Office of Clinical Pharmacology Review

NDA Number	209449 (SDN 1, SDN 3, SDN 7)
Submission Date	09/26/2016, 11/21/2016, 01/17/2017
Submission Type	Original, 505(b)(2)
Brand Name	Nityr
Generic Name	Nitisinone
Dosage Form and Strength	Tablets: 2 mg, 5 mg, 10 mg
Route of Administration	Oral
Indication	Treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine
Applicant	Cycle Pharmaceuticals Ltd.
OCP Reviewer	Shen Li, Ph.D.
OCP Team Leader	Insook Kim, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products

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1. EXECUTIVE SUMMARY

In this submission, the applicant proposes a new nitisinone immediate release tablet product and proposes to rely on the Agency's previous findings on the efficacy and safety of Orfadin capsules (NDA 21232). Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase. Currently, nitisinone is marketed as Orfadin capsules (nitisinone 2 mg, 5 mg, 10 mg, 20 mg; NDA 21232) and Orfadin suspension (nitisinone 4 mg/mL; NDA 206356) for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate.

The applicant proposes a new tablet formulation with 10 mg, 5 mg and 2 mg strengths. The sponsor does not propose tablets with 20 mg strength. To bridge the proposed product to the listed drug (Orfadin 10 mg capsules), the applicant conducted a relative BA/BE study between the nitisinone tablet 10 mg and Orfadin capsule 10 mg (Study CT-003) and demonstrated BE between two products. In addition two additional clinical pharmacology studies conducted to evaluate the food effect (Study CT-002) for nitisinone tablet and the effect of an excipient for nitisinone tablet in support of the formulation development for nitisinone tablet (Study CT-001). No other clinical studies were conducted with the proposed new tablet formulation. For two lower strength 5 mg and 2 mg, no relative BA/BE studies were conducted while the biowaiver request is considered acceptable. Refer to the Biopharmaceutics review by Dr. Peng Duan for the review of biowaiver request.

The proposed dosing regimen is 0.5 mg/kg orally twice daily and the dose may be increased up to 1 mg/kg twice daily based on the evaluation of biochemical and/or clinical response. The proposed dosing regimen is the same as that for the approved Orfadin capsules. The proposed nitisinone tablet is to be taken without regard of food based on no significant food effects on nitisinone pharmacokinetics observed in the food effect study (CT-002). Currently, Orfadin capsules are to be taken at least one hour before, or two hours after a meal, since the food effect on Orfadin capsules is unknown[1]. In addition to swallowing the whole tablets, the applicant proposes dosing methods of either administration of crushed tablets mixed with applesauce or tablets suspended in water using an oral syringe. The administration of crushed tablets or after suspended in water was not studied in humans. Refer to the CMC review for the stability and comparability of crushed tablets in applesauce and tablets suspended in water.

The applicant claims that new nitisinone tablet can be stored at room temperature while Orfadin capsules or Orfadin suspension should be stored in the refrigerator between 2°C to 8°C. In Study CT-003, the applicant also compared the bioavailability between the proposed nitisinone tablets

[1] Clinical Pharmacology Review of NDA 21232 for Orfadin capsules dated 02/02/2001

stored at 40°C/75% RH for 6 months to Orfadin 10 mg capsules. Refer to the CMC review for the storage stability of the drug product.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the submission and found it acceptable from a Clinical Pharmacology standpoint, provided that a mutually satisfactory agreement can be reached between the sponsor and Agency regarding the labeling language.

The OSIS inspection reports recommend that the clinical and bioanalytical data for the pivotal BE study CT-003 be accepted for review (see details in 4.3 OSIS Inspection Reports).

1.2 Post-Marketing Requirements and Commitments

None.

1.3 Labeling Comments

The proposed dosing instruction "Nitisinone tablets may be taken with or without food" is acceptable.

We recommend a description of the food used in the food effect study with respect to total calories and composition (fat, carbohydrate, and protein content) be included in the label.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Bioequivalence of the Proposed Nitisinone Tablet 10 mg and Orfadin Capsule 10 mg

The bioequivalence between the proposed product (nitisinone tablets 10 mg) and the listed drug (Orfadin capsules 10 mg) was demonstrated.

Summary of the statistical analysis for bioequivalence following administration of the proposed nitisinone tablets (nitisinone 10 mg tablets and "aged" nitisinone 10 mg tablets [stored for 6 months at 40°C/75% RH]) and the approved Orfadin capsule under fasting conditions is presented in the table below.

Table 1 Summary of statistical analysis for bioequivalence

Nitisinone 10 mg table vs Orfadin 10 mg capsule				
PK Parameter	**Orfadin 10 mg capsule**	**Nitisinone 10 mg tablet**	**LS Mean Ratio (%)**	**90% Confidence Interval of Ratio**
$AUC_{0\text{-}120h}$ (ng*h/mL)	78149	78041	99.86	(96.34 - 103.51)
C_{max} (ng/mL)	1334	1279	95.90	(91.66 - 100.34)

"Aged" Nitisinone 10 mg table vs Orfadin 10 mg capsule				
PK Parameter	**Orfadin 10 mg capsule**	**"Aged" nitisinone 10 mg tablet [#]**	**LS Mean Ratio (%)**	**90% Confidence Interval of Ratio**
$AUC_{0\text{-}120h}$ (ng*h/mL)	78090	77188	98.84	(94.75 - 103.11)
C_{max} (ng/mL)	1333	1274	95.55	(91.14 - 100.19)

[#] nitisinone 10 mg tablet stored at 40°C/75% RH for 6 months.
LS = least square.
Source: Clinical study report for CT-003.

Food effect

A high-fat (approximately 50% of total caloric content) and high-calorie (approximately 800 to 1000 calories) meal did not affect the nitisinone exposure as the 90% confidence intervals of nitisinone 10 mg tablet fed/fasting ratios for both Cmax and AUC were contained entirely within the range of 0.80 to 1.25. As such, the proposed dosing instruction to administer nitisinone tablets with or without food is appropriate from a Clinical Pharmacology perspective.

Dosing methods for patients who have difficulties swallowing tablets

For patients who have difficulties swallowing tablets, including infants and young children, the applicant proposed that tablets may be crushed before administration and mixed with apple sauce or suspended in water. Of note, bioequivalence was evaluated with the whole nitisinone tablets but not with the crushed tablets or tablet suspended in water. The applicant stated that crushed tablets may result in a slightly faster, if not similar, dissolution release profile than the whole tablet but the significant effects on the bioavailability was not anticipated as the differences in the dissolution time between nitisinone tablets and "aged" nitisinone tablets did not result in significant difference in the in vivo bioavailability of nitisinone in Study CT-003. In addition, the results of in vitro studies for the stability of nitisinone and the recovery of the dose for the crushed tablets in apple sauce were acceptable by the CMC reviewer. We have discussed this issue with the Division Director, Dr. Bashaw and the Deputy Division Director, Dr. Ahn of DCP3 and concluded that the sponsor's approach is acceptable and that the administration of crushed tablets can be supported without additional in vivo bioavailability study provided the in vitro study results are supportive of crushed tablets.

It should be noted that the suspending tablets in water was not proposed in the original submission but proposed for younger patients who cannot take semi-solid food during the review cycle. The additional in vitro studies were submitted in support of suspension of tablets in water in an oral syringe. We defer the review of in-vitro studies to the CMC and Biopharmaceutics reviews.

BE study site inspection

The inspection of the BE clinical study site by the Office of Study Integrity and Surveillance (OSIS) found clinical data for study CT-003 acceptable for our review. OSIS recommends accepting bioanalytical data without an on-site inspection based on the recent favorable inspection results of the bioanalytical study site. The OSIS also commented whether the calibration range for nitisinone concentrations was representative of study sample concentrations. The calibration standard curve was established at concentrations from 19.53 to 2500 ng/mL in human plasma. The reported plasma concentrations reported ranged from 20.02 to 1884 ng/mL in Study CT-003. As such, reviewer's analysis indicates that the calibration curves were representative of study sample concentrations.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Background

The Listed Drug: Orfadin Capsules

NDA 21232 for Orfadin capsules (nitisinone 2 mg, 5 mg, 10 mg) was initially approved in 2002 for the treatment of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine. Supplemental NDA 21232 for adding a new dose strength (Orfadin 20 mg capsules) were approved in June 2016. Orfadin capsules should be stored in the refrigerator between 2°C to 8°C (36°F to 46°F).

Currently approved dosage and administration for Orfadin capsule:

- The recommended initial dosage is 0.5 mg/kg orally twice daily. Titrate the dose based on biochemical and/or clinical response, as described in the full prescribing information. The maximum dosage is 1 mg/kg orally twice daily.
- Take ORFADIN capsules at least one hour before, or two hours after a meal.
- For patients who have difficulties swallowing capsules and who are intolerant to the oral suspension, the capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.

Nitisinone is also available as suspension (NDA 206356; nitisinone 4 mg/mL). Of note, the sponsor did not reference the Orfadin suspension and did not study the proposed tablet in comparison to Orfadin suspension which was originally approved based on a BE to Orfadin tablet.

Proposed Product: Nitisinone Tablets

The Applicant submitted this NDA application for a new tablet formulation (nitisinone 2 mg, 5 mg, and 10 mg tablets). In support of new tablet formulation, three clinical pharmacology studies in healthy subjects were conducted including a pivotal bioequivalence study (CT-003) comparing the proposed nitisinone tablets (nitisinone 10 mg tablets and "aged" nitisinone 10 mg

tablets [stored at 40°C/75% RH for 6 months]) to Orfadin 10 mg capsules. The food effect on nitisinone PK was evaluated in Study CT-002. A relative BA Study CT-001 was conducted to support the early formulation development to investigate the effect of an excipient (i.e., (b) (4) in the final to-be-marketed formulation vs. (b) (4) in an interim formulation). Additionally, the submission also includes several in vitro studies to evaluate the dissolution profile and in vitro dose recovery for the to-be-marketed tablet formulation. The final to-be-marketed tablet formulation was used in the pivotal BE study CT-003 and the food-effect study CT-002.

Summary of the clinical pharmacology studies included in this submission:

Study No.	Study objective(s)	Study design	Test product(s)	Subjects
CT-001	To determine whether the test products (nitisinone 10 mg tablets and nitisinone 10 mg (b) (4) tablets, and the reference product, ORFADIN 10 mg hard capsules are bioequivalent.	This was a single dose, open label, laboratory blind, randomized, three period crossover study with orally administered nitisinone 10 mg (2 test formulations and a reference product) conducted under fasting conditions in at least 18 healthy male and female subjects at a single study center.	Nitisinone tablets 10 mg x 1, oral (to-be-marketed formulation, (b) (4) (b) (4) Nitisinone tablets 10 mg (b) (4) (b) (4) x1, oral	23 healthy subjects
CT-002	To compare the bioavailability of the test product, Nitisinone 10 mg tablets, under fasting and fed conditions (food-effect).	This will be a single-dose, open-label, laboratory-blind, randomized, two-period crossover study with orally administered nitisinone 10 mg conducted under fasting and fed conditions in at least 16 healthy male and female subjects at a single study center.	Nitisinone tablets 10 mg x 1, oral.	19 healthy subjects
CT-003	To determine whether the test products (Nitisinone 10 mg tablets and aged Nitisinone 10 mg tablets (6 months at 40°C/75% RH)), and the reference product, ORFADIN 10 mg hard capsules are bioequivalent.	This was a single center, single- dose, open-label, laboratory-blind, randomized, three-period crossover study to determine the bioequivalence of two oral formulations containing of nitisinone 10 mg compared to the reference formulation ORFADIN 10 mg in at least 18 healthy male and female subjects under fasting conditions.	Nitisinone tablets 10 mg x 1, oral; Aged Nitisinone tablets 10 mg (accelerated stability conditions, 6 months) x1, oral	23 healthy subjects

3.2 Summary of Clinical Pharmacology Assessment

The pivotal BE study (CT-003) demonstrated bioequivalence between the proposed product (nitisinone tablets) and the listed drug (Orfadin capsules).

In Study CT-003 entitled "A single center, single-dose, open-label, laboratory-blind, randomized, two-period crossover study to compare the bioavailability of an oral test formulation containing nitisinone 10 mg in at least 16 healthy male and female subjects under fasting and fed conditions", 24 healthy subjects received single oral 10-mg doses of the proposed nitisinone tablets (nitisinone 10 mg tablets and "aged" nitisinone 10 mg tablets [stored for 6 months at 40°C/75% RH]), and Orfadin 10 mg capsules under fasting conditions in a 3-way crossover fashion.

Nitisinone pharmacokinetic parameters following administration of the proposed nitisinone tablets and the approved Orfadin capsules under fasting conditions are presented in Table 2. Due to the very long half-life of nitisinone, the truncated $AUC_{0\text{-}120h}$ was used in the analysis based on PK samples collected for 120 hours.

Table 2 Summary of geometric mean (range) pharmacokinetic parameters of nitisinone

Treatment	**C_{max} (ng/mL)**	**t_{max} (h)***	**$AUC_{0\text{-}120h}$ (ng*h/mL)**	**$t_{1/2}$ (h)**
Orfadin 10 mg capsule(n=23)	1340 [968.9 to 1884]	2.50 [0.50 to 10.0]	78673 [59351 to 112432]	59.9 [36.5 to 96.4]
Nitisinone 10 mg tablet (n=23)	1278 [779.7 to 1649]	3.50 [1.00 to 4.00]	77874 [42335 to 104211]	58.7 [41.6 to 74.7]
"Aged" nitisinone 10 mg tablet # (n=23)	1272 [843.2 to 1719]	4.00 [2.00 to 10.0]	77295 [49971 to 120848]	60.8 [46.5 to 92.7]

* median (range)

nitisinone 10 mg tablet stored at 40°C/75% RH for 6 months.

Nitisinone Tablets vs. Orfadin® Capsules: Bioequivalence under fasting condition

Bioequivalence testing was conducted and the corresponding geometric mean ratios (and 90% CI) for C_{max}, $AUC_{0\text{-}72h}$, and $AUC_{0\text{-}120h}$ are presented in Table 3.

Table 3 Statistical analysis of bioequivalence

PK Parameter (unit)	LS Mean			Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Orfadin® (Reference product)	Nitisinone (Test product 1)	Nitisinone (Test product 2)			
Test 1 vs Reference						
$AUC_{(0-120)}$ (h•ng/mL)	78149.092	78040.865	NA	99.86	96.34 ; 103.51	7.0
$AUC_{(0-72)}$ (h•ng/mL)	58646.164	57948.259	NA	98.81	95.63 ; 102.09	6.4
C_{max} (ng/mL)	1333.510	1278.828	NA	95.90	91.66 ; 100.34	8.9
t_{max} (h) *	2.50	3.50	NA	p-value: 0.2300		
Test 2 vs Reference						
$AUC_{(0-120)}$ (h•ng/mL)	78090.254	NA	77187.852	98.84	94.75 ; 103.11	8.3
$AUC_{(0-72)}$ (h•ng/mL)	58600.801	NA	57455.264	98.05	93.98 ; 102.28	8.3
C_{max} (ng/mL)	1332.941	NA	1273.675	95.55	91.14 ; 100.19	9.3
t_{max} (h)*	2.50	NA	3.90	p-value: 0.0258		

* median

Reference = Orfadin 10 mg capsule; Test 1 = nitisinone 10 mg tablet; Test 2 = nitisinone 10 mg tablet (stored for 6 months at 40°C/75% RH); CV = coefficient of variation; LS = least square Median.

The 90% confidence intervals for both nitisinone 10 mg tablet/Orfadin 10 mg capsule ratios and nitisinone 10 mg tablet (stored for 6 months at 40°C/75% RH)/Orfadin 10 mg capsule ratios under fasting conditions were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

Reviewer's Comments:

- ***This reviewer was able to reproduce the BE results and conclusion. Bioequivalence was only evaluated between the proposed highest strength (i.e., 10 mg) of nitisinone tablets and the listed drug (Orfadin capsules). This approach is acceptable since the three proposed tablet strengths (2 mg, 5 mg, and 10 mg) are considered proportionally similar. The difference in inactive ingredients between the highest 10 mg and the lowest 2 mg tablet strengths are within Level 2 change (10%) as described in SUPAC-IR. For details on this aspect, refer to the Biopharmaceutics review.***

Food effects on nitisinone PK

There is no significant food effect on the systemic exposure to nitisinone for the proposed nitisinone tablets. The high fat meal delayed the median Tmax by 3 hours to 6 hours compared to that without food. The acute effect of nitisinone is not expected and the delay in Tmax is not concerning for the efficacy. As such, the proposed dosing instruction to administer nitisinone tablets with or without food is acceptable from a Clinical Pharmacology perspective.

In Study CT-002 entitled "A single center, single-dose, open-label, laboratory-blind, randomized, three-period crossover study to determine the bioequivalence of two oral formulations containing nitisinone 10 mg compared to the reference formulation ORFADIN 10 mg in at least 18 healthy male and female subjects under fasting conditions", 20 healthy subjects received single oral 10-mg doses of the proposed nitisinone tablets under fasting and fed conditions. The 90% confidence intervals of nitisinone 10 mg tablet fed/fasting ratios were contained entirely within the range of 0.80 to 1.25 with respect to C_{max}, $AUC_{0\text{-}72h}$, and $AUC_{0\text{-}120h}$.

Statistical analysis of the food effect for the proposed nitisinone tablet formulation is presented in Table 4.

Table 4: Statistical analysis of the food effect

Parameter (unit)	LS Mean		Mean Ratio (Fed/Fast) (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Nitisinone (Fed)	Nitisinone (Fast)			
$AUC_{(0\text{-}120)}$ (h•ng/mL)	67508.639	70841.080	95.30	92.71 ; 97.95	4.9
$AUC_{(0\text{-}72)}$ (h•ng/mL)	49966.954	52560.003	95.07	92.70 ; 97.50	4.5
C_{max} (ng/mL)	1056.884	1159.960	91.11	86.56 ; 95.91	9.1
λ_z (1/h)	0.012	0.011	0.07	-0.05 ; 0.19	-
T_{max} (h)	6.186	3.900	228.61	104.26 ; 352.96	-
T_{max} (h)*	6.00	3.00	p-value: 0.0048		

*Median

CV = coefficient of variation; LS = least square.

Inspection of the BE study site and bioanalytical site by OSIS:

A request to conduct an inspection of the clinical and bioanalytical sites for the pivotal BE study CT-003 was submitted to the Office of Study Integrity and Surveillance (OSIS).

OSIS inspection recommends that clinical data for the study CT-003 be accepted for review (See 4.3 OSIS Inspection Reports of this review). Bioanalytical site inspection was declined by OSIS since OSIS recently inspected the site. Based on the recent inspection results unrelated to this study, OSIS recommends accepting bioanalytical data without an on-site inspection, but also recommends the review division confirm that the calibration curves in the current study were representative of study sample concentrations. The calibration standard curve for Study CT-003 consisted of 8 concentrations ranged from 19.53 to 2500 ng/mL in human plasma. Study sample concentrations contained BLQ and a quantifiable range of 20.02 to 1884 ng/mL. As such, reviewer's analysis indicates that the calibration curves were representative of study sample concentrations.

Formulation of the proposed nitisinone tablets:

The composition of the proposed to-be-marketed drug product is shown in the table below:


(b) (4)

4. APPENDICES

4.1 Individual Study Review

4.1.1 Study CT-001

Title: **A single center, single-dose, open-label, laboratory-blind, randomized, three-period crossover study to determine the bioequivalence of two oral formulations containing of nitisinone 10 mg compared to the reference formulation ORFADIN 10 mg in at least 18 healthy male and female subjects under fasting conditions.**

Sponsor: Cycle Pharmaceuticals Ltd.
Clinical Site: Bloemfontein Early Phase Clinical Unit, PAREXEL International, Bloemfontein, South Africa.
Bioanalytical Site: (b) (4)
Study Date: 10/15/2015 – 01/22/2016

Study Objective:

- To determine whether the test products (nitisinone 10 mg tablets and nitisinone 10 mg (b) (4) tablets), and the reference product, Orfadin 10 mg hard capsules are bioequivalent.

Study Design:

This was a single-dose, open-label, laboratory-blind, randomized, three-period crossover study with orally administered nitisinone 10 mg (two test formulations and a reference product) conducted under fasting conditions in at least 18 healthy male and female subjects at a single study center. There was a wash-out interval of at least 23 days between treatment periods.

Reviewer's Comments:

- ***A washout period of at least 23 days is reasonable, as the mean t1/2 of nitisinone in healthy subjects was reported previously as 54 hours (Orfadin label). Nitisinone pre-dose concentrations were measurable in 8 subjects in Periods 2 or 3, but were all less than 5% of the corresponding C_{max} value. All predose concentrations were included in the pharmacokinetic calculations without any adjustments. This approach is in agreement with the current FDA guidance.***
- ***Nitisinone 10 mg*** (b) (4) ***tablets contain a*** (b) (4) (b) (4) ***in standard nitisinone 10 mg tablets (i.e., the proposed to-be-marketed formulation).***

Excluded Medications:

Subjects were not allowed to use any concomitant medication, prescribed or over-the-counter (including hormonal contraceptives, herbal remedies), for 2 weeks before and for the duration of the study.

Study Population: Twenty-three healthy subjects (18 males and 5 females) were enrolled into this study.

Pharmacokinetic Measurements:

Pharmacokinetic blood samples were collected at the following time points: at pre-dose and at 0.25, 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours post-dose in each treatment period.

Pharmacokinetic and Statistical Analysis:

Pharmacokinetic parameters were calculated using Phoenix WinNonlin version 6.2. Statistical analysis was performed using analysis of variance (ANOVA) with sequence, subject (sequence), treatment and period effects after logarithmic transformation of the data.

Bioanalytical Method:

Bioanalytical analysis of nitisinone in the plasma samples was performed at (b) (4) (b) (4) Plasma samples were stored at approximately -70^{o}C until analysis.

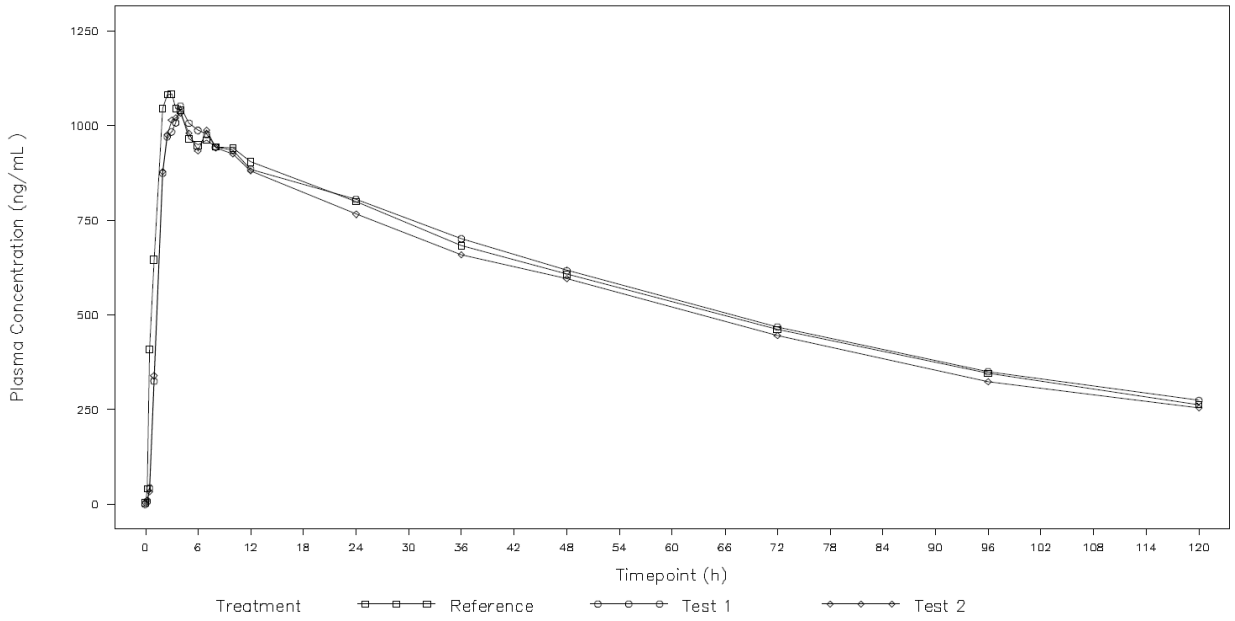
Briefly, plasma nitisinone concentrations were isolated by protein precipitation with methanol and measured using a liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with electrospray ionization in negative mode and using $^{13}C_6$-nitisinone as an internal standard. The assay method had a lower quantification limit of 19.53 ng/mL using 50 µL of plasma (see details in 4.2 Bioanalytical Method Reports).

Reviewer's Comments:

- ***The bioanalytical method used to determine plasma nitisinone concentrations is acceptable.***

PHARMACOKINETIC RESULTS:

Mean nitisinone plasma concentration profiles after a single oral administration of nitisinone 10 mg tablet, nitisinone 10 mg (b) (4) tablet, and Orfadin 10 mg capsule (reference) are presented below.



Reference = Orfadin 10 mg capsule; Test 1 = nitisinone 10 mg tablet; Test 2 = nitisinone 10 mg (b) (4) tablet.

Statistical analyses of key PK parameters for nitisinone are summarized in the table below.

Parameter (unit)	LS Mean			Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Orfadin® 10 mg tablets (Reference product)	Nitisinone 10 mg tablets (Test Product 1)	Nitisinone 10 mg high compritol tablets (Test Product 2)			
Test 1 vs Reference						
$AUC_{(0-120)}$ (h•ng/mL)	65705.989	66251.703	N/A	100.83	96.58 ; 105.27	8.5
$AUC_{(0-72)}$ (h•ng/mL)	49196.050	49408.190	N/A	100.43	96.84 ; 104.15	7.1
C_{max} (ng/mL)	1161.934	1136.332	N/A	97.80	93.77 ; 102.00	8.3
T_{max} (h)*	2.5	3	N/A	p-value: 0.2034		
Test 2 vs Reference						
$AUC_{(0-120)}$ (h•ng/mL)	65798.960	N/A	61998.688	94.22	84.85 ; 104.63	20.8
$AUC_{(0-72)}$ (h•ng/mL)	49269.592	N/A	46472.409	94.32	84.58 ; 105.19	21.7
C_{max} (ng/mL)	1163.756	N/A	1081.736	92.95	84.03 ; 102.82	20.0
T_{max} (h)*	2.5	N/A	3	p-value: 0.1098		

*Median

Reference = Orfadin 10 mg capsule; Test 1 = nitisinone 10 mg tablet; Test 2 = nitisinone 10 mg (b) (4) tablet; CV = coefficient of variation; LS = least square.

The 90% confidence intervals of nitisinone 10 mg tablet/Orfadin 10 mg capsule ratios were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

The 90% confidence intervals of nitisinone 10 mg (b) (4) tablet/Orfadin 10 mg capsule ratios were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

Reviewer's Comments:

- ***The Applicant evaluated AUC_{0-120h} and AUC_{0-72h} instead of AUC_{0-inf} in this BE study, due to the long half-life of nitisinone (54 hours). This approach is acceptable. Per the current FDA guidance, an AUC truncated at 72 hours ($AUC_{0-72\ h}$) can be used in place of AUC_{0-t} or AUC_{0-inf} for drugs that demonstrate low intrasubject variability in distribution and clearance. Intrasubject variability on C_{max} and AUC for nitisinone was less than 22% in this study.***

- ***The Applicant's PK analysis and bioequivalence analysis have been repeated by the reviewer. Reviewer's results confirmed the Applicant's conclusion that the 90% confidence intervals of nitisinone 10 mg tablet/Orfadin 10 mg capsule ratios were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max} and AUC, for both nitisinone 10 mg tablet (proposed to-be-marketed formulation with*** (b) (4)

4.1.2 Study CT-002

Title: **A single center, single-dose, open-label, laboratory-blind, randomized, two-period crossover study to compare the bioavailability of an oral test formulation containing nitisinone 10 mg in at least 16 healthy male and female subjects under fasting and fed conditions**

Sponsor: Cycle Pharmaceuticals Ltd.

Clinical Site: Bloemfontein Early Phase Clinical Unit, PAREXEL International, Bloemfontein, South Africa.

Bioanalytical Site: (b) (4)

Study Date: 11/02/2015 – 01/05/2016

Study Objective:

- To compare the bioavailability of the test product, nitisinone 10 mg tablets, under fasting and fed conditions (food-effect).

Study Design:

This was a single-dose, open-label, laboratory-blind, randomized, two-period crossover study with orally administered nitisinone 10 mg conducted under fasting and fed conditions in at least

16 healthy male and female subjects at a single study center. There was a wash-out interval of at least 23 days between treatment periods.

Reviewer's Comments:

- ***A washout period of at least 23 days is reasonable, as the mean t1/2 of nitisinone in healthy subjects was reported previously as 54 hours (Orfadin label). Nitisinone pre-dose concentrations were measurable in 4 subjects in Period 2, but were all less than 5% of the corresponding C_{max} value. All predose concentrations were included in the pharmacokinetic calculations without any adjustments. This approach is in agreement with the current FDA guidance.***

Excluded Medications:

Subjects were not allowed to use any concomitant medication, prescribed or over-the-counter (including hormonal contraceptives, herbal remedies), for 2 weeks before and for the duration of the study.

Study Population: Twenty healthy subjects (17 males and 3 females) were enrolled into this study. One female subject withdrew from the study after Period 1 for personal reasons. Nineteen subjects (17 males and 2 females) completed the study.

Pharmacokinetic Measurements:

Pharmacokinetic blood samples were collected at the following time points: at pre-dose and at 0.25, 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours post-dose in each treatment period.

Pharmacokinetic and Statistical Analysis:

Pharmacokinetic parameters were calculated using Phoenix WinNonlin version 6.3. Statistical analysis was performed using ANOVA with sequence, subject (sequence), treatment and period effects after logarithmic transformation of the data.

Bioanalytical Method:

Bioanalytical analysis of nitisinone in the plasma samples was performed at (b) (4) (b) (4) Plasma samples were stored at approximately -70 C until analysis.

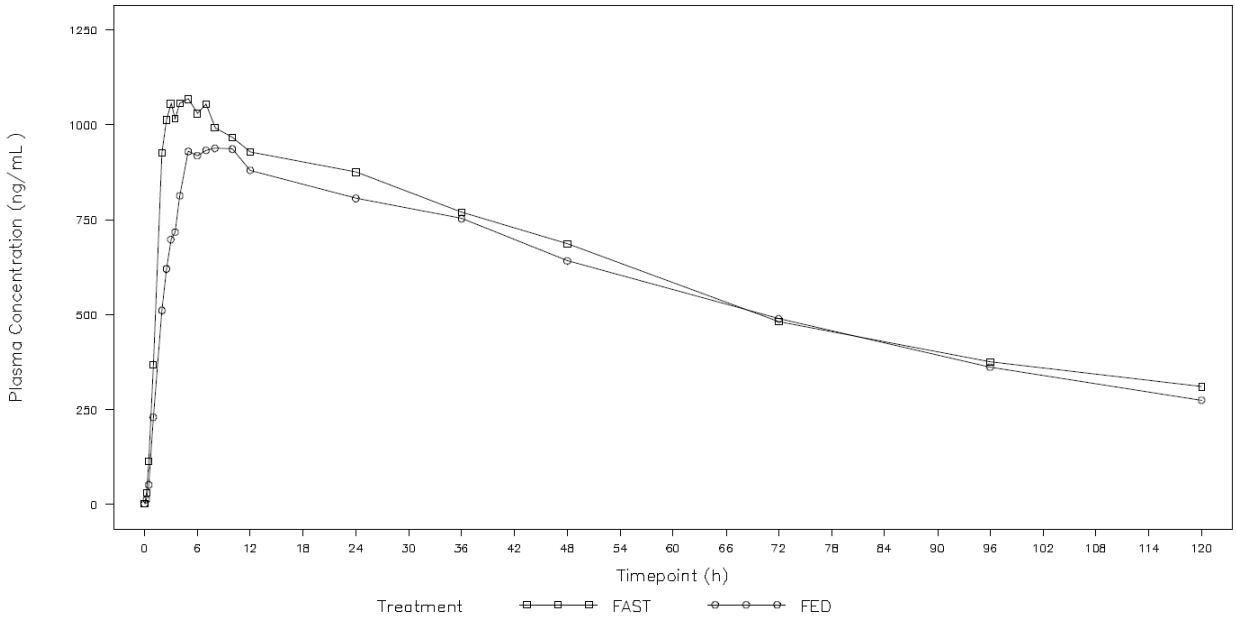
Briefly, plasma nitisinone concentrations were isolated by protein precipitation with methanol and measured using a LC-MS/MS method with electrospray ionization in negative mode and using $^{13}C_6$-nitisinone as an internal standard. The assay method had a lower quantification limit of 19.53 ng/mL using 50 µL of plasma (see details in 4.2 Bioanalytical Method Reports).

Reviewer's Comments:

- ***The bioanalytical method used to determine plasma nitisinone concentrations is acceptable.***

PHARMACOKINETIC RESULTS:

Mean nitisinone plasma concentration profiles after a single oral administration of nitisinone 10 mg tablet under fasting and fed conditions are presented below.



Statistical analyses of key PK parameters for nitisinone are summarized in the table below.

Parameter (unit)	LS Mean		Mean Ratio (Fed/Fast) (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Nitisinone (Fed)	Nitisinone (Fast)			
$AUC_{(0-120)}$ (h•ng/mL)	67508.639	70841.080	95.30	92.71 ; 97.95	4.9
$AUC_{(0-72)}$ (h•ng/mL)	49966.954	52560.003	95.07	92.70 ; 97.50	4.5
C_{max} (ng/mL)	1056.884	1159.960	91.11	86.56 ; 95.91	9.1
λ_z (1/h)	0.012	0.011	0.07	-0.05 ; 0.19	-
T_{max} (h)	6.186	3.900	228.61	104.26 ; 352.96	-
T_{max} (h)*	6.00	3.00	p-value: 0.0048		

*Median
CV = coefficient of variation; LS = least square.

The 90% confidence intervals of nitisinone 10 mg tablet fed/fasting ratios were contained entirely within the range of 0.80 to 1.25 with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

Reviewer's Comments:

- ***The Applicant evaluated AUC_{0-120h} and AUC_{0-72h} instead of AUC_{0-inf} in this BE study, due to the long half-life of nitisinone (54 hours). This approach is acceptable per the current FDA guidance. Intrasubject variability on C_{max} and AUC for nitisinone was less than 10% in this study.***

- ***The Applicant's PK analysis and food effect analysis have been repeated by the reviewer. A high-fat (approximately 50% of total caloric content) and high-calorie (approximately 800 to 1000 calories) meal did not affect the nitisinone exposure as the 90% confidence intervals of nitisinone 10 mg tablet fed/fasting ratios were contained entirely within the range of 0.80 to 1.25 with respect to C_{max} and AUC_{0-120h}. As such, the proposed dosing instruction to administer nitisinone tablets with or without food is appropriate from a Clinical Pharmacology perspective.***

4.1.2 Study CT-003

Title: **A single center, single-dose, open-label, laboratory-blind, randomized, three-period crossover study to determine the bioequivalence of two oral formulations containing nitisinone 10 mg compared to the reference formulation ORFADIN 10 mg in at least 18 healthy male and female subjects under fasting conditions.**

Sponsor:	Cycle Pharmaceuticals Ltd.
Clinical Site:	Bloemfontein Early Phase Clinical Unit, PAREXEL International, Bloemfontein, South Africa.
Bioanalytical Site:	(b) (4)
Study Date:	03/15/2016 – 05/25/2016

Study Objective:

- To determine whether the test products (nitisinone 10 mg tablets and nitisinone 10 mg tablets [6 months @ 40°C/75% RH]), and the reference product, Orfadin® 10 mg hard capsules are bioequivalent.

Study Design:

This was a single-dose, open-label, laboratory-blind, randomized, three-period crossover study with orally administered nitisinone 10 mg (2 test products and a reference product) conducted under fasting conditions in 24 healthy male and female subjects. There was a wash-out interval of at least 23 days between treatment periods.

Reviewer's Comments:

- ***A washout period of at least 23 days is reasonable, as the mean t1/2 of nitisinone in healthy subjects was reported previously as 54 hours (Orfadin label). Nitisinone pre-dose concentrations were measurable in 9 subjects in Periods 2 or 3, but were all less than 5% of the corresponding C_{max} value. All predose concentrations were included in the pharmacokinetic calculations without any adjustments. This approach is in agreement with the current FDA guidance.***

- ***The formulation composition of the proposed to-be-marketed nitisinone tablets is presented in the table below.***

(b) (4)

Reference Product:

9.4.2 Identity of Investigational Medicinal Product(s)

Reference Product (Treatment A)

Generic name	:	Nitisinone
Trade name	:	Orfadin® 10 mg
Dosage form	:	Hard capsules
Dose	:	10 mg (1 capsule)
Route of administration	:	Oral
Manufacturer	:	Apotek Produktion & Laboratorier AB
Country of origin	:	Sweden
Batch number	:	3041069
Manufacturing date	:	16 July 2015
Expiry date	:	31 January 2017
Assay content	:	97%

Source: Clinical study report for CT-003.

Excluded Medications:

Subjects were not allowed to use any concomitant medication, prescribed or over-the-counter (including hormonal contraceptives, herbal remedies), for 2 weeks before and for the duration of the study.

Study Population: Twenty-four healthy subjects (21 males and 3 females) were enrolled into this study. One female subject was withdrawn from the study during Treatment Period 1 because she vomited before 2 times the median tmax.

Pharmacokinetic Measurements:

Pharmacokinetic blood samples were collected at the following time points: at pre-dose and at 0.25, 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, and 120 hours post-dose in each treatment period.

Pharmacokinetic and Statistical Analysis:

Pharmacokinetic parameters were calculated using Phoenix WinNonlin version 6.3. Statistical analysis was performed using ANOVA with sequence, subject (sequence), treatment and period effects after logarithmic transformation of the data.

Bioanalytical Method:

Bioanalytical analysis of nitisinone in the plasma samples was performed at (b) (4) (b) (4) Plasma samples were stored at approximately -70^{o}C until analysis.

Briefly, plasma nitisinone concentrations were isolated by protein precipitation with methanol and measured using a LC-MS/MS method with electrospray ionization in negative mode and using $^{13}C_6$-nitisinone as an internal standard. The assay method had a lower quantification limit of 19.53 ng/mL using 50 μL of plasma (see details in 4.2 Bioanalytical Method Reports).

Reviewer's Comments:

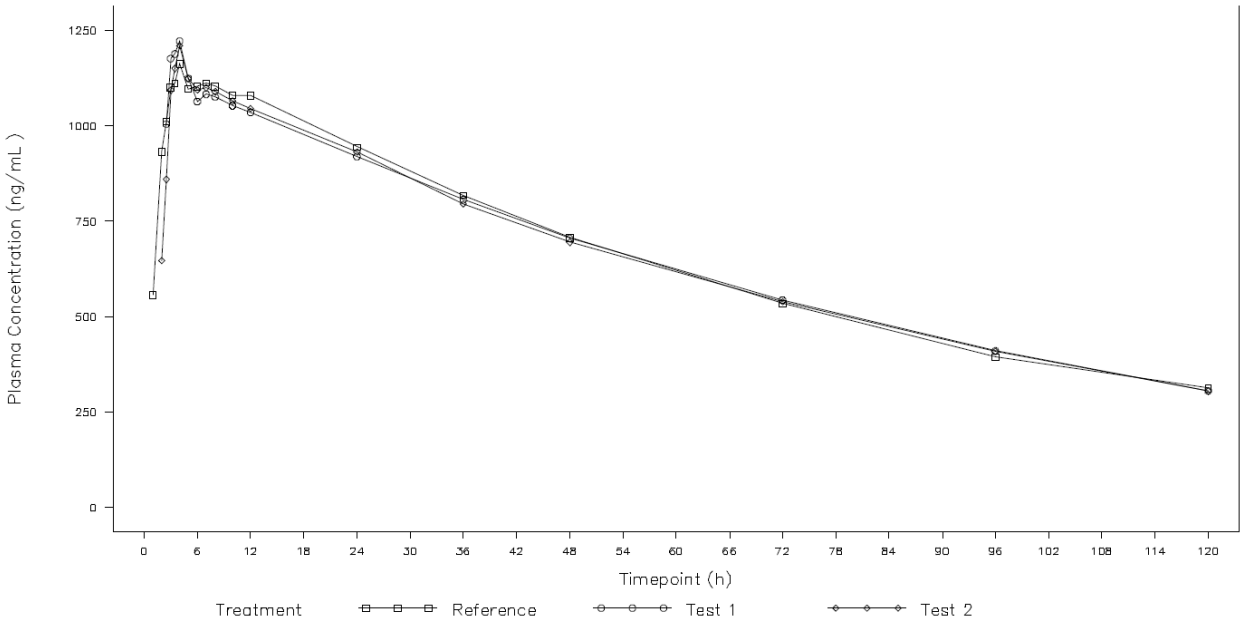
- ***The bioanalytical method used to determine plasma nitisinone concentrations is acceptable.***

- ***A request to conduct a thorough inspection of the clinical and bioanalytical sites to determine acceptability of the data for review for this pivotal BE study was submitted to the Office of Study Integrity and Surveillance (OSIS). OSIS inspection recommends that clinical data for study CT-003 be accepted for review. Bioanalytical site inspection was declined by OSIS since OSIS recently inspected the site. Based on the recent inspection results unrelated to this study, OSIS recommends accepting bioanalytical data without an on-site inspection, but also***

recommends the review division confirm that the calibration curves in the current study were representative of study sample concentrations. The calibration standard curve for study CT-003 consisted of 8 levels ranged from 19.53 to 2500 ng/mL in human plasma. Study sample concentrations contained BLQ and a quantifiable range of 20.02 to 1884 ng/mL. As such, reviewer's analysis indicates that the calibration curves were representative of study sample concentrations.

PHARMACOKINETIC RESULTS:

Mean nitisinone plasma concentration profiles after a single oral administration of nitisinone 10 mg tablet, nitisinone 10 mg tablets [6 months @ 40°C/75% RH]), and Orfadin 10 mg capsule (reference) are presented below.



Reference = Orfadin 10 mg capsule; Test 1 = nitisinone 10 mg tablet; Test 2 = nitisinone 10 mg tablet (6 months @ 40°C/75% RH).

Statistical analyses of key PK parameters for nitisinone are summarized in the table below.

PK Parameter (unit)	LS Mean			Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Orfadin® (Reference product)	Nitisinone (Test product 1)	Nitisinone (Test product 2)			
Test 1 vs Reference						
$AUC_{(0-120)}$ (h•ng/mL)	78149.092	78040.865	NA	99.86	96.34 ; 103.51	7.0
$AUC_{(0-72)}$ (h•ng/mL)	58646.164	57948.259	NA	98.81	95.63 ; 102.09	6.4
C_{max} (ng/mL)	1333.510	1278.828	NA	95.90	91.66 ; 100.34	8.9
t_{max} (h) *	2.50	3.50	NA	p-value: 0.2300		
Test 2 vs Reference						
$AUC_{(0-120)}$ (h•ng/mL)	78090.254	NA	77187.852	98.84	94.75 ; 103.11	8.3
$AUC_{(0-72)}$ (h•ng/mL)	58600.801	NA	57455.264	98.05	93.98 ; 102.28	8.3
C_{max} (ng/mL)	1332.941	NA	1273.675	95.55	91.14 ; 100.19	9.3
t_{max} (h)*	2.50	NA	3.90	p-value: 0.0258		

*Median

Reference = Orfadin 10 mg capsule; Test 1 = nitisinone 10 mg tablet; Test 2 = nitisinone 10 mg tablet (6 months @ 40°C/75% RH); CV = coefficient of variation; LS = least square.

The 90% confidence intervals of nitisinone 10 mg tablet/Orfadin 10 mg capsule ratios were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

The 90% confidence intervals of nitisinone 10 mg tablet (6 months @ 40°C/75% RH)/Orfadin 10 mg capsule ratios were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max}, AUC_{0-72h}, and AUC_{0-120h}.

Reviewer's Comments:

- ***The Applicant evaluated AUC_{0-120h} and AUC_{0-72h} instead of AUC_{0-inf} in this BE study, due to the long half-life of nitisinone (54 hours). This approach is acceptable. Per the current FDA guidance, an AUC truncated at 72 hours (AUC_{0-72h}) can be used in place of AUC_{0-t} or AUC_{0-inf} for drugs that demonstrate low intrasubject variability in distribution and clearance. Intrasubject variability on C_{max} and AUC for nitisinone is less than 10%.***

- ***The Applicant's PK analysis and bioequivalence analysis have been repeated by the reviewer. Reviewer's results confirmed the Applicant's conclusion that the 90% confidence intervals of nitisinone 10 mg tablet/Orfadin 10 mg capsule ratios were contained entirely within the bioequivalence range (0.80 to 1.25) with respect to C_{max} and AUC, for both nitisinone 10 mg tablet and aged nitisinone 10 mg tablet (6 months @ 40°C/75% RH).***

4.2 Bioanalytical Method Reports

Bioanalytical Method Validation Report:

Bioanalytical analysis of nitisinone in the plasma samples was performed at (b) (4) (b) (4) Plasma samples were stored at approximately -70°C until analysis.

Plasma nitisinone concentrations were isolated by protein precipitation with methanol and measured using a LC-MS/MS method with electrospray ionization in negative mode and using $^{13}C_6$-nitisinone as an internal standard. The assay method had a lower quantification limit of 19.53 ng/mL using 50 µL of plasma.

Assay validation calibration standard curve consisted of 8 levels ranged from 19.53 to 2500 ng/mL in human plasma, and was calculated using weighted (1/x) linear regression. The R^2 ranged between 0.9988 and 0.9995.

Precision (% CV) for the calibration standards ranged from 2.2% to 5.7%, while accuracy (% Bias) ranged from -2.8% to 1.9%. Stability of nitisinone in human plasma was demonstrated to be 18.1 hours at room temperature and 83 days at ~ -70 ºC. Stability was shown up to three freeze-thaw cycles. No matrix interference was noted. Dilution integrity was demonstrated for a 2-fold dilution.

Bioanalytical Study Report for CT-001:

Calibration standard curve for study CT-001 consisted of 8 levels ranged from 19.53 to 2500 ng/mL in human plasma, and the R^2 ranged between 0.9908 and 0.9997. Quality control samples at 5 different concentrations (50.00, 150.0, 500.0, 1000, and 2000 ng/mL) were prepared.

Precision (% CV) for the calibration standards for this study ranged from 4.3% to 7.5%, while precision for the quality controls ranged from 4.3% to 7.4%. Accuracy (% Bias) ranged from –0.6% to 0.8% for calibration standards, and -3.7% to -1.3% for quality controls.

No interfering peaks were detected at the expected retention time of the analyte or internal standard. 128 samples (8.8% of a total of 1458 samples) were included in the incurred sample reanalysis, and at least 95.3% of the repeat results and original results were within 20% of each other. There were 19 samples (1.3% of a total of 1458 samples) reanalyzed, including 10 samples with a quantifiable concentration at pre-dose, 2 samples with incongruous BLQ between two quantifiable concentrations, and 7 for analytical reasons (i.e., internal standard deviation, sample lost in process, or analytically suspect).

Bioanalytical Study Report for CT-002:

Calibration standard curve for study CT-002 consisted of 8 levels ranged from 19.53 to 2500 ng/mL in human plasma, and the R^2 ranged between 0.9957 and 0.9996. Quality control samples at 5 different concentrations (50.00, 150.0, 500.0, 1000, and 2000 ng/mL) were prepared.

Precision (% CV) for the calibration standards for this study ranged from 2.0% to 9.5%, while precision for the quality controls ranged from 4.8% to 13.9%. Accuracy (% Bias) ranged from -4.3% to 3.4% for calibration standards, and -7.4% to -2.1% for quality controls.

No interfering peaks were detected at the expected retention time of the analyte or internal standard. 84 samples (10.3% of a total of 817 samples) were included in the incurred sample reanalysis, and at least 96% of the repeat results and original results were within 20% of each other. There were 11 samples (1.3% of a total of 817 samples) reanalyzed, including 5 samples with a quantifiable concentration at pre-dose and 6 samples for analytical reasons (i.e., internal standard deviation, sample lost in process, or analytically suspect).

Bioanalytical Study Report for CT-003:

Calibration standard curve for study CT-003 consisted of 8 levels ranged from 19.53 to 2500 ng/mL in human plasma, and the R^2 ranged between 0.9962 and 0.9999. Quality control samples at 5 different concentrations (50.00, 150.0, 500.0, 1000, and 2000 ng/mL) were prepared.

Precision (% CV) for the calibration standards for this study ranged from 2.1% to 5.2%, while precision for the quality controls ranged from 2.4% to 7.3%. Accuracy (% Bias) ranged from -1.0% to 0.6% for calibration standards, and 3.2% to 5.7% for quality controls.

No interfering peaks were detected at the expected retention time of the analyte or internal standard. 126 samples (8.7% of a total of 1450 samples) were included in the incurred sample reanalysis, and at least 96.8% of the repeat results and original results were within 20% of each other. There were 16 samples (1.1% of a total of 1450 samples) reanalyzed, including 9 samples with a quantifiable concentration at pre-dose, 2 samples with an upward trend at the last timepoint, 1 sample with incongruous BLQ between two quantifiable concentrations, and 4 for analytical reasons (i.e., above limit of quantification, sample lost in process, or analytically suspect).

Reviewer's Comments:

- ***The bioanalytical method used to determine plasma nitisinone concentrations is acceptable.***

4.3 OSIS Inspection Reports

4.3.1 Clinical Site for Study CT-003

M E M O R A N D U M

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

DATE: April 24, 2017

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Surveillance Inspection of PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of study PXL227430 (CT-003) conducted at PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa. At the conclusion of the inspection, no significant deficiencies were observed and no Form FDA 483 was issued. The final classification is No Action Indicated (NAI). After review of the establishment inspection report (EIR) and the inspectional findings, I found the clinical data from the audited study to be reliable. Therefore, I recommend that the data from the clinical portion of Study PXL227430 (CT-003) submitted to NDA 209449 be accepted for further agency review.

Audited Study

NDA 209449
Study Number#: PXL227430 (CT-003)

Study Title: "A Single Center, Single-Dose, Open-Label, Laboratory-Blind, Randomized, Three-Period Crossover Study To Determine The Bioequivalence Of Two Oral Formulations Containing Nitisinone 10 Mg Compared To The Reference Formulation Orfadin® 10 Mg In At Least 18 Healthy Male And Female Subjects Under Fasting Conditions"

Study Dates: March 15 – May 25, 2016

The ORA investigator James M. Mason (PHI-DO) audited the clinical portion of the in vivo bioequivalence study at PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa from March 27-30, 2017.

The inspection included a review of the study protocol, IRB submissions and approvals, informed consent forms (ICFs), case report forms, source documents, adverse event reporting, drug accountability, employee training, and interviews and discussions with the firm's management and staff. No significant deficiencies were observed and no Form FDA 483 was issued at the conclusion of the inspection. Reserve samples were collected and sent to CDER-DPA, St. Louis, MO for analysis.

Recommendations:

After review of the EIR and the inspectional findings, the audited study was found to be reliable. Therefore, I recommend that the data from the clinical portion of Study PXL227430 (CT-003) be accepted for further agency review.

Srinivas R. Chennamaneni, Ph.D.
DNDBE, OSIS

Final Classification:

Clinical Site
NAI: PAREXEL Bloemfontein Early Phase Clinical Unit, Kampuslaan Suid, Bloemfontein, South Africa (FEI# 3010924245)

CC:
OTS/OSIS/Kassim/Choe/Taylor/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Choi/Skelly/Au
OND/ODEIII/DGIEP/Vu/Bashaw/Griebel
ORA/PHI-DO/Mason/Karnick

Draft: SRC 4/21/2017
Edit: GB 4/21/2017; CB 4/23/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ PAREXEL Bloemfontein Early Phase Clinical Unit, Bloemfontein, South Africa/NDA 209449_Nitisinone Tab, 10 mg

BE File #: 7328
FACTS: 11706081

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/s/

SRINIVAS RAO N CHENNAMANENI
04/24/2017

GOPA BISWAS
04/24/2017

CHARLES R BONAPACE
04/25/2017

Reference ID: 4088511

4.3.1 Bioanalytical Site for Study CT-003

MEMORANDUM

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

DATE: 2/24/2017

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Decline to Conduct Biopharmaceutical Inspection**

RE: NDA 209449

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below under NDA 021292/S-004. The last inspection was classified as a VAI because the calibration curve was not representative of the study sample concentrations, and OSIS recommended to reject the analytical data unless the firm reanalyzed the subject samples.

Typically, OSIS will conduct a re-inspection involving studies that were conducted after the last inspection in order to confirm corrective actions. However, the conduct dates of the current study were prior to the last inspection. Therefore, OSIS is unable to use the current study in NDA 209449 to confirm that the firm implemented corrective actions.

OSIS recommends the review division confirm that the calibration curves in the current study were representative of study sample concentrations during their data review.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

Reference ID: 4060707

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/s/

SHILA S NKAH
02/24/2017

Reference ID: 4060707

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEN LI
06/28/2017

INSOOK KIM
06/28/2017