension and Celebrex capsule at doses above 200 mg

	has not been determined. An earlier formulation of oral suspension at single dose 400 mg was shown to have 20% greater AUCs and 51% C_{max} than a single dose Celebrex capsule. The Applicant proposed in their label that celecoxib oral suspension is not recommended at a single dose greater than 200 mg, single doses of oral suspension greater than 200 mg may result in celecoxib concentrations higher than expected and for patients who require a single dose over 200 mg, use a different celecoxib product.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Same as the Celebrex oral capsule (NDA 020998)
Labeling	See Section 3 of this review.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable because the Applicant confirmed that the final to-be-marketed formulation was used in the comparative bioavailability and food effect study 915/22.
Other (specify)	Not applicable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

(1) Comparative Bioavailability of the Proposed Celecoxib Oral suspension versus Celebrex Capsules under Fasting Condition: The proposed celecoxib oral suspension following a 200 mg single dose administration under fasting condition showed equivalent AUC_{0-t} and AUC_{0-inf} but 22% lower C_{max} than a 200 mg single dose administration of Celebrex capsule under fasting condition. The geometric mean ratios (90% CIs) (celecoxib oral suspension/Celebrex capsule) for celecoxib AUC_{0-t}, AUC_{0-inf}, and C_{max} were 91.84% (86.79% – 97.19%), 94.32% (89.50% - 99.40%), 77.92% (71.08% - 85.41%), respectively. Median T_{max} (range) of celecoxib was 1.5 hours (range 0.67 – 8.00 hours) and 2.5 hours (range 1.00 – 8.00 hours) for proposed oral suspension and Celebrex capsules, respectively. In addition, the PK modeling and simulation for 200 mg BID dosing showed that the simulated steady state AUC_{0-12} values for the proposed celecoxib oral suspension under fasting condition are equivalent to Celebrex capsule under fasting condition, while the simulated steady state C_{max} values for celecoxib suspension are 19% lower than Celebrex capsule. The geometric mean ratios (90% CIs) (celecoxib oral suspension/Celebrex capsule) for simulated steady state celecoxib AUC_{0-12} and steady state C_{max} were 99.80% (84.86% – 117.36%) and 80.80% (69.52% - 93.91%), respectively. Because the Applicant is seeking approval for only the chronic pain indications and not for the acute pain indications, therefore, the difference in C_{max} (lower C_{max}) is not relevant as compared to AUC values which are more relevant to efficacy than C_{max}. Equivalent single dose AUC_{0-t} and AUC_{0-inf}, and equivalent simulated steady state AUC_{0-12} are expected to result in similar efficacy and safety between proposed oral suspension and Celebrex capsules when administered under fasting condition for chronic indications.

(2) Effect of Food on Proposed Celecoxib Oral suspension: When a single dose of 200 mg celecoxib oral suspension was taken with a high-fat high-calorie meal, median T_{max} of celecoxib was delayed by 1.5 hours from 1.50 hours to 3.00 hours. In comparison to fasted state, high-fat high-calorie meal significantly increased the single dose AUC_{0-t}, AUC_{0-inf}, and C_{max} of celecoxib by 50%, 35%, and 144%, respectively. The geometric mean ratios (90% CIs) (celecoxib oral suspension under fed condition/celecoxib oral suspension under fasting condition) for celecoxib AUC_{0-t}, AUC_{0-inf}, and C_{max} were 149.64% (139.58% – 160.44%), 134.96% (125.94% - 144.63%), and 244.36% (224.42% - 266.08%), respectively. The food effect for proposed celecoxib oral suspension is significantly greater than the food effect for the LD product Celebrex capsule reported in the approved label for Celebrex capsule. Based on the LD label, high fat meal delayed T_{max} by 1 to 2 hours and increased AUC by 10-20%. Because of only marginal changes in exposure with food, Celebrex is labeled to be given without regard to timing of meals.

(3) Comparison of Simulated Steady State AUC_{0-12} and C_{max} of Celecoxib between the Proposed Celecoxib Oral suspension and Celebrex Capsules under High-fat Fed condition: Following 200 mg BID dosing under high-fat fed condition, simulated steady state AUC_{0-12} values for the proposed celecoxib oral suspension were 25% greater that for Celebrex capsules. Simulated steady state C_{max} values for proposed celecoxib oral suspension were equivalent to Celebrex capsule. The geometric mean ratios (90% CIs) (celecoxib oral suspension under high-fat fed condition/Celebrex capsule under high-fat fed condition) for simulated steady state celecoxib AUC_{0-12} and C_{max} were 124.73% (107.43% – 144.81%) and 107.62% (92.93% - 124.62%), respectively.

There is significant increase in exposure of celecoxib when taken with food, with a mean 50% increase in AUC and 144% increase in C_{max} in single dosing. Even though the sponsor is seeking chronic indications where, steady state exposures are more relevant than initial exposures, the increased exposures on initial doses when taken with high fat meals may still increase tolerability issues is patients who are initiating treatment with celecoxib oral suspension. At steady state the C_{max} changes are significantly narrowed but there is still 25% increase in exposure. Though, the food effect studies were performed using a high fat meal, which represent the extreme scenario for food effect, without actual studies it would not be possible to determine how much food effect would be observed with other meals, such as intermediate or low-fat meals or light snacks. Because the proposed celecoxib oral suspension exhibits greater food effect than Celebrex capsule and is expected to result in 25% greater steady state AUC values than Celebrex capsule based on PK modeling and simulation, the proposed celecoxib oral suspension should not be given with food unless there are clinical data to support the safety of celecoxib oral suspension under fed condition (see Clinical review). We will defer to clinical team regarding whether there are safety concerns associated with the 25% higher AUC values for the proposed oral suspension under fed condition.

- **Regulatory History**

The original 505(b)(2) NDA 211759 for an earlier formulation of celecoxib oral suspension was submitted for chronic indications including OA, RA, JRA in patients 2 years and older, AS, (b) (4) [redacted] As a 505(b)(2) NDA, the Applicant proposed to rely on the Agency's previous findings on efficacy and safety of the Listed Drug product,

Celebrex (celecoxib) capsule (NDA 020998). The Applicant submitted a comparative bioavailability study (Study 083-17) comparing the PK of a 400 mg single dose of the earlier formulation of celecoxib oral suspension and a 400 mg single dose of Celebrex capsule, and a food effect study (Study 087-17) evaluating the effect of high-fat meal on the PK of a 400 mg single dose of the earlier formulation of celecoxib oral suspension. It was refuse-to-file (RTF) on 4/30/2018 because of clinical and nonclinical deficiencies. The RTF letter also included the following clinical pharmacology comments: (1) Confirm the final to-be-marketed formulation was used in the comparative bioavailability study (Study 083-17) and food effect study (Study 087-17); (2) (b) (4) in the context of greater food effect with your product (i.e., 78% increase in C_{max} and 55 - 58% increases in AUCs) than Celebrex capsule (i.e., 10 – 20% in AUCs). A Type A teleconference was held on 6/29/2018 to discuss the Applicant's responses to refuse-to-file letter. The Division recommended the Applicant "*Given that your product is not bioequivalent to the Listed Drug, include a description of how these impacts considerations related to efficacy and safety of the proposed product. Since your product shows an increase in relative systemic exposure compared to the listed product, there are safety concerns associated with the higher systemic exposure. The current Celebrex prescribing information notes an increase in safety risks at higher doses and instructs patients to use the lowest effective dose for the shortest duration possible. Given these considerations, you will need to provide additional clinical data to support the safety of the proposed product that has a higher systemic exposure than Celebrex. We do not anticipate that use of the* (b) (4) *will be adequate to support the safety of your product. Alternatively, modify the drug product so that it is bioequivalent to the Listed Drug"*. Post meeting notes *"The data show that your celecoxib oral suspension is not bioequivalent to Celebrex. Attempting to find a dose that is within the AUC and C_{max} of Celebrex does not change the fact that the products are not bioequivalent. Additional pharmacokinetic studies will not solve this problem. To rely on the safety and efficacy of Celebrex without the need for additional efficacy or safety studies, the appropriate approach is to reformulate your celecoxib oral suspension so that it is bioequivalent to Celebrex*."

In this resubmission, the Applicant reformulate the oral suspension and conducted a comparative bioavailability and food effect study 915/22 with the reformulated oral suspension at 200 mg dose level because the Applicant determined that the revised formulation cannot be bioequivalent to Celebrex capsules when administered at doses levels above 200 mg based on their studies with a similar earlier formulation using single doses of 400 mg and a pilot study at 200 mg dose level. The Applicant plans to seek regulatory approval limited to indications requiring treatment with a dose not more than 200 mg BID of Celebrex capsules. For treatment of indications requiring a single dose higher than 200 mg, patients will be required to use an alternative drug product. Study 915/22 is entitled "Single Dose Crossover Comparative Bioavailability and Food Effect Study of Celecoxib 10 mg/1 mL Oral suspension versus Celebrex® (celecoxib) 200 mg Capsules Following the Administration of a 200 mg Dose in Healthy Adult Volunteers / Fasting and Fed State" and was the study submitted to support this application. OSIS inspection for Study 915/22 was requested because it is the pivotal study comparing the bioavailability of proposed product and the Listed Drug product, Celebrex capsule, and it is the only clinical data supporting approval.

At the filing stage for this resubmission, clinical pharmacology review comments were included in the Filing Communication – Filing Review Issues Identified letter dated 12/12/2024. These

review comments were *"(1) Your proposed product showed 22% lower C_{max} following a single 200 mg dose administration than Celebrex capsule 200 mg under fasting condition in Study 915/22. We recommend you conduct steady state PK simulation for your proposed product following dosing regimen in your proposed label and for Celebrex according to approved label. Compare the simulated steady state C_{max} and AUC of your proposed product and Celebrex and provide justification to support the efficacy of your product under fasting condition. (2) Your proposed product showed significant food effect (i.e., high fat, high-calorie meal increased the mean AUC_{0-t}, AUC_{0-inf}, and C_{max} of celecoxib by 50%, 35%, and 144%, respectively). According to the Celebrex label, a high fat meal increased AUC by 10% to 20% as compared to fasted AUC.* [redacted] (b) (4) *In addition, we recommend you conduct steady state PK simulation for your product and Celebrex under fed condition, compare the simulated steady state C_{max} and AUC, and provide* [redacted] (b) (4) *. (3) Confirm the final to-be-marketed formulation was used in the comparative bioavailability and food effect study 915/22"*. In the response, the Applicant submitted steady state PK modeling and simulation, justification to address review comments, and confirmed that the final formulation to-be-marketed was used in the comparative bioavailability and food effect study 915/22. This review focuses on review of Study 915/22 and the steady state PK modeling and simulation.

- **Summary of Pharmacokinetic Results**

Study 915/22

Study 915/22 was an open-label, randomized, single-dose, three-period, six-sequence, two-treatment crossover study in healthy male and female adults under fasting and fed condition. The primary objectives were to evaluate the PK and to compare the bioavailability of proposed celecoxib oral suspension (Test product) versus Celebrex capsule (Reference product) under fasted condition and to evaluate the effect of food on the PK of proposed celecoxib oral suspension.

Study participants received a single dose of 200 mg celecoxib oral suspension under fasted condition (Test under FAsting condition, aka TFA), a single dose of 200 mg celecoxib oral suspension under high-fat high-calorie fed condition (Test under FEd condition, aka TFE) and a single dose of 200 mg Celebrex capsules under fasting condition (Reference under FAsting condition, aka RFA) in a randomized manner with at least 7 days of washout period between treatment periods, which is adequate considering the half-life values of 11 hours reported in Celebrex capsule label. A total of 54 subjects (25F/29M) were randomized and 51 subjects finished the study.

Blood samples for determination of celecoxib concentrations in plasma were collected prior to dosing and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, 24, 36, 48, and 72 hours post-dose in each study period.

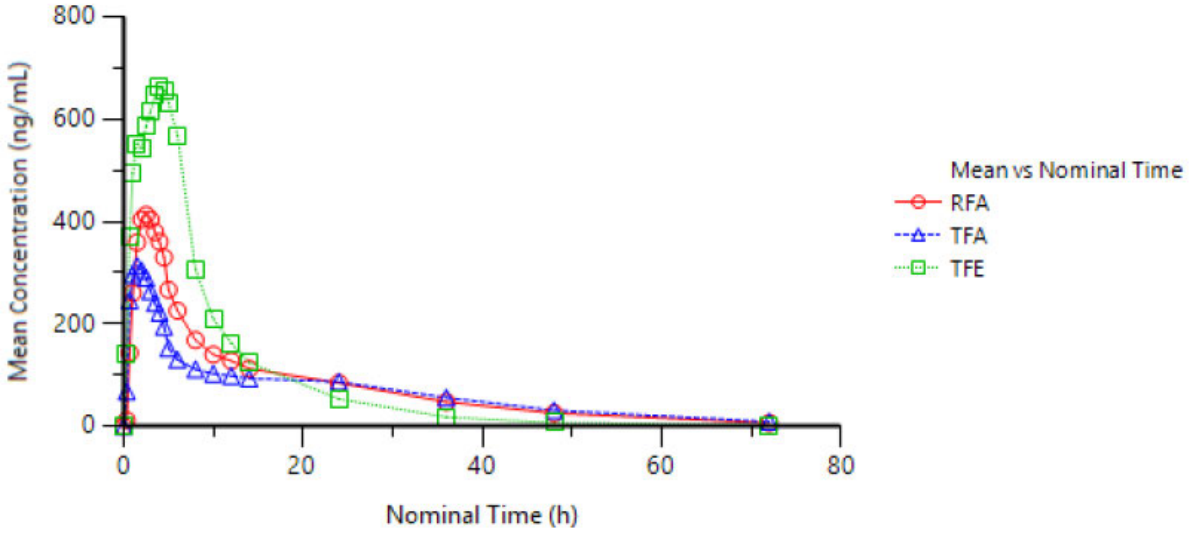
The mean celecoxib plasma concentration-time profiles following a single dose administration of 200 mg celecoxib oral suspension under fasted condition (TFA) and fed condition (TFE), and 200 mg Celebrex capsules under fasting condition (RFA) are shown in **Figure 1**. Celecoxib PK

parameters for the study are summarized in **Table 1**. The comparison of celecoxib AUC_{0-t}, AUC_{0-inf}, and C_{max} for proposed celecoxib oral suspension under fasting condition and Celebrex capsules under fasting condition are shown in **Table 2**.

The median T_{max} values were 1.50 hours (range 0.67 to 8.00 hours) and 2.50 hours (range 1.00 to 8.00) hours for the proposed celecoxib oral suspension and Celebrex capsules, respectively. Mean half-life values of celecoxib were similar: 16.49 hours for celecoxib oral suspension and 14.43 hours for Celebrex capsules, respectively (**Table 1**). The marginal difference in T_{max} is not expected to result in clinically meaningful difference in efficacy or safety.

Statistical analysis of AUC_{0-t} and AUC_{0-inf} showed that a single dose of 200 mg celecoxib oral suspension under fasting condition (TFA) exhibited equivalent AUC_{0-t} and AUC_{0-inf} values to a single dose of 200 mg Celebrex capsules under fasting condition (RFA) because the geometric mean ratios (TFA/RFA) (90% CI) for AUC_{0-t} and AUC_{0-inf} were 91.84% (86.79% – 97.19%) and 94.32% (89.50% - 99.40%), respectively, which fell within the 80 – 125% bioequivalence criteria (**Table 2**). Celecoxib oral suspension showed approximately 22% lower C_{max} than Celebrex capsules because the geometric mean ratios (TFA/RFA) (90%CI) for C_{max} was 77.92% (71.08% - 85.41%), where the lower bound of 90% CI (71.08%) were below the lower limit of 80 to 125% bioequivalence criteria (**Table 2**).

Figure 1 Mean Plasma Concentration Time Profiles of Celecoxib Following A Single Dose Administration of 200 mg Celecoxib Oral Suspension under Fasting Condition (TFA) and Fed Condition (TFE), and A Single Dose Administration of 200 mg Celebrex Capsules under Fasting Condition (RFA) (N = 51) (Study 915/22)



Source: Study report 915/22 Page 8

Table 1 Mean ± SD (%CV) Celecoxib Pharmacokinetic Parameters for A Single Dose of 200 mg Celecoxib Oral Suspension under Fasting Condition (TFA) and Fed Condition (TFE), and A Single Dose of Celebrex Capsules under Fasting Condition (RFA) (Study 915/22)

PK Parameter	200 mg Celecoxib Oral Suspension under Fasting Condition (TFA) (N = 52)#	Celebrex Capsule under Fasting Condition (RFA) (N = 51)##	200 mg Celecoxib Oral Suspension under High-Fat Fed Condition (TFE) (N = 52)#
T_{max} (h)*	1.50 (0.67 – 8.00)	2.50 (1.00 – 8.00)	3.00 (0.67 – 6.05)
C_{max} (ng/mL)	346.2 ± 130.9 (37.81%)	476.3 ± 287.8 (60.42%)	825.9 ± 266.6 (32.28%)
AUC_{0-t} (ng.h/mL	4720.8 ± 4291.8 (90.91%)	5379.0 ± 6148.2 (114.30%)	6631.0 ± 4993.1 (75.30%)
AUC_{0-inf} (ng.h/mL)	5506.8 ± 5511.3 (100.08%)	6035.8 ± 7146.9 (118.41%)	6892.7 ± 5395.0 (78.27%)
K_{el} (1/h)	0.050 ± 0.020 (41.26%)	0.056 ± 0.020 (36.38%)	0.119 ± 0.046 (38.91%)
$T_{1/2}$ (h)	16.49 ± 7.06 (42.80%)	14.43 ± 6.63 (45.91%)	6.70 ± 2.73 (40.78%)

*Reported as median (min, max); # dropouts (Subjects (b) (6) and (b) (6) ## dropouts (Subjects (b) (6) and (b) (6)
Source: PK and Statistical Report for Study 915/22 Pag 6, 7, Tables 9, 11; Appendix 1 Tables 7, 8, 10, 11, 12, and 13

Table 2 Statistical Analysis of Celecoxib AUC_{0-t}, AUC_{0-inf}, and C_{max} for A Single Dose of 200 mg Celecoxib Oral Suspension under Fasting Condition (TFA) and A Single Dose of 200 mg Celebrex Capsules under Fasting Condition (RFA) in Healthy Volunteers (Study 915/22)

Parameter	Celecoxib Oral Suspension 200 mg under Fasting Condition (TFA)		Celebrex Capsule 200 mg under Fasting Condition (RFA)		Ratio (TFA/RFA) (%)	90% Confidence Interval	
	N	GLSM	N	GLSM		Lower	Upper
AUC_{0-t} (ng.h/mL)	51	3932.2	51	4281.5	91.84	86.79	97.19
AUC_{0-inf} (ng.h/mL)	51	4512.7	51	4784.3	94.32	89.50	99.40
C_{max} (ng/mL)	51	324.2	51	416.1	77.92	71.08	85.41

GLSM: Geometric Least Squares Means
Source: PK and Statistical Report for Study 915/22 Page 6; Study report 915/22 Page 9

Reviewer's Comments: Per Celebrex label, celecoxib exhibits dose-proportional increase in exposure after oral administration up to 200 mg twice daily and less than proportional increase at doses above 200 mg, which is thought to be due to the low solubility of the drug in aqueous media. The Applicant determined that the revised oral suspension formulation cannot be bioequivalent to Celebrex capsules when administered at doses levels above 200 mg based on their studies with an earlier formulation in a pilot study using single doses of (b) (4) mg and 200 mg dose level. Therefore, the Applicant conducted the comparative bioavailability and food effect study (Study 915/22) using a single dose of 200 mg reformulated celecoxib oral suspension under fasting and fed condition and a single 200 mg dose of Celebrex capsules under fasting condition. Since their product is expected to show significantly higher bioavailability when given at doses higher than 200 mg compared to the reference product, The applicant limited its regulatory approval to indications requiring treatment with not more than a 200 mg dose BID of celecoxib (i.e., OA, RA, JRA in patients 2 years and older, and AS). The Applicant proposed in their label that celecoxib oral suspension is not recommended at a single dose greater than 200 mg, single doses of oral

suspension greater than 200 mg may result in celecoxib concentrations higher than expected and for patients who require a single dose over 200 mg, use a different celecoxib product.

The proposed celecoxib oral suspension under fasting condition showed equivalent AUC values to Celebrex capsules under fasting condition, but it showed 22% lower C_{max} than Celebrex capsules. The Applicant was recommended to conduct steady state PK modeling and simulation, and to provide justification to support the efficacy of the proposed oral suspension under fasting condition.

Steady State PK Modeling and Simulation for the Proposed Celecoxib Oral suspension in Comparison with Celebrex Capsules under Fasting Condition

The Applicant developed population PK models based on the PK data collected in Study 915/22. PK data obtained for a single dose of 200 mg Celebrex capsule or a single dose of 200 mg celecoxib oral suspension under fasting condition. A single dose of 200 mg Celebrex capsule under fasting condition, or a single dose of 200 mg celecoxib oral suspension under fasting and fed condition were analyzed and modeled separately. Two-compartment models with linear elimination were used to describe the disposition of celecoxib.

Simulations were performed to predict concentration-time profiles following 200 mg BID dosing under fasting condition for 14 days for oral suspension and Celebrex capsules and the derived PK parameters are summarized in **Table 3**.

Table 3. Descriptive Statistics – Celecoxib Exposure Parameters – 200 mg Celebrex Capsule under Fasting Condition (RFA) and 200 mg Celecoxib Oral Suspension under Fasting Condition (TFA) on Day 1 and Day 15

	RFA		TFA	
Parameters	**Day 1 (N=54)**	**Day 15 (N=54)**	**Day 1 (N=54)**	**Day 15 (N=54)**
AUC_{0-12} (ng.h/mL)				
Arithmetic Mean (CV%)	2740 (63.7%)	5820 (104.9%)	1930 (47.1%)	5810 (105.0%)
Geometric Mean (CV%)	2430 (46.6%)	4790 (54.2%)	1780 (40.2%)	4780 (54.3%)
Median [Min, Max]	2160 [987, 11400]	4440 [2110, 36800]	1840 [869, 6010]	4430 [2100, 36800]
C_{max} (ng/mL)				
Arithmetic Mean (CV%)	529 (56.7%)	819 (80.8%)	297 (39.6%)	653 (83.1%)
Geometric Mean (CV%)	466 (53.0%)	701 (52.3%)	278 (38.1%)	566 (47.3%)
Median [Min, Max]	436 [130, 1680]	676 [343, 4030]	276 [103, 685]	535 [296, 3380]
C_{min} (µg/mL)				
Arithmetic Mean (CV%)	117 (88.8%)	322 (133.2%)	97.0 (68.3%)	369 (128.3%)
Geometric Mean (CV%)	98.4 (55.2%)	243 (67.1%)	85.8 (46.7%)	282 (64.8%)
Median [Min, Max]	89.5 [44.2, 680]	234 [79.9, 2480]	79.4 [41.5, 446]	250 [101, 2760]
$AR_{AUC0-12}$				
Arithmetic Mean (CV%)	NA	2.03 (27.5%)	2.84 (38.7%)	2.84 (38.7%)
Geometric Mean (CV%)	NA	1.97 (25.5%)	2.68 (33.4%)	2.68 (33.4%)
Median [Min, Max]	NA	1.91 [1.34, 3.90]	2.71 [1.66, 7.75]	2.71 [1.66, 7.75]

Abbreviations: $AR_{AUC0-12}$ = Accumulation ratio based on AUC_{0-12}; AUC_{0-12} = area under the curve from 0 to 12 h; C_{max} = maximum concentration; C_{min} = minimum concentration; N = number of subjects

The results for the bioequivalence assessment of simulated steady state AUC_{0-12} and C_{max} of celecoxib on Day 15 following administrations of 200 mg celecoxib oral suspension BID (Test) and 200 mg Celebrex capsule BID (Reference) under fasting condition are shown in **Table 4**. The ratio of geometric means and 90% CI for steady state $AUC0_{-12}$ of the 200 mg Celebrex capsule versus 200 mg celecoxib oral suspension under fasting condition were contained within 80.00%

to 125.00% bioequivalence criteria so the simulated steady state AUC_{0-12} values were equivalent. The simulated steady state C_{max} values for celecoxib oral suspension under fasting condition were 19% lower than Celebrex capsule.

Table 4 Bioequivalence Assessment of Simulated Steady State AUC_{0-12} and C_{max} – Celecoxib Oral Suspension (Test) versus Celebrex Capsule (Reference) under Fasting Condition

Comparison	Day	Parameters	Ratio (%) Test/Reference	90% Confidence Interval (%)
Celecoxib Oral Suspension (test) formulation fasting conditions vs Celebrex® capsule (reference) formulation fasting conditions	15	Ln(AUC_{0-12})	99.80	84.86 to 117.36
		Ln(C_{max})	80.80	69.52 to 93.91

Abbreviations: AUC_{0-12}=area under the curve from 0 to 12h; C_{max} = maximum plasma concentration;

Reviewer's Comment: Based on the steady state PK modeling and simulation, the simulated steady state AUC_{0-12} values following 200 mg BID dosing for celecoxib oral suspension were equivalent to Celebrex capsules under fasting condition because the ratio of geometric means and 90% CI were contained within 80% to 125% bioequivalence criteria. The simulated steady state C_{max} values for celecoxib oral suspension were 19% lower. The Applicant seeks approval of celecoxib oral suspension for only the chronic pain indications but not for the acute pain indications, therefore, AUC measures reflecting drug exposure over time, are more relevant to efficacy than C_{max}. Thus, equivalent single dose AUCs and simulated steady state AUC_{0-12} under fasting condition for proposed oral suspension and Celebrex capsules are expected to result in similar efficacy when these products are administered under fasting condition for chronic indications.

(1) Comparative Bioavailability of the Proposed Celecoxib Oral Suspension and Celebrex Capsules under Fasting Condition

A single dose of 200 mg celecoxib oral suspension under fasting condition exhibited equivalent AUC_{0-t} and AUC_{0-inf} values to a single dose of 200 mg Celebrex capsules under fasting condition. The geometric mean ratios (celecoxib oral suspension/Celebrex capsule) (90% CI) for AUC_{0-t} and AUC_{0-inf} were 91.84% (86.79% – 97.19%) and 94.32% (89.50% - 99.40%), respectively, which fell within the 80% to 125% bioequivalence criteria. Celecoxib oral suspension showed approximately 22% lower C_{max} than Celebrex capsules. The geometric mean ratio (celecoxib oral suspension/Celebrex capsule) (90%CI) for Cmax was 77.92% (71.08% - 85.41%) (**Table 2**). In addition, the simulated steady state AUC_{0-12} values for 200 mg celecoxib oral suspension BID under fasting condition were equivalent 200 mg Celebrex capsule BID under fasting condition. The simulated steady state C_{max} values for celecoxib oral suspension under fasting condition were 19% lower (**Table 4**). Because the Applicant seeks the chronic pain indications (i.e., OA, RA, JRA, and AD) with dosing up to 200 mg BID but not the acute indications (i.e., AP and PD), therefore, AUC measures reflecting drug exposure over time are more relevant to efficacy than C_{max}. Therefore, equivalent single dose AUCs and simulated steady state AUC_{0-12} under fasting condition for proposed oral suspension and Celebrex capsules are expected to result in similar efficacy for chronic indications.

(2) Food Effect on the Proposed Celecoxib Oral Suspension (Study 915/22)

The median T_{max} values were 1.50 hours (range 0.67 to 8.00 hours) and 3.0 hours (range 0.67 to 6.05 hours) for the proposed celecoxib oral suspension under fasting and fed condition, respectively. High-fat high-calorie meals delayed median T_{max} of celecoxib by 1.5 hours. Mean terminal half-life values of celecoxib were 16.49 hours and 6.70 hours for celecoxib oral suspension under fasting and fed condition, respectively (**Table 1**).

Statistical analysis of AUC_{0-t}, AUC_{0-inf}, and C_{max} showed that high-fat high-calorie meals significantly increased the rate and extent of absorption of celecoxib for celecoxib oral suspension: AUC_{0-t}, AUC_{0-inf}, and C_{max} of celecoxib were increased by 50%, 35%, and 144%, respectively. The geometric mean ratios (oral suspension under fed condition/oral suspension under fasting condition) (90% CI) for AUC_{0-t}, AUC_{0-inf}, and C_{max} were 149.64% (139.58% – 160.44%), 134.96% (125.94% - 144.63%), and 244.36% (224.42% - 266.08%), respectively (**Table 5**).

Table 5 Statistical Analysis of PK Parameters of Celecoxib following A Single Dose Administration of 200 mg Celecoxib Oral Suspension under Fasted Condition (TFA) and Fed Condition (TFE) in Healthy Volunteers (Study 915/22)

Parameter	**TFE**		**TFA**		**Ratio (TFE/TFA) (%)**	**90% Confidence Interval**	
	N	GLSM	N	GLSM		Lower	Upper
AUC_{0-t} (ng.h/mL)	52	5834.9	52	3899.2	149.64	139.58	160.44
AUC_{0-inf} (ng.h/mL)	52	6048.8	52	4481.9	134.96	125.94	144.63
C_{max} (ng/mL)	52	791.3	52	323.8	244.36	224.42	266.08

GLSM: Geometric Least Squares Means
Source: PK and Statistical Report for Study 915/22 Page 7; Study report 915/22 Page 9

Reviewer's Comments: Proposed oral suspension showed greater food effect than Celebrex capsule. Per Celebrex label, when Celebrex capsules were taken with a high-fat meal, T_{max} was delayed for about 1 to 2 hours. Food resulted in an increase in AUC of 10% to 20% for Celebrex. Because the proposed celecoxib oral suspension showed significant food effect (i.e., 35% to 50% increase in AUCs and 144% increase in C_{max}) and the Applicant proposed that celecoxib oral suspension can be (b) (4) the Applicant was recommended to conduct steady state PK modeling and simulation and compare the simulated steady state PK for the proposed celecoxib oral suspension and Celebrex capsules under fed condition, and to provide additional clinical data (b) (4) with the proposed product when administered under fed conditions.

(3) Steady State PK Modeling and Simulation for the Proposed Celecoxib Oral Suspension versus Celebrex Capsule under Fed Condition

The Applicant developed a population PK model for Celebrex capsule under fasting condition based on the PK data collected in Study 915/22. The Celebrex capsule fasting population PK model

was customized to account for the effect of food on Celebrex capsule. The Applicant also developed a population PK model for oral suspension under fasting and fed condition based on the PK data obtained in Study 915/22. PK simulations were performed to predict concentration-time profiles following 200 mg BID dosing for 14 days under fed condition for both oral suspension and Celebrex capsule. The derived PK parameters for Celebrex capsules and oral suspension are shown in **Tables 6** and **7**, respectively.

Table 6. Descriptive Statistics – Celecoxib Exposure Parameters on Day 1 and Day 15– 200 mg Celebrex Capsule BID under Fed Condition (RFE)

	RFE	
Parameters	**Day 1 (N=52)**	**Day 15 (N=52)**
AUC_{0-12} (ng.h/mL)		
Arithmetic Mean (CV%)	4420 (85.1%)	6100 (113.5%)
Geometric Mean (CV%)	3760 (52.8%)	4920 (56.2%)
Median [Min, Max]	3550 [1730, 23400]	4590 [2020, 40800]
C_{max} (ng/mL)		
Arithmetic Mean (CV%)	717 (71.9%)	877 (89.9%)
Geometric Mean (CV%)	609 (58.0%)	730 (57.4%)
Median [Min, Max]	606 [222, 3050]	711 [302, 4840]
C_{min} (µg/mL)		
Arithmetic Mean (CV%)	191 (133.2%)	259 (162.8%)
Geometric Mean (CV%)	139 (77.7%)	170 (91.9%)
Median [Min, Max]	132 [24.4, 1420]	172 [24.6, 2330]
$AR_{AUC0-12}$		
Arithmetic Mean (CV%)	NA	1.33 (20.0%)
Geometric Mean (CV%)	NA	1.31 (18.7%)
Median [Min, Max]	NA	1.23 [1.03, 2.18]

Abbreviations: $AR_{AUC0-12}$ = Accumulation ratio based on AUC_{0-12}; AUC_{0-12} = area under the curve from 0 to 12 h; C_{max} = maximum concentration; C_{min} = minimum concentration; N = number of subjects

Table 7. Descriptive Statistics – Celecoxib Exposure Parameters on Day 1 and Day 15– 200 mg Celebrex Oral Suspension BID under Fed Condition (TFE)

	TFE	
Parameters	**Day 1 (N=53)**	**Day 15 (N=53)**
AUC_{0-12} (ng.h/mL)		
Arithmetic Mean (CV%)	4800 (38.4%)	6740 (75.6%)
Geometric Mean (CV%)	4560 (30.8%)	5980 (43.7%)
Median [Min, Max]	4240 [2960, 13500]	5340 [3640, 37900]
C_{max} (ng/mL)		
Arithmetic Mean (CV%)	660 (31.8%)	852 (56.4%)
Geometric Mean (CV%)	634 (27.9%)	785 (36.8%)
Median [Min, Max]	613 [405, 1560]	732 [480, 3670]
C_{min} (µg/mL)		
Arithmetic Mean (CV%)	155 (73.4%)	260 (133.1%)
Geometric Mean (CV%)	134 (51.9%)	197 (66.7%)
Median [Min, Max]	127 [50.2, 786]	179 [70.8, 2480]
$AR_{AUC0-12}$		
Arithmetic Mean (CV%)	NA	1.32 (18.2%)
Geometric Mean (CV%)	NA	1.31 (13.9%)
Median [Min, Max]	NA	1.27 [1.14, 2.80]

Abbreviations: $AR_{AUC0-12}$ = Accumulation ratio based on AUC_{0-12}; AUC_{0-12} = area under the curve from 0 to 12 h; C_{max} = maximum concentration; C_{min} = minimum concentration; N = number of subjects

Bioequivalence assessment of derived celecoxib steady state C_{max} and AUC_{0-12} on Day 15 following administrations of 200 mg celecoxib oral suspension or 200 mg Celebrex capsule BID for 14 days under fed condition are shown in **Table 8**. The ratio of geometric means (oral suspension/Celebrex capsule) and 90% CI for C_{max} were contained within 80.00% to 125.00%

bioequivalence criteria. The simulated steady state AUC_{0-12} for celecoxib oral suspension under fed condition were 25% greater than that for Celebrex capsule under fed condition.

Table 8 Bioequivalence Assessment of Simulated Steady State AUC_{0-12} and C_{max} – Celecoxib Oral Suspension (Test) versus Celebrex Capsule (Reference) under Fed Condition

Comparison	Day	Parameters	Ratio (%) Test/Reference	90% Confidence Interval (%)
Celecoxib Oral Suspension (test) fed conditions vs Celebrex® Capsule formulation (reference) fed conditions	15	Ln(AUC_{0-12})	124.73	107.43 to 144.81
		Ln(C_{max})	107.62	92.93 to 124.62

Abbreviations: AUC_{0-12}=area under the curve from 0 to 12h; C_{max} = maximum plasma concentration;

Reviewer's Comment: Celecoxib oral suspension showed significant food effect (i.e., high fat, high-calorie meal increased the mean AUC_{0-t}, AUC_{0-inf}, and C_{max} of celecoxib by 50%, 35%, and 144%, respectively). Based on the simulated steady state AUC_{0-12} following 200 mg BID dosing for celecoxib oral suspension were 25% greater than Celebrex capsules under fed condition. The sponsor did not have actual data for the reference product (Celebrex Capsule) under fed conditions. Instead, they used a correction factor based on literature data to simulate the fed state for the reference product. The Celebrex label states that when taken with a high fat meal there was an increase in AUC of 10% to 20%, but the sponsor chose the highest reported AUC change for correction factor (AUC: 22%). In addition, there were additional issues with the PK parameters the sponsor applied the correction factors to, in their modeling exercise. The sponsor's simulations indicate that under fed conditions at steady state, the AUC ratio between the test and reference products is 125% (with a 90% confidence interval of 107% to 145%). However, if a smaller correction factor had been used for the reference product's food effect, the comparative food effect of the test product (Celecoxib Oral Suspension) would appear more pronounced. This would likely result in a higher AUC ratio between the test and reference products and wider confidence intervals in the bioequivalence assessment under fed conditions.

The labeling for all NSAIDs in dosage and administration state that the lowest effective dosage for shortest duration consistent with individual patient treatment goals. The acute pain indications allow for a loading dose of 400 mg followed by 200 mg which may provide some safety for increased exposures in patients initiating the dose. The labeling for Celebrex for the indication of Ankylosing Spondylitis (AS) states that 200 mg once daily single dose or 100 mg twice daily; If no effect is observed after 6 weeks, a trial of 400 mg (single or divided doses) may be of benefit. So if a patient takes 400 mg QD there would be higher AUC_{0-12} expected in these subjects. But based on discussions with clinical team during the review process, it was discussed that the median age of onset for AS is typically between 20 and 40 years old with most patients experiencing symptoms before age 45. Also the increased dose is allowed in this population only after the lower dose has been well tolerated for 6 weeks with no benefit. Thus, the applicability of the safety from the potential increased exposures in this specific population may not be generally applicable to broader chronic pain indications being applied for by the applicant such as OA and RA. (b) (4) [redacted] (b) (4) . Thus, the proposed celecoxib oral suspension should not be given with food unless there are clinical data to support the safety of celecoxib oral

suspension under fed condition (see Clinical review). We ultimately defer to clinical team regarding whether there will be safety issues associated with increased exposures for patients initiating dosing with this product and the potentially 25% greater steady state AUC values for oral suspension.

2.1 Formulation of the Proposed Celecoxib Oral suspension

Table 9 Celecoxib Oral suspension Formulation (10 mg/1 mL)

Ingredient	Function	%w/v
Celecoxib, USP	Active Pharmaceutical Ingredient	1.0
Xanthan Gum, (b) (4) NF	(b) (4)	
Citric Acid Anhydrous, USP		
Methyl Paraben, NF		
Propyl Paraben, NF		
Sodium Citrate Dihydrate, USP		
Glycerin, USP		
Sucralose, NF		
Magnesium Aluminometasilicate, NF (b) (4)		
Purified Water, USP, Ph.Eur.		

2.2 Dosing and Therapeutic Individualization

2.2.1 Proposed Dosage and Administration

Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (b) (4)

• OA: 200 mg (20 mL) once daily or 100 mg (10 mL) twice daily.

• RA: 100 mg (10 mL) to 200 mg (20 mL) twice daily.

• JRA: 50 mg (5 mL) twice daily in patients 10 kg to 25 kg. 100 mg (10 mL) twice daily in patients more than 25 kg.

• AS: 200 mg (20 mL) once daily single dose or 100 mg (10 mL) twice daily. If no effect is observed after 6 weeks, a trial of 200 mg (20 mL) twice daily may be of benefit.

Important: VYSCOXA is not recommended at a single dose greater than 200 mg (20 mL). Single doses of the oral suspension greater than 200 mg (20 mL) may result in celecoxib concentrations higher than expected. For patients who require a single dose over 200 mg (20 mL), use a different celecoxib formulation.

(b) (4)

Hepatic Impairment: Reduce daily dose by 50% in patients with moderate hepatic impairment (Child-Pugh Class B).

Poor Metabolizers of CYP2C9 Substrates: Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers.

2.3 Outstanding Issues

None.

3. SUMMARY OF LABELING RECOMMENDATIONS

As of today (6/24/2025), 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:

1. INDICATIONS AND USAGE

Limitation of Use
VYSCOXA must be administered on an empty stomach at least 2 hours before or 1 hour after food. Taking VYSCOXA with food results in plasma exposures of celecoxib up to 50% higher than intended. If patients cannot tolerate VYSCOXA in the fasted state, discontinue use of VYSCOXA (reference Sections 12, 2.1, 5).

2.1 General Dosing Instructions

…

The maximum single dose of VYSCOXA is 200 mg (20 mL) (b) (4) Administering more than 200 mg (20 mL) in a (b) (4) single dose of the VYXCOXA suspension (b) (4) may result in higher than intended plasma concentrations of celecox (b) (4) In patients requiring a single dose greater than 200 mg (b) (4) (b) (4) product.

VYSCOXA (b) (4) (b) (4) must be taken on an empty stomach at least 2 hours before or 1 hour after food [see Clinical Pharmacology (12.3)].

For patients who cannot tolerate dosing with VYSCOXA on an empty stomach, discontinue the use of this product. Do not advise the patients to take VYSCOXA with food.

Reviewer's Comment: because of the significant food effect, VYXCOXA should not be taken with meals. The team determined that VYXCOXA must be taken on an empty stomach at least 2 hours before or 1 hour after food.

12.3 Pharmacokinetics

Celecoxib has extensive distribution and high protein binding. It is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours.

Absorption

Following a single dose administration of 200 mg VYSCOXA and 200 mg celecoxib capsules (b) (4) under fasting condition in 52 healthy subjects, the median time to (b) (4) peak plasma levels (i.e., Tmax) of celecoxib (b) (4) was 1.5 hours (range 0.67 – 8.00 hours) and 2.5 hours (range 1.00 – 8.00 hours), respectively (b) (4) (b) (4) The overall systemic exposure (AUC) of a 200 mg dose of VYSCOXA was equivalent to celecoxib (b) (4) capsules with a decrease in peak plasma levels (i.e., Cmax) of 22% (b) (4) (b) (4) There were no significant alterations in (b) (4) (b) (4) terminal half-life values between VYSCOXA and celecoxib capsules (b) (4) When celecoxib capsules were administered under fasting condition, both Cmax and AUC were roughly dose-proportional up to 200 mg twice daily, at higher dose there were less than proportional increases in Cmax and AUC which is thought to be due to the low solubility of the drug in aqueous media. The comparative bioavailability between VYSCOXA and celecoxib capsules at doses above 200 mg has not been determined. Absolute bioavailability studies have not been conducted. With multiple dosing of celecoxib, steady-state conditions are reached on or before Day 5.

Effects of Food (b) (4)

When a single dose of 200 mg VYSCOXA was taken with a high fat, high-calorie meal, the median Tmax was delayed by 1.5 hours. The extent and rate of absorption of c (b) (4) elecoxib was significantly increased when a single dose of 200 mg VYSCOXA was administered under fed conditions compared to the fasting state and showed an increase in the mean AUC(0-t), AUC(0-∞), and Cmax of (b) (4) celecoxib by 50%, 35%, and 144%, respectively. (b) (4) (b) (4) [see Dosage and Administration (2.1)].

Reviewer's Comment: the last sentence should be removed from this section because per Clinical Pharmacology labeling guidance, "specific instructions on how a drug is to be administered relative to the ingestion of food should be included in the DOSAGE AND ADMINISTRATION section".

Drug Interaction Studies

…

Aluminum- and Magnesium Containing Antacids

Coadministration of celecoxib with an aluminum- and magnesium-containing antacids resulted in reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC.

Reviewer's Comment: This paragraph is in Celebrex label and should be added back.

Other Drugs

…

4 APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical LC/MS/MS methods for the determination of celecoxib concentrations in human plasma in Study 915/22 was adequately validated. The lower limit of quantitation is 10.0 ng/mL and the standard calibration curve covered the range from 10.0 to 2000.0 ng/mL. The assay precision (%CV) and accuracy (% of nominal concentrations) for QC samples of 30.0 ng/mL, 300.0 ng/mL, and 1600.0 ng/mL were from 1.97% to 2.59% and from 97.20% to 98.99%, respectively.

4.2 Office of Study Integrity and Surveillance (OSIS) Inspection Assessment

OSIS inspection on the clinical site at Quinta-Analytica, Prague, Czech Republic and analytical site at (b) (4) for the comparative bioavailability and food effect study 915/22 was requested on 12/3/2024.

Per OSIS memo in DARRTS dated 1/31/2025, OSIS inspected the analytical portion of Study 915/22 conducted at (b) (4) It was concluded that there was no concern with the reliability of analytical data generated from Study 915/22.

OSIS review of clinical portion is pending.

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