CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209661Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 209661	Submission Dates: 10/7/2015, 11/20/2015, 3/24/2016, 5/25/2016, 5/26/2016, 5/31/2016, 6/13/2016, and 10/13/2016
Brand Name:	TRADENAME
Generic Name:	Doxylamine succinate, Pyridoxine hydrochloride
Clinical Pharmacology Primary Reviewer:	Chongwoo Yu, PhD
Clinical Pharmacology Division Director:	E. Dennis Bashaw, PharmD
OCP Division:	Division of Clinical Pharmacology 3 (DCP-3)
OND Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor:	Duchesnay Inc.
Submission Type:	Original / 505(b)(2)
Formulation, Strength, and Dosing Regimen	Extended-release tablet; One 20 mg doxylamine succinate/20 mg pyridoxine hydrochloride tablet daily at bedtime, if not effective, one tablet in the morning and one tablet at bedtime
Indication:	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management

A Required Office Level Clinical Pharmacology Briefing was held on Thursday, June 9, 2016. The attendees were as follows: C. Yu, M-J Kim, E. D. Bashaw, H. Y. Ahn, I. Zineh, T. Van Der Vlugt, N. McNeal-Jackson, S. Slaughter, H. Joffe, A. Gassman, J. Beitz, G. Lyght, J. Shon, M. Ahn, L. Zhang, M. Pacanowski, M. Mehta, D. Abernethy, R. Madabushi, L. Oh, Y. Lu, G. Fernandez, and K. Hatfield.

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1 Executive Summary

The Sponsor submitted a 505(b)(2) new drug application (NDA) to seek approval of new strength, dosage regimen, and formulation (i.e., 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride tablet) for Diclegis® for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management.

Diclegis® is a fixed dose combination drug product containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride as a delayed release (DR) tablet. It was approved for the treatment of NVP in women who do not respond to conservative management under NDA 021876 on April 8, 2013. The approved starting dose is 2 tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, patients should continue taking 2 tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, patients should take the usual dose of 2 tablets at bedtime that night then take 3 tablets starting on Day 3 (i.e., 1 tablet in the morning and 2 tablets at bedtime). If these 3 tablets adequately control symptoms on Day 4, patients should continue taking 3 tablets daily. Otherwise, patients should take 4 tablets starting on Day 4 (i.e., 1 tablet in the morning, 1 tablet mid-afternoon, and 2 tablets at bedtime). This staggered dosing regimen is designed to both minimize the sedating effect of the doxylamine component and to reduce the incidence of "morning sickness." The maximum recommended dose is 4 tablets daily. Diclegis® should be given on an empty stomach with a glass of water.

The new product, TRADENAME contains 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. TRADENAME consists of an enteric-coated core containing 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride. (b) (4) . An immediate release (IR) layer of 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride is added to the enteric-coated core. As noted above the current Diclegis® formulation was classified as a DR tablet while TRADENAME will be classified as an ER tablet. The Sponsor intends to (b) (4) The proposed new dosing regimen will be one TRADENAME tablet orally at bedtime (Day 1). If the symptoms are controlled, patients should continue taking one TRADENAME tablet orally at bedtime every day. If symptoms persist (b) (4) take two tablets starting on Day (b) (4) (one tablet in the morning and one tablets at bedtime). Therefore, under the proposed new regimen, patients will start maximum daily dose of 40 mg doxylamine succinate and 40 mg pyridoxine hydrochloride from Day (b) (4) (b) (4) when symptoms are not controlled with the initial doses. Thus, it should be noted that the currently approved intermediate daily dose of 30 mg doxylamine succinate / 30 mg pyridoxine hydrochloride for Diclegis® will not be available via the new formulation, TRADENAME.

In this current NDA, the Sponsor submitted 3 Clinical Pharmacology studies including a single dose bioequivalence (BE) study (Study 150336), a multiple dose BE study (Study 150033), and a food effect study (Study 140115). The to-be-marketed (TBM) formulation of TRADENAME was used in these 3 studies. Diclectin® (i.e., Diclegis® is sold under the name Diclectin® in Canada but the two are identical products) was used as the reference listed drug (RLD) in the pivotal BE study.

For the multiple dose BE study (Study 150033), a formal consult to the Office of Study Integrity and Surveillance (OSIS) was made on January 4, 2016 for inspections of the clinical and bioanalytical study sites. An OSIS memorandum was issued on February 22, 2016 with a recommendation to accept the data without on-site inspection, based on previous inspection

findings.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 209661 submitted on October 7, 2015, November 20, 2015, March 24, 2016, May 25, 2016, May 26, 2016, May 31, 2016, June 13, 2016, and October 13, 2016. The overall Clinical Pharmacology information submitted to support this NDA is **acceptable** and the proposed product, TRADENAME is **recommended for approval** from the Clinical Pharmacology standpoint.

1.2 Post-marketing Requirements or Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Formulation
TRADENAME contains 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. TRADENAME consists of an enteric-coated core containing 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride. (b) (4) An IR layer of 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride is added as an outer layer to the enteric-coated core.

BE Assessment
Single Dose BE Study
Single dose BE between TRADENAME tablets and Diclectin® tablets was assessed in a single-center, open-label, randomized, 2-way crossover study (Study 150336) conducted in 52 healthy premenopausal females (48 completed; 20-45 years of age) with a body mass index (BMI) within the range of 19.3-29.8 kg/m^2.

In each period, according to randomization schedule, all subjects received single oral doses of either Test or Reference study medication as follows:

- Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride), at between 7-8 am
- Reference: Two Diclectin® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride), at between 7-8 am

It should be noted that Diclectin® and Diclegis® are two different trade names of the same drug product. Diclegis® is sold under the name Diclectin® in Canada.

The point estimates and 90% confidence intervals (CIs) for the difference between the Test and Reference with respect to doxylamine for the parameters, AUC(0-24) and C_{max} using natural log transformed data are summarized in Table 1.

Table 1: Summary of BE Analysis Results of Doxylamine Pharmacokinetic (PK) Parameters Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) (Study 150336; N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-60) (ng·hr/mL)	1325.3	1301.4	102.0	98.4-105.7
AUC(0-inf) (ng·hr/mL)	1375.6	1353.9	101.7	98.1-105.5
C_{max} (ng/mL)	91.0	96.7	94.2	90.8-97.7

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

The point estimates and 90% CIs for the difference between the Test and Reference with respect to pyridoxal 5′-phosphate for the baseline corrected parameters, AUC(0-72) and C_{max} using natural log transformed data are summarized in Table 2.

Table 2: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) (Study 150336; N=48)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-72) (ng·hr/mL)	1006.9	964.9	104.2	97.9-111.0
C_{max} (ng/mL)	28.8	27.5	104.8	101.1-108.7

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Based on these results, it was concluded that BE regarding the rate and extent of both doxylamine and baseline corrected pyridoxal 5′-phosphate exposures between the TRADENAME and Diclectin® was established following a single dose of 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride.

Multiple Dose BE Study

Multiple dose BE between TRADENAME tablets and Diclegis® tablets was assessed in an open-label, randomized, 3-period, 3-sequence, reference replicated, crossover study (Study 150033) conducted in 39 healthy premenopausal females (31 completed; 18-45 years of age).

In each period, according to randomization schedule, all subjects received multiple oral doses of either Test or Reference study medication for 11 consecutive days as follow:

- Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride), BID (1 tablet each at 9 am and 9 pm)
- Reference: Diclectin® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet each at 9 am and 3 pm and 2 tablets at 9 pm)

The point estimates and 90% CIs for the difference between the Test and Reference with respect to doxylamine for the parameters AUC(0-24) and C_{max} on Days 1 and 11 using natural log transformed data are summarized in Tables 3 and 4.

Table 3: Summary of BE Analysis Results of Doxylamine PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 1 (Study 150033; N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	1397.1	1010.6	140.0	130.2-150.6
C_{max} (ng/mL)	92.3	117.0	79.6	76.1-83.2

[a] Median (minimum-maximum)

Table 4: Summary of BE Analysis Results of Doxylamine PK Parameters
Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 11 (Study 150033; N=34)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	2802.2	2720.4	99.1	95.7-102.5
C_{max} (ng/mL)	168.3	155.6	105.3	100.9-109.9

[a] Median (minimum-maximum)

The point estimates and 90% CIs for the difference between the Test and Reference with respect to baseline corrected pyridoxal 5′-phosphate for the parameters AUC(0-24) and C_{max} on Days 1 and 11 using natural log transformed data are summarized in Tables 5 and 6.

Table 5: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters
Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 1 (Study 150033; N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	644.8	406.1	161.5	147.6-176.7
C_{max} (ng/mL)	42.5	40.4	105.6	99.6-112.0

[a] Median (minimum-maximum)

Table 6: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters
Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 11 (Study 150033; N=34)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	1661.5	1657.4	100.1	95.8-104.5
C_{max} (ng/mL)	82.2	81.4	100.8	96.7-105.0

[a] Median (minimum-maximum)

BE was established for both doxylamine and baseline corrected pyridoxal 5′-phosphate based on AUC(0-24) and C_{max} on Day 11 but not for Day 1 in Study 150033. While Study 150033 assessed the BE between the maximum daily doses of TRADENAME BID and Diclectin® TID (i.e., 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride per day) on Day 1 and Day 11, it lacks the bridging for the proposed starting dose of TRADENAME (i.e., one 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride tablet) to the currently approved starting dose for Diclegis® (i.e., two 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride tablets). Establishment of bridging for the starting dose is important as patients will remain on this initial dose if symptoms are controlled. This was addressed in Study 150336.

Pharmacokinetics (PK)

Doxylamine and pyridoxine are absorbed in the gastrointestinal tract, mainly in the jejunum. The C_{max} of doxylamine, pyridoxine, and pyridoxal 5′-phosphate for TRADENAME were achieved within 4.5, 0.5, and 9.0 hours, respectively, following a single dose of TRADENAME tablets under fasting condition. The C_{max} of doxylamine, pyridoxine, and pyridoxal 5′-phosphate for TRADENAME were achieved within 3.5, 1.5, and 15.0 hours, respectively, following the maximum daily dose of 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride (i.e., 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride given twice daily) for 11 days.

Food Effect

Food effect was assessed in a 2-way crossover study (Study 140115) in 24 healthy premenopausal females. Food caused a delay in the median T_{max} of doxylamine and pyridoxine 5-phosphate to 6.5 and 16.0 hours, respectively. In addition, food decreased the C_{max} for doxylamine by 26.4%. TRADENAME tablets should be administered under fasting conditions to avoid food affecting the rate of absorption (i.e., T_{max}) and the extent of exposure (i.e., C_{max} and AUC). Summary of food effect assessments are shown in Tables 7 and 8.

Table 7: Summary of Geometric Means, Point Estimates, and 90% CI of Doxylamine PK Parameters following a Single dose of a TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	1219.1	1247.0	97.6	93.6-101.7
AUC(0-inf) (ng·hr/mL)	1253.5	1289.1	97.0	92.9-101.3
C_{max} (ng/mL)	62.7	85.3	73.6	68.0-79.8

Table 8: Summary of Geometric Means, Point Estimates, and 90% CI of Baseline Corrected Pyridoxal 5′-phosphate PK Parameters following a Single dose of a TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	1005.4	975.1	103.4	95.6-111.8
C_{max} (ng/mL)	28.7	26.4	109.3	103.4-115.5

Distribution, Metabolism, and Excretion

No new distribution, metabolism, and excretion studies were conducted with TRADENAME. Distribution, metabolism, and excretion of doxylamine and pyridoxine are expected to be the same as those from Diclegis®. The Sponsor is proposing to use the information regarding doxylamine and pyridoxine distribution, metabolism, and excretion from Diclegis® for labeling.

Drug-Drug Interactions (DDI)

No new DDI studies were conducted with TRADENAME. The Sponsor is proposing to use the information used regarding DDI from Diclegis® for labeling.

Use in Specific Populations

- Pediatric use: No pediatric studies were conducted with TRADENAME. The Agency's Pediatric Review Committee (PeRC) granted a partial waiver for studies in (b) (4) patients 0-11 years of age and granted a deferral in (b) (4) patients 12-17 years of age on July 6, 2016.
- Renal or hepatic impairment: No studies were conducted with TRADENAME in patients with renal or hepatic impairment.

Bioanalytical Methods

Acceptance criteria and method performance for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate concentration measurements are in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods are acceptable.

Bioanalysis was conducted at the (b) (4). Study samples were analyzed using a validated liquid chromatography - tandem mass spectrometry (LC-MS/MS) method for the determination of doxylamine, pyridoxine, and pyridoxal 5′-phosphate concentrations in human plasma and for determination of pyridoxal concentrations in human whole blood in Studies 150336, 150033, and 140115.

Incurred sample reanalysis (ISR) was conducted on 6.9-7.3% of the study samples for each analyte in Study 150336, 5.6-5.8% of the study samples for each analyte in Study 150033, and 8.8-9.2% of the study samples for each analyte in Study 140115, respectively. More than 95.8% of the ISR results from the Study 150336, more than 96.1% of the ISR results from Study 150033, and more than 89.7% of the ISR results from Study 140115 met the acceptance criteria of being within ±20% of the original reported concentration value for at least 67% of the ISR samples.

For the multiple dose BE study (Study 150033), a formal consult to the OSIS was made on January 4, 2016 for inspections of the clinical and bioanalytical study sites. An OSIS memorandum was issued on February 22, 2016 with a recommendation to accept the data without on-site inspection based on previous inspection findings.

2 Question Based Review

2.1 General Attributes

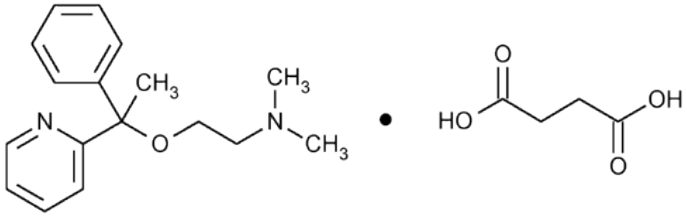
2.1.1 What are TRADENAME tablets and what are its active pharmacological ingredients?

TRADENAME is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B6 analog, indicated for the treatment of NVP in women who do not respond to conservative management.

TRADENAME is an ER tablet that consists of an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and an outer IR [redacted] (b) (4) coating of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride (i.e., a total dose of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride per TRADENAME tablet).

Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1). The empirical formula is $C_{17}H_{22}N_2O \bullet C_4H_6O_4$ and the molecular mass is 388.46. The structural formula is shown in Figure 1:

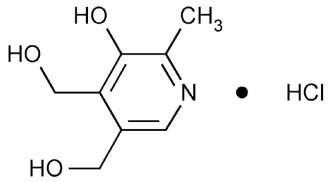
Figure 1: Structural Formula of Doxylamine Succinate



Doxylamine succinate is a white to creamy white powder that is very soluble in water and alcohol, freely soluble in chloroform and very slightly soluble in ether and benzene.

Pyridoxine hydrochloride is a vitamin B6 analog. The chemical name for pyridoxine hydrochloride is 3,4-pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride. The empirical formula is $C_8H_{11}NO_3 \bullet HCl$ and the molecular mass is 205.64. The structural formula is shown in Figure 2:

Figure 2: Structural Formula of Pyridoxine Hydrochloride



Pyridoxine hydrochloride is a white or practically white crystalline powder that is freely soluble in water, slightly soluble in alcohol and insoluble in ether.

2.1.2 What are Diclegis® and Diclectin® tablets and what are their active pharmacological ingredients?

Diclegis® is a fixed dose combination drug product containing 10 mg doxylamine succinate, an antihistamine, and 10 mg pyridoxine hydrochloride, a vitamin B6 analog for the treatment of NVP in women who do not respond to conservative management. Diclegis® formulation is classified as a DR tablet. Per Sponsor, the DR action of Diclegis® permits the nighttime dose to be effective in the morning hours.

It was originally approved in 1956 under the tradename Bendectin® (NDA 010598) and was subsequently removed from the U.S. market in 1983 due to reports of its potential teratogenic effect. Since its removal from the market, additional research including a number of epidemiological and reproductive animal studies demonstrated that the existence of a teratogenic risk posed by this combination has not been demonstrated. It should be noted that during the period that the combination prescription product was off of the market, both entities were available over-the-counter (OTC) as separate products. Doxylamine is available as sleeping aide (e.g., Unisom 25 mg tablets) and pyridoxine is available by several suppliers (e.g., tablets and capsules ranging 25-500 mg) as a dietary supplement.

This fixed dose combination product was reintroduced as Diclegis® and was approved under NDA 021876 on April 8, 2013. NDA 021876 included the following:

- Single and multiple dose PK study (Study 70281)
- Food effect study (Study 70294)
- Phase 3, efficacy and safety study (Study DIC-301)
- Relative bioavailability (BA) study between Diclegis® tablets and a combined oral solution (Study 02163)

The approved starting dose is 2 tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, patients should continue taking 2 tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, patients should take the usual dose of 2 tablets at bedtime that night then take 3 tablets starting on Day 3 (i.e., 1 tablet in the morning and 2 tablets at bedtime). If these 3 tablets adequately control symptoms on Day 4, patients should continue taking 3 tablets daily. Otherwise, patients should take 4 tablets starting on Day 4 (i.e., 1 tablet in the morning, 1 tablet mid-afternoon, and 2 tablets at bedtime). The maximum recommended dose is 4 tablets daily. Diclegis® should be given on an empty stomach with a glass of water.

Diclectin® and Diclegis® are two different tradenames of the same drug product. Ten (10) mg doxylamine succinate and 10 mg pyridoxine hydrochloride DR tablets are sold under the name Diclectin® in Canada and under the name Diclegis® in the United States. Even though both names are mentioned throughout this review, it refers to the same Reference product.

Reference is made to Dr. Sayed Al Habet's Clinical Pharmacology reviews dated March 4, 2013 and April 5, 2013 under NDA 021876 for detail information regarding the basis for the original approval.

2.2 General Clinical Pharmacology

2.2.1 What is the relevant Clinical Pharmacology information submitted in this NDA?

This NDA contains the following:

- Draft product label in physician labeling rule (PLR) format

- Information on the composition of drug products used in the clinical studies
- Full clinical study reports of 3 Clinical Pharmacology studies
- Bioanalytical study reports and method validation reports
- (b) (4) for pediatric studies

The Clinical Pharmacology studies submitted to this NDA are summarized in Table 9.

Table 9: Summary of Clinical Pharmacology Studies Submitted in this NDA

Study	Objective	Population	Dosing Regimen	Design
150336 TBM formulation	Single dose (starting dose) BE	52 healthy premenopausal females (20-45 yrs)	The following treatments were given as a single dose under fasting condition: Treatment A: 1 x 20 mg/20 mg TRADENAME ER tablet Treatment B: 2 x 10 mg/10 mg Diclectin® tablets	Open-label, single dose, 2-way crossover study
150033 TBM formulation	Multiple dose (maximum dose) BE	39 healthy premenopausal females (20-45 yrs)	The following treatments were given for 11 consecutive days under fasting condition: Treatment A: TRADENAME ER tablets, BID Treatment B: Diclectin® tablets, TID	Open label, multiple dose, 3-period, 3-sequence reference replicated, crossover study
140115 TBM formulation	Food Effect	24 healthy premenopausal females (18-44 yrs)	Single dose of the following treatments were given: Treatment A: TRADENAME ER tablet (fed) Treatment B: TRADENAME ER tablet (fasted)	Open label, single dose, two treatment, two-way crossover study

2.2.2 Was this NDA fileable from the Clinical Pharmacology perspective?

No. The Clinical Pharmacology review team found the Clinical Pharmacology section of this NDA not fileable for the following reason:

> *In the proposed label for TRADENAME, patients will start with a 20 mg/20 mg daily dose (one tablet at bedtime) and may remain with this regimen if symptoms are adequately controlled. Per survey results for Diclegis® (provided by the Sponsor in the meeting package submitted in 2013), about 20% of study subjects may stay at the 20 mg/20 mg daily dose. However, no BE assessment was conducted for this dosing regimen. Therefore, whether safety and efficacy of TRADENAME will be similar to those of Diclegis® at dosing regimen of 20 mg/20 mg is not known.*

It was decided at the multi-disciplinary review team meeting held on December 1, 2015 that failure to demonstrate BE on Day 1 in Study 150033 will be a review issue and this NDA is fileable. Reference is made to Dr. Li Li's Clinical Pharmacology Filing Review dated December 4, 2015 under NDA 209661 for detail information.

2.2.3 What is the proposed mechanism of action?

Morning NVP is a common condition that affects 70-85% of pregnant women. The etiology of NVP is unknown. Whereas changes in nutrition and lifestyle may alleviate the symptoms for some women, pharmacotherapy is needed in many cases.

Doxylamine is an antihistamine and pyridoxine is one form of vitamin B6. Both compounds, although unrelated, provide anti-nauseant and anti-emetic activity. As described in the current Diclegis® product label, pyridoxine is a pro-drug primarily metabolized in the liver to its metabolites that contribute to the anti-nauseant and anti-emetic pharmacological activity.

While the mechanism of action of Diclegis® and TRADENAME is unknown, the American College of Obstetricians and Gynecologist (ACOG) (2015) recommends therapy with pyridoxine

or pyridoxine plus doxylamine in patients where conservative measures, such as dietary and lifestyle modifications, have failed.

2.2.4 What is the Sponsor's rationale of developing TRADENAME?

Sponsor believes that the new formulation, TRADENAME will have the following advantages:

- Reduced variation of doxylamine and pyridoxal 5′-phosphate concentrations at steady state
- Improved patient compliance by reducing the number of tablets from 4 to 2 tablets daily
- A faster rate of absorption delivered by the IR portion in the coating layer while maintaining the extent and exposure of the DR

2.2.5 What are the administration instructions and dosage regimen for TRADENAME?

The proposed dosage regimen is one TRADENAME tablet orally at bedtime (Day 1). If the symptoms are controlled, patients should continue taking one TRADENAME tablet orally at bedtime every day. If symptoms persist (b) (4) take two tablets starting on Day (b) (4) (one tablet in the morning and one tablets at bedtime). Therefore, under the proposed new regimen, patients will start maximum daily dose of 40 mg doxylamine succinate and 40 mg pyridoxine hydrochloride from Day (b) (4) (b) (4) when symptoms are not controlled with the initial doses. Thus, it should be noted that the currently approved intermediate daily dose of 30 mg doxylamine succinate / 30 mg pyridoxine hydrochloride for Diclegis® will not be available via the new formulation, TRADENAME.

2.2.6 What analytes were the Sponsor's BE assessment based on and what was the rationale?

Sponsor performed their BE assessment based on doxylamine and pyridoxal 5′-phosphate. The Sponsor was asked to provide their rationale as to why the BE assessment was based on metabolite, pyridoxal 5′-phosphate rather than the parent drug, pyridoxine. In their March 24, 2016 response, the Sponsor provided the following rationale:

> *"While a BE assessment should always be performed on the active ingredient whenever possible, in this case pyridoxine acts as a pro-drug. Once phosphorylated, it crosses the membranes much easier and therefore, is absorbed very fast (i.e., less than 2.5 hrs in its DR form; the half-life is extremely fast, less than 15 mins). This type of kinetics makes it challenging to measure appropriately and furthermore because of the fast elimination there is no accumulation and therefore no steady state is reached and therefore no steady state value to compare.*
>
> *Furthermore, the current formulation of Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) is ideal for the night dose (around 10 pm), in that the DR allows maximum concentrations of pyridoxine in the systemic circulation to be reached at around 2 am. Pyridoxine will be converted into pyridoxal by 3 am which will be then converted to pyridoxal 5'-phosphate which will reach maximum concentrations around 9 am. It is unlikely that pyridoxine and pyridoxal are the active vitamin B6 metabolites acting on morning NVP since by 8 am there is no pyridoxine in the systemic circulation due to a short half-life and pyridoxal concentrations are almost negligible. Therefore,*

pyridoxal 5'-phosphate is believed to be the most active component against NVP reaching peak concentrations at around 9 am."

While the mechanism of action is unknown (See Section 2.2.3), it appears that the Sponsor's rationale regarding T_{max} does not account for doxylamine while TRADENAME is a combination product of doxylamine and pyridoxine.

The following information request was made to the Sponsor via the filing communication letter dated December 18, 2015 and an information request letter dated March 16, 2016:

"Submit supporting information that different shapes of PK profiles on Day 11 following multiple doses of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets and Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) delayed-release administration will not significantly affect the safety and efficacy of the drug product. If available, submit the dose-response or concentration-response data to support your justification."

The Sponsor also submitted the following response on March 24, 2016:

"In reference to the shapes of PK profiles, it is important to consider the following:

- *In the BE Study 150033, AUC(0-24) as well as AUC(0-12), and AUC(0-6) were measured at steady state on Day 11 to ensure that throughout the day the patient would have the same exposure during all 3 concentration-time profiles. The PK results from this study show equivalent AUC values between Diclegis® and TRADENAME. These measurements are more indicative of exposure variations than shapes of PK profiles.*
- *In addition, Diclegis® under fed vs. fasted conditions showed T_{max} for doxylamine varying from 14.9 ± 7.4 hrs (fed) vs. 5.1 ± 3.4 hrs (fasting), respectively. These results indicate that, Diclegis® time-to-peak varies from 5 hrs when fasting to 15 hrs after food intake. Food creates a variation in T_{max}, C_{max}, and AUC, therefore, the variation observed on Day 11 is not a variation of Diclegis® vs. TRADENAME.*
- *In single dose administration the T_{max} for Diclegis® and TRADENAME are the same. Hence, variations between morning vs. evening in T_{max} present within formulation are as high as between formulations.*
- *In addition, the posology also allows for additional variation: daily doses are not prescribed at specific times but rather morning and mid-afternoon.*

In light of this, it can be concluded that there is no difference in the PK profiles of Diclegis® and TRADENAME in terms of AUC, T_{max}, and C_{max} and therefore, the safety and efficacy of TRADENAME is similar to Diclegis®.

Furthermore, Diclegis® is not given as an acute treatment; it is a treatment based on attainment of steady state levels. In the Clinical Phase 3 trial, A Double-Blind, Multicenter, Randomized, Placebo-Controlled Trial of the Efficacy of Diclectin® for Nausea and Vomiting of Pregnancy efficacy was demonstrated based on daily clinical outcome, not hourly, using the Pregnancy Unique-Quantification of Emesis (PUQE) score, a validated scoring system which

quantifies the severity of NVP. Based on pharmacokinetic (PK) modeling and taking the food effect into consideration, the 8 am dose of Diclegis®, only reaches maximum systemic levels at 8 pm for doxylamine whereas pyridoxal 5'-phosphate levels were maximal at 11 pm. Furthermore, the mid-afternoon (4 pm) dose reaches maximum doxylamine levels at 12 pm and maximum pyridoxal 5'-phosphate levels at 3 pm. Therefore, Diclegis® is not acting on daily NVP symptoms. Due to this gap between maximal dosage levels, optimum dose levels at steady state are reached only after 4 days based on a half-life of 12 and 60 hrs for doxylamine and pyridoxal 5'-phosphate, respectively.

A study demonstrated an inverse relationship between doxylamine or pyridoxal 5-phosphate (PLP) plasma levels, the active components in the treatment of NVP and the PUQE scores (Matok et al., 2014). The concentration-response data is presented in the Figure 3 below:

Figure 3: Correlation between plasma levels of Doxylamine and Pyridoxal 5-Phosphate (PLP) vs. change in Pregnancy Unique-Quantification of Emesis (PUQE) score

In terms of safety, in the BE study, comparison of the adverse drug reactions between formulations did not show more sedation with the TRADENAME formulation."

Dr. Theresa van der Vlught's Clinical review of NDA 021876 dated March 13, 2013 states the following:

"*Per the application, doxylamine is biotransformed in the liver by N-dealkylation to its principle metabolites, N-desmethyldoxylamine and N, N-didesmethyldoxylamine, which are excreted by the kidneys.*

Pyridoxine is a prodrug that undergoes complex metabolic transformation in the blood resulting in the metabolites: pyridoxal, pyridoxal 5'-phosphate, pyridoxamine, and pyridoxamine 5'-phosphate. Pyridoxine is readily absorbed in the gastrointestinal tract, mainly in the jejunum and is primarily metabolized in the liver. The PK and disposition of vitamin B6 are very complex and some metabolites have biological activity.

Per the application, vitamin B6 in coenzyme form performs a wide variety of functions in the body with involvement in more than 100 enzyme reactions. These are mostly concerned with protein metabolism, amino acid metabolism and metabolism of one-carbon units, carbohydrates, and lipids. Vitamin B6

plays a role in cognitive development through the biosynthesis of neurotransmitters and in maintaining normal levels of homocysteine, an amino acid in the blood. Vitamin B6 is also involved in gluconeogenesis and glycogenolysis, immune function (it promotes lymphocyte and interleukin-2 production), and hemoglobin formation."

The Phase 3, clinical trial mentioned above in the Sponsor's March 24, 2016 response is Study DIC-301 that was submitted on the June 8, 2012 in support of approval of the original NDA 021876.

Study DIC-301 was a double-blind trial conducted across 6 centers that randomized 280 pregnant women with NVP to 14 days of treatment with either Diclegis® (the TBM formulation) or placebo. Participants were to be at least 18 years old with a confirmed singleton gestation of 7-14 weeks and were to have failed non-pharmacologic treatment for nausea and vomiting.

Patients took two tablets of study medication at bedtime on Day 1. If nausea and vomiting was controlled on Day 2, patients continued taking two tablets daily at bedtime. However, if symptoms had persisted into the afternoon of Day 2, patients were to take two tablets at bedtime that night then take three tablets starting on Day 3 (one tablet in the morning and two tablets at bedtime). If these three tablets adequately controlled symptoms on Day 4, the patient was to continue taking three tablets daily. Otherwise, the patient was instructed to take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime). The drug was taken on an empty stomach (i.e., subjects fasted for at least 2 hours prior to each dose) with water. Dosage & Administration including food intake instructions of the current Diclegis® product label reflect the dosage regimen and Dosage & Administration instructions of this Phase 3 trial. It should be noted that about 20% of Diclegis®-treated patients remained on 2 tablets daily, 20% required 3 tablets daily and 60% required 4 tablets daily during the treatment period.

This study had a 15-day study period consisting of 14 dosing days. Blood samples were drawn before the start of therapy, and then on Days 4, 8, and 15 before the morning dose of the drug, to measure plasma concentrations of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate. The agreed-upon primary efficacy endpoint was the change from baseline in the PUQE score at Day 15. The Clinical reviewer, Dr. Theresa van der Vlugt explains the rationale for using the PUQE score in her review dated March 13, 2013. The PUQE score is a composite endpoint that captures the duration of nausea during the preceding 24 hours, the number of times the patient vomited during the preceding 24 hours, and the number of times the patient had retching without vomiting during the preceding 24 hours. Table 10 shows how each of the components of the composite endpoint were scored. These data were captured on diaries that patients completed every morning. The scores for the individual components of the composite endpoint were added to yield an overall score that ranged from 3 (no symptoms) to 15 (most severe). Patients were to have a PUQE score ≥ 6 at enrollment to be eligible for the trial.

Table 10: Scoring System for Each Component of the PUQE Score
(Based on symptoms during the preceding 24 hours)

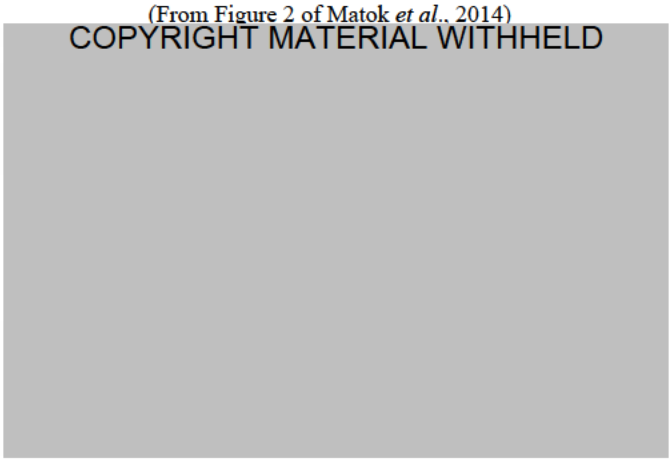
Duration of nausea	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	> 6 hours (5)
Vomiting	7 or more times (5)	5-6 (4)	3-4 (3)	1-2 (2)	I didn't throw up (1)
Retching/dry heaves	No time (1)	1-2 (2)	3-4 (3)	5-6 (4)	7 or more (5)

Reproduced from Page 39 of Dr. Theresa van der Vlught's Clinical review on NDA 021876 dated March 13, 2013.

Diclegis® resulted in a statistically significant improvement in symptoms of nausea and vomiting compared to placebo, as assessed using the PUQE score. However, the treatment effect was small.

Bioanalysis in this study was conducted using LC-MS/MS methods with dynamic ranges of 1-200 ng/mL for pyridoxine, 10-405 ng/mL for pyridoxal, and 2-102 ng/mL pyridoxal 5′-phosphate, respectively. Measured concentrations of vitamin B6 and its metabolites revealed that median pyridoxine steady concentrations were zero (i.e., below the limit of detection) on Days 4, 8, and 15, pyridoxal was undetectable in half of the patients, whereas pyridoxal 5′-phosphate concentrations were measurable at all time points and stable from Days 4 to 8 (Figure 3). It should be noted that this study was published (Matok *et al*., 2014). Figure 4 was presented in the manuscript (including Day 15 data). Matok *et al*. states that this observation for pyridoxine is not surprising, as the elimination half-life of pyridoxine has been previously shown to be short (i.e., 1-2 hours) even in the DR formulation used in Diclectin®. In contrast, pyridoxal 5′-phosphate plasma concentrations plateaued and were measurable in most patients on Days 4, 8, and 15, in association with the increase in the antiemetic effect (Figures 3 and 4). Matok *et al*. concludes that during the 15-day trial there appears to be a steady and significant improvement in the PUQE score in general, in the presence of unmeasurable concentrations of pyridoxine and apparent steady state concentrations of pyridoxal 5′-phosphate (Figure 4).

Figure 4: Median PUQE Score vs. Median Serum Concentrations of Pyridoxine, Pyridoxal, and Pyridoxal 5′-phosphate (From Figure 2 of Matok *et al*., 2014)



Vitamin B6 is a water-soluble vitamin present in 3 major forms: pyridoxine, pyridoxal, and pyridoxamine. These 3 forms are inter-convertible to their phosphorylated forms. As described in the current Diclegis® product label, pyridoxine is a pro-drug primarily metabolized in the liver. Once phosphorylated, it crosses the membranes much easier and therefore is absorbed very quickly and has an extremely short half-life of approximately 0.4 hours. The fast elimination makes it challenging to adequately characterize steady state and conduct BE assessment based on pyridoxine. In addition, its main active metabolite, pyridoxal 5′-phosphate is known to be the major active form in the blood, accounting for at least 60% of circulating vitamin B6 (Diclegis® product label). Therefore, it appears to be a reasonable approach to conduct the BE assessment based on pyridoxal 5′-phosphate instead of pyridoxine.

It should be noted that the following comment was provided to the Sponsor via the Division's December 10, 2013 written response:

"... we recommend that you provide us with graphical comparisons of pyridoxal 5-phosphate and doxylamine PK at steady state for approved and proposed dosing regimen."

Reference is made to Dr. Sayed Al Habet's Clinical Pharmacology review dated December 23, 2013 under NDA 021876 in DARRTS regarding the basis for the original approval and recommendation on the approach for BE assessment.

Based on the information above, the Sponsor's approach appears to be reasonable.

2.2.7 Was there any discussion about the study design with the Sponsor prior to conducting the BE study?

Yes. The study design of the multiple dose BE study (Study 150033) was discussed in the Division's written responses to the Sponsor's questions provided on December 10, 2013 in lieu of the proposed Type C, Guidance meeting between the Division and the Sponsor. The following specific comment regarding the study design was conveyed to the Sponsor:

"We concur that a BE study, and single and multiple dose PK studies may be sufficient to bridge efficacy and safety information between this new formulation/regimen and the previously approved regimen. However, acceptability of these data will depend on the results and will be a review issue. For the BE study, we recommend using a single day crossover design as follows:

Day 1:
Treatment A (Twice Daily Arm): One tablet of test formulation (20 mg x 20 mg) given twice daily as follows: one on the morning and one at night
Treatment B (Three Times Daily Arm): Reference formulation (10 mg x 10 mg) given three times daily as follows: one in the morning, one at 4 pm, and 2 tablets at night.

Day 10:
The same segment of a single day study described above can be repeated for the multiple doses segment on Day 10. In this case, BE can be assessed after single dose and multiple doses in one study in the same subjects.

We also recommend that you conduct a fed/fasted BA study for the new formulation.

In the absence of acceptable BE results, you will need clinical trial data to establish the efficacy and safety of your new formulation/regimen. In this situation, we would likely recommend that you conduct with the proposed new formulation (with IR and DR components), a randomized, placebo-controlled clinical trial, in pregnant adult women, 7 to 14 weeks gestation, with nausea and vomiting of pregnancy unresponsive to conservative management. This clinical trial should have the same study design that was conducted in support of the approval of Diclegis (10 mg doxylamine plus 10 mg pyridoxine) delayed-release product. Submit the protocol for such a trial with sufficient lead time to allow for our review and comment."

Reference is made to Dr. Sayed Al Habet's Clinical Pharmacology review dated December 23, 2013 and the official written responses dated December 10, 2013 under NDA 021876 in DARRTS regarding the correspondence between the Division and the Sponsor on this matter.

2.2.8 Is BE between TRADENAME tablets and Diclectin® tablets established adequately?

Yes. The October 7, 2015 original NDA submission only included a multiple dose BE Study 150033 that assessed the BE between maximum daily doses of TRADENAME BID and Diclectin® TID (i.e., 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride daily) on Day 1 and Day 11. However, Study 150033 lacked the bridging for the proposed starting dose of TRADENAME (i.e., one 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride tablet) to the currently approved starting dose for Diclegis® (i.e., two 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride tablets). There was no information supporting that the efficacy and safety of one TRADENAME tablet will be comparable to those of two Diclegis® tablets in the original NDA. Establishment of bridging for the starting dose is important as patients will remain on this initial dose if symptoms are controlled.

On March 16, 2016, the Division sent the Sponsor the following information request:

> *"Submit supporting information that the safety and efficacy of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets will be similar to those of Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) delayed-release tablets, at the dosing regimen of a 20 mg/20 mg daily dose."*

The same information request was conveyed to the Sponsor in the "Filing Review Issues Identified" letter, dated December 18, 2015.

In the response to the Division's information request, on March 24, 2016, the Sponsor notified the Division that a single dose BE Study 150336 that evaluated the BE of the starting dose of TRADENAME and Diclectin® has been conducted. On June 9, 2016, the Division requested the study report of the single dose BE Study 150336 and subsequently, the Sponsor submitted the study report on June 13, 2016. As a result, on June 27, 2016, the review clock was extended with a new user fee goal date of November 7, 2016 as it was considered to be a major amendment.

Single Dose BE Study 150336

Single dose BE between TRADENAME tablets and Diclectin® tablets was assessed in a single-center, open-label, randomized, 2-way crossover study (Study 150336) conducted in 52 healthy premenopausal females (48 completed; 20-45 years of age) with a BMI within the range of 19.3-29.8 kg/m^2.

Subjects were confined to the clinical from evening of Day -1 (at least 10 hours prior to drug administration) until after the 24 hour post-dose blood draw in each period. The treatment phases were separated by washout periods of at least 21 days between the last dose of each period and the first dose of the subsequent period. Blood samples were collected pre-dose and up to 72 hours post-dose for PK characterization depending on analyte.

In each period, according to randomization schedule, all subjects received single oral doses of either Test or Reference study medication as follows:

- Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride), at between 7-8 am

- Reference: Two Diclectin® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride), at between 7-8 am

All tablets were administered orally with 240 mL water. No food was allowed from 10 hours before until at least 4 hours after each dosing. Fluids were not permitted from 1 hour pre-dose and to 1 hour post-dose. Water was allowed *ad libitum* at all other times.

Pyridoxine and its metabolites, pyridoxal and pyridoxal 5′-phosphate are endogenous compounds and baseline corrections were needed. For baseline correction, for each subject and treatment period, the baseline value was defined as the mean of the -1, -0.5 hour, and within 5 minutes pre-dose samples obtained for that same subject. The calculated mean baseline concentration was considered as the pre-dose value. The data for each subject and each treatment period was corrected for baseline by subtracting the mean baseline value from pre-dose and all post-dose values. If baseline-adjusted concentrations are negative, concentrations were to be set to zero. Pre-dose samples for the evaluation of steady-state attainment were collected at approximately the same time each day and within 10 minutes prior to dosing.

It should be noted that the Sponsor did not assess the BE regarding pyridoxamine and pyridoxamine 5′-phosphate PK in this BE study.

Doxylamine

Mean (SD) plasma PK parameters of doxylamine are summarized in Table 11.

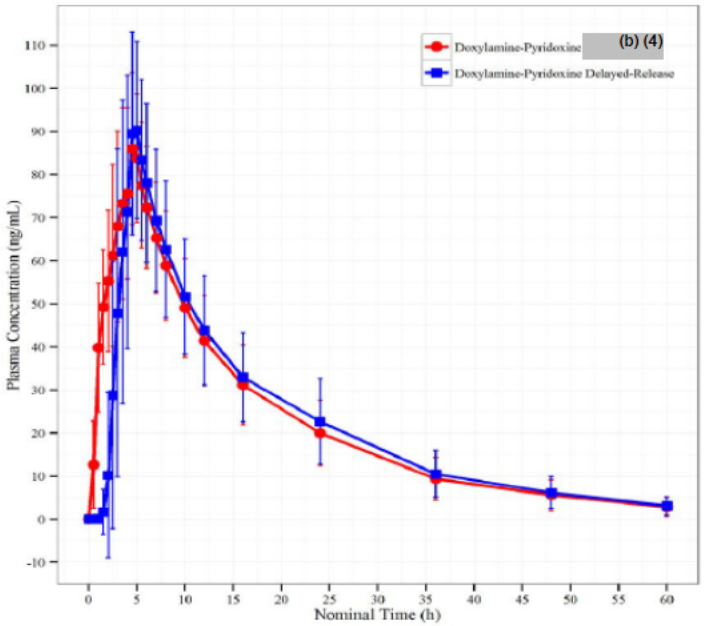
Table 11: Mean (SD) Plasma PK Parameters of Doxylamine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) (Study 150336)

Parameter	Test (N=48)	Reference (N=48)
AUC(0-60) (ng·hr/mL)	1367.0 (356.7)	1340.0 (340.2)
AUC(0-inf) (ng·hr/mL)	1425.8 (405.1)	1400.8 (386.0)
C_{max} (ng/mL)	92.3 (15.7)	98.1 (17.2)
T_{max} (hr)[a]	4.5 (2.5-5.5)	4.5 (3.0-24.0)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Mean (± SD) concentration-time profiles for doxylamine for each treatment are shown in Figure 5. It should be noted that the mean profiles for both the Test and Reference are plotted based on the mean plasma concentrations calculated per time point. Therefore, the maximum concentrations observed in the mean data figures may not reflect the mean C_{max}, as the C_{max} and the time of maximum concentration (T_{max}) vary between individuals.

Figure 5: Mean (±SD) concentration-time profile for Doxylamine for each treatment (Study 150336; N=48)



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to doxylamine for the parameters AUC(0-24) and C_{max} using natural log transformed data are summarized in Table 12.

Table 12: Summary of BE Analysis Results of Doxylamine PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) (Study 150336; N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-60) (ng·hr/mL)	1325.3	1301.4	102.0	98.4-105.7
AUC(0-inf) (ng·hr/mL)	1375.6	1353.9	101.7	98.1-105.5
C_{max} (ng/mL)	91.0	96.7	94.2	90.8-97.7

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Based on these results, it was concluded that BE regarding the rate and extent of doxylamine exposure between the TRADENAME and Diclectin® was established following a single dose of 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride.

Pyridoxal 5'-phosphate

Mean (SD) plasma PK parameters of baseline corrected pyridoxal 5′-phosphate are summarized in Table 13.

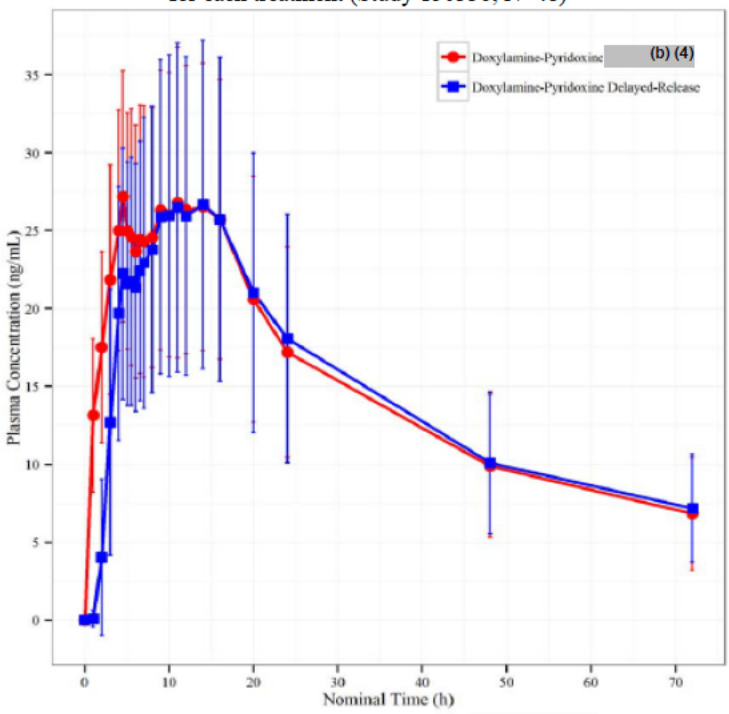
Table 13: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) (Study 150336)

Parameter	Test (N=48)	Reference (N=48)
AUC(0-72) (ng·hr/mL)	1076.2 (382.2)	1037.9 (381.9)
C_{max} (ng/mL)	30.1 (9.2)	29.0 (9.9)
T_{max} (hr)[a]	9.0 (3.0-16.0)	11.0 (4.0-24.0)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Mean (±SD) concentration-time profiles for baseline corrected pyridoxal 5′-phosphate for each treatment are shown in Figure 6. It should be noted that the mean profiles for both the Test and Reference are plotted based on the mean plasma concentrations calculated per time point. Therefore, the maximum concentrations observed in the mean data figures may not reflect the mean C_{max}, as the C_{max} and the time of maximum concentration (T_{max}) vary between individuals.

Figure 6: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal 5′-Phosphate for each treatment (Study 150336; N=48)



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to pyridoxal 5′-phosphate for the baseline corrected parameters AUC(0-72) and C_{max} using natural log transformed data are summarized in Tables 14.

Table 14: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) (Study 150336; N=48)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-72) (ng·hr/mL)	1006.9	964.9	104.2	97.9-111.0
C_{max} (ng/mL)	28.8	27.5	104.8	101.1-108.7

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Based on these results, it was concluded that BE regarding the rate and extent of baseline corrected pyridoxal 5′-phosphate exposure between the TRADENAME and Diclectin® was established following a single dose of 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride. This finding is consistent with the results of the multiple dose study, where on Day 1 bio-INequivalence is seen. In that case the inequivalence was due to the pattern of dosing. In this study, with head-to-head dosing, the issue of dosing pattern is removed from the test

matrix and one can more clearly assess the impact of the formulation on BA with the subsequent finding of no significant impact.

Details of the single dose BE study (Study 150336) can be found in Appendix Section 4.1.1 of this review.

Multiple Dose BE Study 150033

From the multiple dose BE Study 150033, the Sponsor concludes that BE is established for both doxylamine and pyridoxal 5′-phosphate based on AUC(0-24) and C_{max} on Day 11 but not for Day 1.

Multiple dose BE between TRADENAME tablets and Diclectin® tablets was assessed in a single-center, open-label, randomized, 3-period, 3-sequence, reference replicated, crossover study (Study 150033) conducted in 39 healthy premenopausal females (31 completed; 18-45 years of age) with a BMI within the range of 18.6-29.9 kg/m^2. Subjects were confined to the clinic from evening of Day -1 until after the last blood draw on the morning of Day 12, in each period.

In each period, according to randomization schedule, all subjects received multiple oral doses of either Test or Reference study medication for 11 consecutive days as follow:

- Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride), BID (1 tablet each at 9 am and 9 pm)
- Reference: Diclectin® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride), TID (1 tablet each at 9 am and 3 pm and 2 tablets at 9 pm)

All tablets were administered orally with 240 mL water. No food was allowed from at least 2.5 hours before until at least 2 hours after each dosing. Fluids were not permitted from 1 hour pre-dose and to 1 hour post-dose. Water was allowed *ad libitum* at all other times.

The treatment phases were separated by washout periods of at least 28 days between the last dose of each period and the first dose of the subsequent period. Blood samples were collected pre-dose and through 24 hours post-dose on Days 1 and 11 for PK characterization.

Pyridoxine and its metabolites, pyridoxal and pyridoxal 5′-phosphate are endogenous compounds and baseline corrections were needed. For baseline correction, for each subject and treatment period, the baseline value was defined as the mean of the -1, -0.5 hour, and within 10 minutes pre-dose samples obtained for that same subject and period on Day 1. The calculated mean baseline concentration was considered as the pre-dose value. The data for each subject and each treatment period was corrected for baseline by subtracting the mean baseline value from pre-dose and all post-dose values. If baseline-adjusted concentrations are negative, concentrations were to be set to zero. Pre-dose samples for the evaluation of steady-state attainment were collected at approximately the same time each day and within 10 minutes prior to dosing.

It should be noted that the Sponsor did not assess the BE regarding pyridoxamine and pyridoxamine 5′-phosphate PK in this BE study.

Doxylamine

Mean (SD) plasma PK parameters of doxylamine are summarized in Tables 15 and 16.

Table 15: Mean (SD) Plasma PK Parameters of Doxylamine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 1 (Study 150033)

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	1421.7 (271.7)	1041.1 (273.5)	1049.6 (286.7)
AUC(0-12) (ng·hr/mL)	614.1 (143.7)	287.5 (137.7)	300.3 (105.1)
AUC(0-6) (ng·hr/mL)	321.0 (72.2)	105.8 (59.1)	106.1 (44.0)
C_{max} (ng/mL)	94.5 (20.7)	125.9 (35.7)	116.5 (29.5)
T_{max} (hr)[a]	20.0 (2.2-23.0)	22.0 (15.5-23.9)	22.0 (15.5-23.9)

Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a reference replicated study. There were different number of subjects from whom data were available between Reference 1 and Reference 2.
[a] Median (minimum-maximum)

Table 16: Mean (SD) Plasma PK Parameters of Doxylamine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 11 (Study 150033)

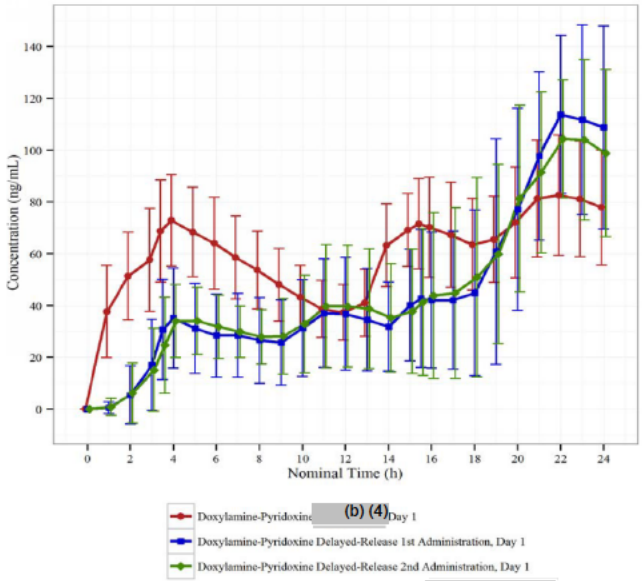
Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	2879.4 (696.0)	2813.6 (767.2)	3016.0 (647.2)
AUC(0-12) (ng·hr/mL)	1573.2 (406.5)	1437.6 (426.7)	1550.9 (373.5)
AUC(0-6) (ng·hr/mL)	883.6 (228.5)	767.5 (217.2)	827.4 (205.1)
C_{max} (ng/mL)	173.6 (45.5)	159.6 (37.0)	168.9 (34.5)
T_{max} (hr)[a]	3.5 (1.0-20.0)	19.5 (0.0-24.0)	21.0 (3.0-23.0)

Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a reference replicated study. There were different number of subjects from whom data were available between Reference 1 and Reference 2.
[a] Median (minimum-maximum)

The doxylamine T_{max} values represented in Tables 15 and 16 did not truly reflect the T_{max} values that would be expected from a single dose as it appears that the T_{max} from the second or third doses from the BID and TID regimens have been reflected instead.

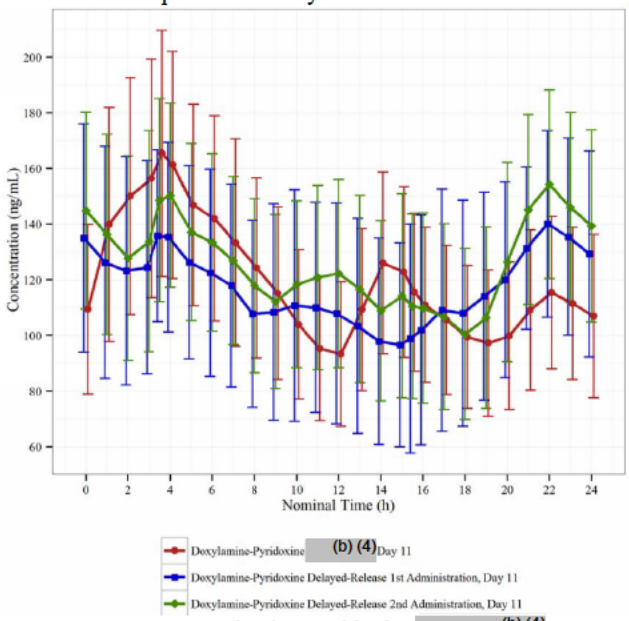
Mean (±SD) concentration-time profiles for doxylamine for each treatment on Days 1 and 11 are shown in Figures 7 and 8. It should be noted that the mean profiles for both the Test and Reference are plotted based on the mean plasma concentrations calculated per time point.

Figure 7: Mean (±SD) concentration-time profile for Doxylamine for each treatment on Day 1 (Study 150033; N=37)



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure 8: Mean (±SD) concentration-time profile for Doxylamine for each treatment on Day 11 (Study 150033; N=34)



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to doxylamine for the parameters, AUC(0-24) and C_{max} on Days 1 and 11 using natural log transformed data are summarized in Tables 17 and 18.

Table 17: Summary of BE Analysis Results of Doxylamine PK Parameters
Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 1 (Study 150033; N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	1397.1	1010.6	140.0	130.2-150.6
C_{max} (ng/mL)	92.3	117.0	79.6	76.1-83.2

Table 18: Summary of BE Analysis Results of Doxylamine PK Parameters
Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 11 (Study 150033; N=34)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	2802.2	2720.4	99.1	95.7-102.5
C_{max} (ng/mL)	168.3	155.6	105.3	100.9-109.9

Pyridoxal 5'-Phosphate

Mean (SD) plasma PK parameters of baseline corrected pyridoxal 5′-phosphate are summarized in Tables 19 and 20.

Table 19: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 1 (Study 150033)

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	680.5 (230.1)	423.4 (136.7)	425.9 (138.1)
AUC(0-12) (ng·hr/mL)	245.2 (85.2)	116.1 (64.2)	110.1 (48.2)
AUC(0-6) (ng·hr/mL)	101.9 (36.8)	34.2 (20.9)	31.7 (20.6)
C_{max} (ng/mL)	44.9 (15.1)	43.2 (19.5)	41.7 (11.7)
T_{max} (hr)[a]	21.0 (15.0-23.9)	22.0 (10.0-23.9)	21.5 (18.0-23.9)

Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study. There were different number of subjects from whom data were available between Reference 1 and Reference 2.
[a] Median (minimum-maximum)

Table 20: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 11 (Study 150033)

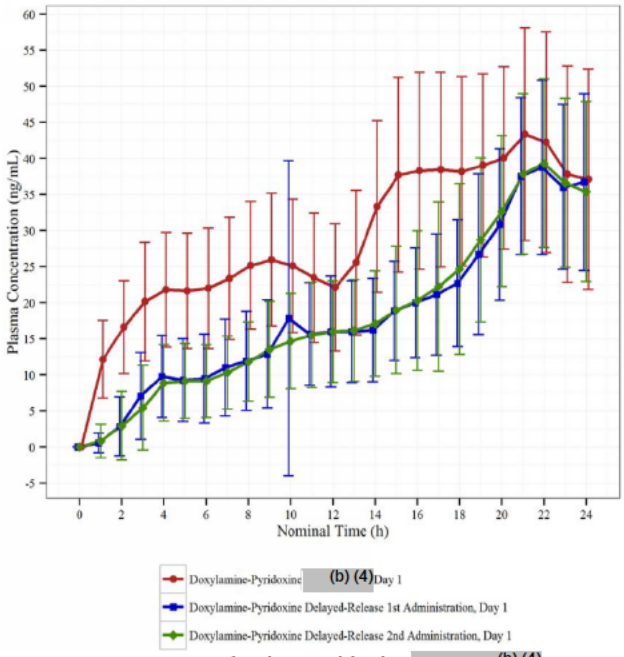
Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	1742.3 (554.3)	1722.6 (517.8)	1773.7 (571.3)
AUC(0-12) (ng·hr/mL)	831.7 (274.5)	835.1 (266.1)	843.4 (296.3)
AUC(0-6) (ng·hr/mL)	426.2 (144.0)	418.6 (134.7)	420.1 (153.1)
C_{max} (ng/mL)	85.9 (26.2)	82.6 (23.4)	87.7 (26.2)
T_{max} (hr)[a]	15.0 (2.0-24.0)	21.0 (0.0-24.0)	19.0 (4.0-24.0)

Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study. There were different number of subjects from whom data were available between Reference 1 and Reference 2.
[a] Median (minimum-maximum)

The pyridoxal 5′-phosphate T_{max} values represented in Tables 19 and 20 did not truly reflect the T_{max} values that would be expected from a single dose as it appears that the T_{max} from the second or third doses from the BID and TID regimens have been reflected instead.

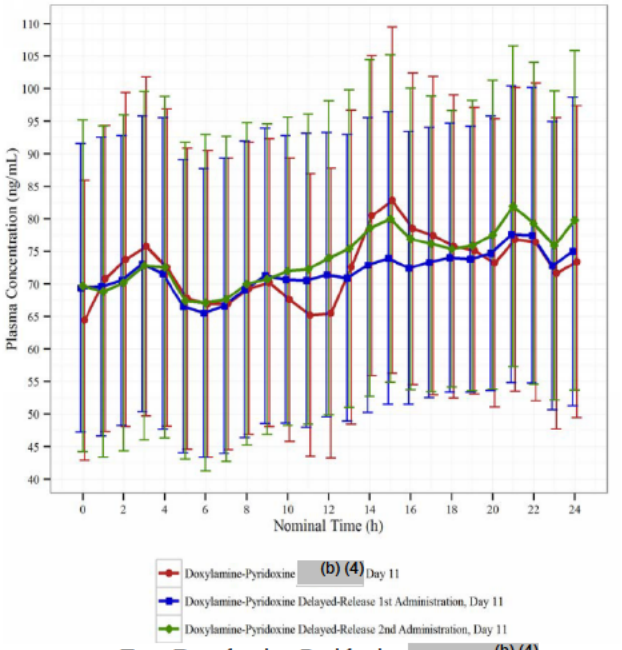
Mean (±SD) concentration-time profile for baseline corrected pyridoxal 5′-phosphate for each treatment on Days 1 and 11 are shown in Figures 9 and 10.

Figure 9: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal 5′-Phosphate for each treatment on Day 1 (Study 150033; N=37)



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure 10: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal 5′-Phosphate for each treatment on Day 11 (Study 150033; N=34)



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to baseline corrected pyridoxal 5′-phosphate for the parameters, AUC(0-24) and C_{max} on Days 1 and 11 using natural log transformed data are summarized in Tables 21 and 22.

Table 21: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 1 (Study 150033; N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	644.8	406.1	161.5	147.6-176.7
C_{max} (ng/mL)	42.5	40.4	105.6	99.6-112.0

[a] Median (minimum-maximum)

Table 22: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 11 (Study 150033; N=34)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	1661.5	1657.4	100.1	95.8-104.5
C_{max} (ng/mL)	82.2	81.4	100.8	96.7-105.0

[a] Median (minimum-maximum)

The PK profiles between the Test (TRADENAME given BID) and Reference (Diclegis® given TID) show some differences (e.g., at Hour 12 where the same total dose of 20 mg doxylamine / 20 mg pyridoxine was given) and this is not surprising as they are given under different dosing intervals (BID vs. TID). This also explains the lack of "BE" for C_{max} on Day 1. The different dosing regimens yield quantitatively different C_{max} values dependent upon the dosing pattern (BID of equal doses vs TID of UN-equal doses). Accumulation at steady-state nullifies the different dosing patterns such that the resulting steady-state CIs meet the FDA acceptance criteria

Details of the multiple dose BE study (Study 150033) can be found in Appendix Section 4.1.2 of this review.

2.2.9 What are the PK parameters of doxylamine, pyridoxine, and pyridoxine metabolites following a single dose and multiple doses of TRADENAME tablets?

Mean (SD) PK parameters of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate obtained following a single dose oral administration of TRADENAME tablets (i.e., 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) under fasting condition in an open label, single dose, two treatment, two-way crossover study (Study 150336) conducted in 52 healthy premenopausal females (48 completed) are summarized in Table 23.

Table 23: Mean (SD) Plasma PK Parameters Following a Single Dose of a TRADENAME Tablet without Food (Study 150336; N=48)

Parameter	Doxylamine	Pyridoxine[c]	Pyridoxal[d,e]	Pyridoxal 5′-phospahte[d]
AUC(0-t) (ng·hr/mL)[a]	1367.0 (356.7)	42.3 (14.7)	203.7 (51.7)	1076.2 (382.2)
AUC(0-inf) (ng·hr/mL)	1425.8 (405.1)	42.5 (14.7)	233.6 (55.9)[f]	N/A
C_{max} (ng/mL)	92.3 (15.7)	47.1 (18.7)	58.9 (17.0)	30.1 (9.2)
T_{max} (hr)[b]	4.5 (2.5-5.5)	0.5 (0.5-4.7)	3.0 (0.8-5.0)	9.0 (3.0-16.0)
$t_{½}$ (hr)	12.4 (2.7)	0.3 (0.1)	7.7 (1.4)[f]	N/A

N/A: Not available

[a] t= 60 hours (doxylamine), 72 hours (pyridoxal 5′-phosphate), 8 hours (pyridoxine), 16 hours (pyridoxal)

[b] Median (minimum-maximum)

[c] N=47, for Subject 20, all pyridoxine concentrations were below limit of quantitation (BLQ) in Period 1 (Treatment B), thus the PK profile could not be adequately characterized.

[d] Baseline corrected values; [e] Matrix: whole blood

[f] N=46, for Subjects 2 and 20, the elimination rate constant could not be properly estimated due to a low correlation coefficients of the natural log-linear portion of the terminal elimination phase (as per (b) (4) standard operating procedures)

Mean (SD) PK parameters of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate obtained following daily doses of TRADENAME tablets (i.e., 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride by taking one tablet in the morning and one tablet at bedtime) for 1 day and 11 consecutive days in an open label, multiple dose, three-period, three-sequence reference replicated, crossover study (Study 150033) conducted in 39 healthy premenopausal females are summarized in Table 24.

Table 24: Mean (SD) Plasma PK Parameters Following Daily Doses of TRADENAME Tablets on Day 1 or Day 11 (Study 150033)

		AUC(0-24) (ng·hr/mL)	AUC(0-12) (ng·hr/mL)	AUC(0-6) (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)[b]
Doxylamine	Day 1 (N=37)	1421.7 (271.7)	614.1 (143.7)	321.0 (72.2)	94.5 (20.7)	20.0 (2.2-23.0)
	Day 11 (N=34)	2879.4 (696.0)	1573.2 (406.5)	883.6 (228.5)	173.6 (45.5)	3.5 (1.0-20.0)
Pyridoxine	Day 1 (N=37)	68.8 (20.4)	32.8 (12.1)	32.7 (12.1)	37.7 (14.7)	1.5 (0.5-20.0)
	Day 11 (N=34)	80.0 (22.7)	46.3 (15.4)	45.3 (16.3)	48.2 (23.7)	1.5 (0.3-16.5)
Pyridoxal[a,d]	Day 1 (N=37)	524.9 (167.6)	224.0 (84.7)	182.0 (68.2)	76.1 (25.0)	4.0 (1.0-22.0)
	Day 11 (N=34)	1511.3 (300.0)	848.1 (183.6)	647.2 (149.6)	189.6 (48.3)	3.0 (2.0-15.0)
Pyridoxal 5′-phosphate[a]	Day 1 (N=37)	680.5 (230.1)	245.2 (85.2)	101.9 (36.8)	44.9 (15.1)	21.0 (15.0-23.9)
	Day 11 (N=34)	1742.3 (554.3)	831.7 (274.5)	426.2 (144.0)	85.9 (26.2)	15.0 (2.0-24.0)

Treatment: TRADENAME ER tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride), BID (1 tablet each at 9 am and 9 pm) for 11 consecutive days
[a] Baseline corrected values
[b] Median (range)
[d] Matrix: whole blood

2.2.10 Did food intake affect the PK of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate?

Yes. When TRADENAME tablets were administered with a high fat and high calorie meal, food caused a delay in the median T_{max} of doxylamine, pyridoxine, baseline corrected pyridoxal, and baseline corrected pyridoxal 5′-phosphate to 6.5, 8.0, 6.0, and 16.0 hours, respectively. In addition, food decreased the C_{max} of doxylamine, pyridoxine, and baseline corrected pyridoxal for 26.4%, 77.3%, and 45.8%, respectively and AUC(0-t) of pyridoxine for 37.2%.

Sponsor conducted a food effect study (Study 140115) to assess the effect of food on the BA of for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate following a single oral administration of a TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride). This was a single-center, open-label, randomized, 2-way crossover study that was conducted in 24 healthy premenopausal females (age: 18-44 years). All subjects received Test (fed) and Reference (fasting) treatments orally with 240 mL water following an overnight fasting of at least 10 hours.

The results for the assessment of food effect on doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate PK are summarized in Tables 25, 26, 27, and 28 below.

Table 25: Summary of Geometric Means, Point Estimates, and 90% CI of Doxylamine PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	1219.1	1247.0	97.6	93.6-101.7
AUC(0-inf) (ng·hr/mL)	1253.5	1289.1	97.0	92.9-101.3
C_{max} (ng/mL)	62.7	85.3	73.6	68.0-79.8

Table 26: Summary of Geometric Means, Point Estimates, and 90% CI of Pyridoxine PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	20.6	33.1	62.8	54.5-72.3
AUC(0-inf) (ng·hr/mL)	25.3	34.2	70.7	53.8-92.9
C_{max} (ng/mL)	11.4	35.1	32.7	26.9-39.6

Table 27: Summary of Geometric Means, Point Estimates, and 90% CI of Baseline Corrected Pyridoxal PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	202.5	207.4	97.9	93.4-102.6
AUC(0-inf) (ng·hr/mL)	245.4	242.0	101.8	96.2-107.8
C_{max} (ng/mL)	32.6	59.7	54.2	48.6-60.5

Table 28: Summary of Geometric Means, Point Estimates, and 90% CI of Baseline Corrected Pyridoxal 5′-phosphate PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	1005.4	975.1	103.4	95.6-111.8
C_{max} (ng/mL)	28.7	26.4	109.3	103.4-115.5

Subject 20 had many consecutive missing samples in Period 2 (Test) and she was excluded from the PK population for all analytes since it was not possible to adequately characterize her PK profiles (making the PK population 23 subjects).

The currently approved product label of Diclegis® states the following regarding food effect:

> *"The administration of food delays the absorption of both doxylamine and pyridoxine. This delay is associated with a lower peak concentration of doxylamine, but the extent of absorption is not affected.*
>
> *The effect of food on the peak concentration and the extent of absorption of the pyridoxine component is more complex because the pyridoxal, pyridoxamine, pyridoxal 5'-phosphate, and pyridoxamine 5'-phosphate metabolites also contribute to the biological activity. Food significantly reduces the BA of pyridoxine, lowering its C_{max} and AUC by approximately 50% compared to fasting conditions. Similarly, food significantly reduces pyridoxal AUC and reduces its C_{max} by 50% compared to fasting conditions. In contrast, food slightly increases pyridoxal 5'-phosphate C_{max} and extent of absorption. As for pyridoxamine and pyridoxamine 5'-phosphate, the rate and extent of absorption seem to decrease under fed conditions."*

It should be noted that the Sponsor did not evaluate the food effect on pyridoxamine and pyridoxamine 5′-phosphate PK in this food effect study.

Based on this information, the Diclegis® product label instructs Diclegis® to be taken on an empty stomach with a glass of water. The same food intake instruction should be recommended for TRADENAME.

Arithmetic mean (SD) PK parameters of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate obtained following administration of a TRADENAME tablet with food (Test) or without food (Reference) are summarized in Tables 29, 30, 31, and 32.

Table 29: Mean (SD) Plasma PK Parameters of Doxylamine Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	1242.8 (254.0)	1273.7 (276.2)
AUC(0-inf) (ng·hr/mL)	1281.4 (282.9)	1321.9 (315.5)
C_{max} (ng/mL)	64.5 (15.2)	85.9 (10.6)
T_{max} (hr)[a]	6.5 (2.0-24.0)	3.5 (2.5-5.5)
$t_{½}$ (hr)	12.7 (2.6)	11.9 (2.2)

[a] Median (minimum-maximum)

Table 30: Mean (SD) Plasma PK Parameters of Pyridoxine Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	22.8 (9.9)	34.7 (10.6)
AUC(0-inf) (ng·hr/mL)	27.0 (10.1)[b]	35.1 (8.5)[b]
C_{max} (ng/mL)	12.7 (5.7)	38.9 (19.3)
T_{max} (hr)[a]	8.0 (1.0-21.0)	0.75 (0.3-4.3)
$t_{½}$ (hr)	1.2 (2.4)[b]	0.4 (0.2)[b]

[a] Median (minimum-maximum)
[b] n=12, For Subjects 3, 4, 7, 8, 15, 17, 18, 21, 22, 23, and 24, AUC(0-inf) and $t_{½}$ could not be properly estimated due to an insufficient number of detectable concentrations in the terminal elimination phase and these subjects were excluded from all analyses involving AUC(0-inf) and $t_{½}$.

Reviewer's Comment: *All pre-dose pyridoxine concentrations were below the LLOQ for all subjects and therefore, no baseline adjustments were performed on pyridoxine concentrations.*

Table 31: Mean (SD) Whole Blood PK Parameters of Baseline Corrected Pyridoxal Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	204.2 (25.7)	209.4 (30.0)
AUC(0-inf) (ng·hr/mL)	249.2 (43.0)	244.0 (32.5)
C_{max} (ng/mL)	33.1 (6.2)	62.0 (17.8)
T_{max} (hr)[a]	6.0 (1.0-21.0)	2.3 (0.8-5.0)
$t_{½}$ (hr)	12.5 (7.6)	8.0 (1.7)

[a] Median (minimum-maximum)

Table 32: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-phosphate Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	1064.6 (386.9)	1021.7 (318.5)
C_{max} (ng/mL)	30.2 (10.0)	27.4 (7.7)
T_{max} (hr)[a]	16.0 (6.0-22.0)	5.0 (3.0-71.8)

[a] Median (minimum-maximum)

The mean concentration-time profiles for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate obtained following administration of a TRADENAME tablet with food (Test) or without food (Reference) are shown in Figures 11, 12, 13, and 14, respectively.

Figure 11: Mean Plasma Concentration-Time Profiles of Doxylamine Following a Single Dose of TRADENAME Tablet with or without Food (Study 140115; N=23)

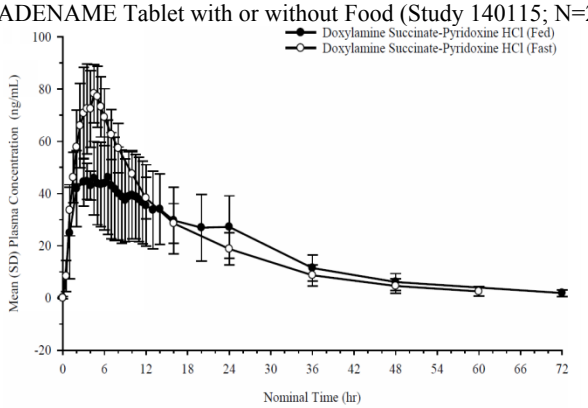


Figure 12: Mean Plasma Concentration-Time Profiles of Pyridoxine Following a Single Dose of TRADENAME Tablet with or without Food (Study 140115; N=23)

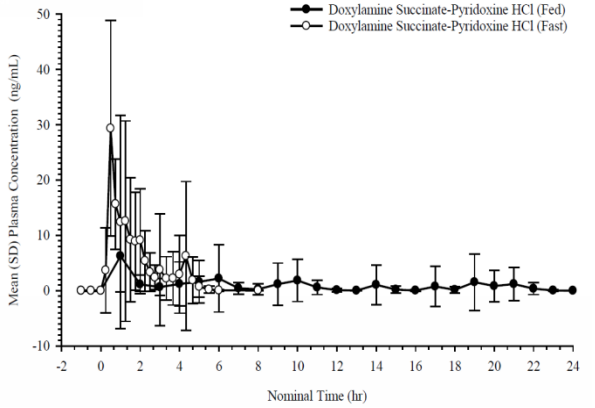


Figure 13: Mean Whole Blood Concentration-Time Profiles of Baseline Corrected Pyridoxal Following a Single Dose of TRADENAME Tablet with or without Food (Study 140115; N=23)

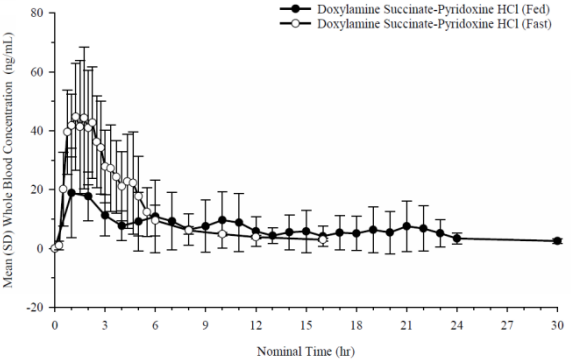
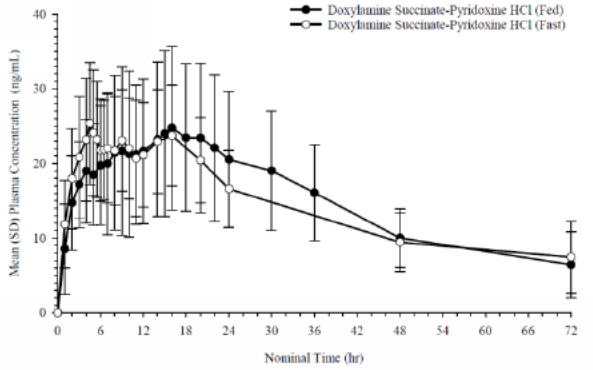


Figure 14: Mean Plasma Concentration-Time Profiles of Baseline Corrected Pyridoxal 5′-phosphate Following a Single Dose of TRADENAME Tablet with or without Food (Study 140115; N=23)



In summary, TRADENAME tablets should be administered under fasting conditions to avoid food affecting the rate of absorption (i.e., T_{max}) and the extent of exposure (i.e., C_{max} and AUC). Details of the food effect study (Study 140115) can be found in Appendix Section 4.1.3 of this review.

2.3 Intrinsic Factors

2.3.1 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

No studies were performed in post-pubertal adolescents under the age of 18 under this NDA. The Sponsor is requesting a waiver for pediatric study requirements in (b) (4) for TRADENAME (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) tablets.

(b) (4) the Sponsor is requesting a waiver from pediatric development in children from birth to (b) (4) years of age. (b) (4)

The Agency's PeRC granted a partial waiver for studies in (b) (4) patients 0-11 years of age because studies are impossible or highly impractical and granted a deferral in (b) (4) patients 12-17 years of age on July 6, 2016.

Currently, the approved product, Diclegis® (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride tablets), indicated to treat NVP in women who do not respond to conservative management, is under a pediatric research equity act (PREA) commitment with the Agency to conduct a pediatric assessment for pregnant adolescents aged 12 to 17 years with the specified milestone:

> *2033-1: An adequately powered safety and efficacy study in pregnant adolescent girls, 12 to 17 years of age with nausea and vomiting of pregnancy who are appropriate candidates for pharmacologic therapy*
> - *Final Protocol Submission: January 2014*
> - *Study/Trial Completion: January 2018*
> - *Final Report Submission: July 2018*

On January 14, 2015, the Sponsor requested [redacted] (b) (4)

[redacted] (b) (4)

The Division [redacted] (b) (4) on March 23, 2015. The Sponsor was advised that a PREA Deferral Extension could be submitted up to 90 days prior to the final report milestone.

On May 26, 2016, the Sponsor reported the current status as the following:

> *'Diclegis® (10 mg/10 mg) PED-301 pediatric study is ongoing. As of May 10, 2016, 13 investigators with 16 sites in total have enrolled 71 subjects of whom, 58 have completed the study and 7 were discontinued/early termination. Currently, there are 7 investigators with 7 active sites. Sites are screening a significant number of patients, specifically, 1,124 patients have been screened since recruitment was initiated in February 2014. The total number of planned subjects is 160 pregnant adolescents to achieve 128 evaluable participants based on a drop-out rate of 20%.'*

2.3.2 Did the Sponsor conduct PK studies with TRADENAME in population with renal or hepatic impairment?

No. The Sponsor did not conduct studies with TRADENAME tablets nor Diclegis® tablets in patients with renal or hepatic impairment. Given that the target population is premenopausal women, usage of TRADENAME in patients with renal or hepatic impairment would be relatively small and therefore, is less of a concern. However, it should be mentioned in the product label that no renal or hepatic impairment studies were conducted using TRADENAME.

2.4 Extrinsic Factors

2.4.1 Did the Sponsor conduct any DDI studies with TRADENAME?

No new DDI studies were conducted with TRADENAME tablets. The Sponsor is proposing to use [redacted] (b) (4) the following information:

> "*Use of TRADENAME is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic* [redacted] (b) (4) *effects of antihistamines. Concurrent use of alcohol and other CNS depressants (such as hypnotic sedatives and tranquilizers) with TRADENAME is not recommended.*"

Sponsor's proposal is acceptable from the Clinical Pharmacology standpoint.

2.5 General Biopharmaceutics

2.5.1 What is the quantitative composition of the TRADENAME tablets used in the clinical trials of this application?

The new product, TRADENAME contains 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. TRADENAME consists of an enteric-coated core containing 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride. This core is (b) (4) (b) (4) An IR layer of 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride is added to the enteric-coated core. Diclegis® formulation is classified as a DR tablet while TRADENAME will be classified as an ER tablet. The composition of TRADENAME is summarized in the Table 33 below:

Table 33: Comparison of the TBM Formulation of TRADENAME Tablets

Component and Quality Standard (and Grade, if applicable)	Function	20 mg/20 mg (b) (4) (b) (4) Tablets
		Quantity per unit (mg)
Doxylamine Succinate, USP	API	(b) (4)
Pyridoxine HCl, USP	API	
Microcrystalline Cellulose (b) (4) 102, NF		(b) (4)
Magnesium Trisilicate, USP		
Croscarmellose Sodium, NF		
Magnesium Stearate, NF		
Colloidal Silicone Dioxide, NF		
		(b) (4)
Triethyl Citrate, NF		(b) (4)
Simethicone (b) (4)		
		(b) (4)
Carnauba Wax Powder, NF		(b) (4)
		(b) (4)
(b) (4) Pink, In-house	Printing ink	trace
OVERALL TABLET TOTAL		*232.6*

Studies 150336, 150033, and 140115 were conducted with the TBM formulation of TRADENAME tablets.

It should be noted that the following Division's comment regarding labeling and nomenclature of the Sponsor's new formulation has been conveyed to the Sponsor via an Information Request letter dated March 18, 2016:

> "*As the product contains a DR core plus an immediate release coating,* (b) (4) *The most appropriate acceptable terminology is ER.* (b) (4) "

2.6 Bioanalytical Methods

2.6.1 Did the Sponsor use validated bioanalytical methods to generate data in the clinical studies?

Yes. Bioanalytical method validation and study reports were submitted for all studies that were reviewed. Acceptance criteria and method performance for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate concentration measurements are in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods are acceptable.

Bioanalysis was conducted at the (b) (4) . Study samples were analyzed using a LC-MS/MS method for the determination of doxylamine, pyridoxine, and pyridoxal 5′-phosphate concentrations in human plasma and for determination of pyridoxal concentrations in human whole blood in Studies 150336, 150033, and 140115. ISR was conducted on 6.9-7.3% of the study samples for each analyte in Study 150336, 5.6-5.8% of the study samples for each analyte in Study 150033, and 8.8-9.2% of the study samples for each analyte in Study 140115, respectively. More than 95.8% of the ISR results from the Study 150336, more than 96.1% of the ISR results from Study 150033, and more than 89.7% of the ISR results from Study 140115 met the acceptance criteria of being within ±20% of the original reported concentration value for at least 67% of the ISR samples.

For the multiple dose BE study (Study 150033), a formal consult to the OSIS was made on January 4, 2016 for inspections of the clinical and bioanalytical study sites. An OSIS memorandum was issued on February 22, 2016 with a recommendation to accept the data without on-site inspection based on previous inspection findings.

The bioanalytical methods are summarized in Table 34.

Table 34: Summary of Bioanalytical Methods

Study Number	Study Type	Biological matrix	Analyte	Method	Dynamic Range
150336	Single dose BE Study	Plasma	Doxylamine	LC-MS/MS	0.5-250 ng/mL
		Plasma	Pyridoxine		0.25-100 ng/mL
		Whole blood	Pyridoxal		0.5-400 ng/mL
		Plasma	Pyridoxal 5′-phosphate		2.0-200 ng/mL
150033	Multiple dose BE Study	Plasma	Doxylamine	LC-MS/MS	0.5-250 ng/mL
		Plasma	Pyridoxine		0.25-100 ng/mL
		Whole blood	Pyridoxal		0.5-400 ng/mL
		Plasma	Pyridoxal 5′-phosphate		2.0-200 ng/mL
140115	Food Effect Study	Plasma	Doxylamine	LC-MS/MS	0.5-250 ng/mL
		Plasma	Pyridoxine		0.25-100 ng/mL
		Whole blood	Pyridoxal		0.5-200 ng/mL
		Plasma	Pyridoxal 5′-phosphate		2.0-200 ng/mL

3 Detailed Labeling Recommendations

The following Clinical Pharmacology related sections of the Sponsor's final proposed label were submitted to this NDA on October 13, 2016. ~~Strikes~~ are used for deletion and double underline is used for addition for the OCP's preliminary response to the Sponsor's proposal. Note that sections illustrated below do not necessarily reflect the entire corresponding sections of the product label.

Highlights

----------INDICATIONS AND USAGE----------

(b) (4) TRADENAME is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a Vitamin B_6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. (1)

----------DOSAGE AND ADMINISTRATION ----------

Take one tablet (b) (4) at bedtime. If symptoms are not adequately controlled, the dose can be increased to (b) (4) (one in the morning and one at bedtime) as described in the full prescribing information. (2)

----------DOSAGE FORMS AND STRENGTHS ----------

(b) (4) extended release tablets containing 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. (3)

----------DRUG INTERACTIONS ----------

- Severe drowsiness can occur when used in combination with alcohol or other sedating medications. (7)

Full Prescribing Information

1. INDICATIONS AND USAGE

(b) (4) TRADENAME is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

(b) (4) TRADENAME has not been studied in women with hyperemesis gravidarum.

2. DOSAGE AND ADMINISTRATION

2.1 Dosage Information

Initially, take one (b) (4) TRADENAME, (b) (4) extended release tablet orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking one tablet daily at bedtime. However, if symptoms persist on Day 2, (b) (4) (one tablet in the morning and one tablet at bedtime).

The maximum recommended dose is two tablets (b) (4)

Take on an empty stomach with a glass of water *[see Clinical Pharmacology (12.3)]*. Swallow tablets whole. Do not crush, chew, or split (b) (4) TRADENAME tablets.

Take (b) (4) daily (b) (4) and not on an as needed basis. Reassess the woman for continued need for (b) (4) TRADENAME as her pregnancy progresses.

3. DOSAGE FORMS AND STRENGTHS

(b) (4) TRADENAME, (b) (4) extended release tablets are pink, round, film coated tablets containing 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. (b) (4) imprinted with the pink image of a pregnant woman on one side and a "D" on the other side.

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Somnolence *[see Warnings and Precautions (5.1)]*
- Falls or other accidents resulting from the effect of the combined use of (b) (4) TRADENAME with CNS depressants including alcohol *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

(b) (4)

Reviewer's Comment: The statement of (b) (4) .

7. DRUG INTERACTIONS

7.1 Drug Interactions

Use of (b) (4) TRADENAME is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (b) (4) effects of antihistamines. Concurrent use of alcohol and other CNS depressants (such as hypnotic sedatives and tranquilizers) with (b) (4) TRADENAME is not recommended.

7.2 Drug-Food Interactions

A food-effect study demonstrated that the delay in the onset of action of (b) (4) TRADENAME may be further delayed, and a reduction in absorption may occur when tablets are taken with food *[see Dosage and Administration (2), Clinical Pharmacology (12.3)]*. Therefore, (b) (4) TRADENAME should be taken on an empty stomach with a glass of water *[see Dosage and Administration (2)]*.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of (b) (4) TRADENAME is unknown.

(b) (4)

Reviewer's Comment: (b) (4)

12.3 Pharmacokinetics

The pharmacokinetics of (b) (4). TRADENAME has been characterized in healthy non-pregnant adult women. (b) (4)

Absorption

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

(b) (4)

Reviewer's Comment: The text above should be replaced with the following text.

In a single-dose, crossover clinical study conducted in 48 healthy, premenopausal women under fasting condition, TRADENAME tablets were bioequivalent to two of doxylamine succinate 10 mg/pyridoxine hydrochloride 10 mg tablets based on the exposure (AUC) and peak concentration (C_{max}) of doxylamine and baseline corrected pyridoxal 5'-phosphate. Mean ± SD plasma (whole blood for pyridoxal) PK parameters are summarized in Table 2.

(b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comment: The text above should be replaced with the following text.

In a mulitple-dose, crossover clinical study conducted in 31 healthy, premenopausal women, TRADENAME tablets given twice daily for 11 days were bioequivalent to doxylamine succinate 10 mg/pyridoxine hydrochloride 10 mg tablets given trice daily (1 tablet each in the morning and afternoon and 2 tablets in the evening) for 11 days based on the exposure (AUC) and peak concentration (C_{max}) of doxylamine and baseline corrected pyridoxal 5'-phosphate. Mean ± SD plasma (whole blood for pyridoxal) PK parameters are summarized in Table 3.

(b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

(b) (4)

Food Effect

In a single-dose, crossover clinical (b) (4) conducted in 23 healthy, premenopausal women, tThe administration of (b) (4) a high fat, high calorie meal delayeds the absorption of (b) (4) doxylamine, pyridoxine, and pyridoxine metabolites. This delay sociated with a lower peak concentrations of doxylamine, pyridoxine, and pyridoxal. (b) (4). The extent of absorption for pyridoxine (b) (4) was decreased (b) (4)

The effect of food on the peak concentration and the extent of absorption of the pyridoxine component is more complex because the pyridoxine metabolites such as pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5' phosphate (b) (4) also contribute to the biological activity. Food significantly reducesd the bioavailability of pyridoxine, lowering its C_{max} and AUC by approximately 67% and 37 (b) (4) %, respectively, compared to fasting conditions. Similarly, food significantly reducesd pyridoxal (b) (4). C_{max} by approximately 46 (b) (4) % compared to fasting conditions. In contrast, food (b) (4). did not affect pyridoxal 5'-phosphate C_{max} and extent of absorption. (b) (4).

(b) (4).

(b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

(b) (4)

Distribution

Pyridoxine is highly protein bound, primarily to albumin. Its main active metabolite, pyridoxal 5'-phosphate (PLP) accounts for at least 60% of circulating vitamin B_6 concentrations.

Metabolism

Doxylamine is biotransformed in the liver by N-dealkylation to its principle metabolites N-desmethyl-doxylamine and N, N-didesmethyldoxylamine.

Pyridoxine is a prodrug primarily metabolized in the liver.

Excretion

The principle metabolites of doxylamine, N-desmethyl-doxylamine and N, N-didesmethyldoxylamine, are excreted by the kidney. The terminal elimination half-life of doxylamine and pyridoxine are 11.9 hours and 0.4 hours, respectively (see **Table ~~7~~ 5**).

(b) (4)

Reviewer's Comment: (b) (4)
(b) (4)

Use in Specific Populations
Race No pharmacokinetic studies have been conducted related to race.
Hepatic Impairment No pharmacokinetic studies have been conducted in hepatic impaired patients.
Renal Impairment No pharmacokinetic studies have been conducted in renal impaired patients.

14. CLINICAL STUDIES

(b) (4)

Reviewer's Comment: (b) (4)

APPEARS THIS WAY ON ORIGINAL

4 Appendices

4.1 Individual Study Reviews

4.1.1 BE Study: Study 150336

Title: Randomized, open-label, 2-way crossover BE study of TRADENAME and Diclegis® (Reference) following a 20 mg-20 mg dose in healthy subjects under fasting conditions

Objectives: To compare the rate and extent of absorption of doxylamine, pyridoxine, and its metabolites following single oral administration of a TRADENAME (Test) administered as 1 x 20 mg-20 mg tablet compared to Diclectin® (Reference) administered as 2 x 10 mg-10 mg tablets in healthy female subjects under fasting conditions.

Clinical Study Center: InVentiv Health Clinique, Inc., Quebec, Canada
Clinical Study Period: October 17, 2015-November 16, 2015

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: November 12, 2015-December 1, 2015

Study Design, Treatments, and Drug Administration:
This was a single-center, open-label, randomized, 2-way crossover study conducted in 52 healthy premenopausal females (48 completed; 20-45 years of age) with a BMI within the range of 19.3-29.8 kg/m^2.

Subjects were confined to the clinical from evening of Day -1 (at least 10 hours prior to drug administration) until after the 24 hour post-dose blood draw in each period. The treatment phases were separated by washout periods of at least 21 days between the last dose of each period and the first dose of the subsequent period.

Blood samples were collected pre-dose and up to 72 hours post-dose for PK characterization (See *PK Characterization* section for details).

In each period, according to randomization schedule, all subjects received single oral doses of either Test or Reference study medication as follows:

- Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride), at between 7-8 am
- Reference: Two Diclectin® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride), at between 7-8 am

All tablets were administered orally with 240 mL water. No food was allowed from 10 hours before until at least 4 hours after each dosing. Fluids were not permitted from 1 hour pre-dose and to 1 hour post-dose. Water was allowed *ad libitum* at all other times.

> **Reviewer's Comment**: This new formulation consists of an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. (b) (4) . To this core, an immediate-release layer of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride is added. Diclectin® and Diclegis® are two different trade names of the same drug product. Ten (10) mg doxylamine succinate and 10 mg pyridoxine hydrochloride DR tablets are

sold under the name Diclectin® in Canada and under the name Diclegis® in the United States.

Inclusion Criteria:

- Healthy, non-smoking or moderate smoking (i.e., < 10 cigarettes daily), premenopausal females of ages from 18 to 45 years.
- Females with BMI in the range of > 18.5 and < 30 kg/m².
- Females of childbearing potential who are sexually active with a male partner must be willing to use one of the following acceptable contraceptive methods throughout the study and for 30 days after the last study drug administration:
  - Intra-uterine contraceptive device placed at least 4 weeks prior to study drug administration;
  - Condom with intravaginally applied spermicide starting at least 14 days prior to study drug administration;
  - Hormonal contraceptives starting at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study;
  - Sterile male partner (vasectomized for at least 6 months).

Exclusion Criteria:

Subjects who had any of the following criteria were excluded from the study:

- Any clinically significant abnormality or abnormal laboratory test results found during medical screening or positive test for hepatitis B, hepatitis C, or HIV found during medical screening.
- Positive urine drug screen at screening.
- History of allergic reactions to doxylamine, other ethanolamine derivative antihistamines, pyridoxine, or other related drugs and any inactive ingredient in the Diclegis® formulation.
- Positive pregnancy test at screening.
- Any reason which, in the opinion of the medical sub-investigator, would prevent the subject from participating in the study.
- Clinically significant ECG abnormalities or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at screening.
- History of significant alcohol abuse within 1 year prior to screening or regular use of alcohol within six months prior to the screening visit (more than 14 units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).
- History of significant drug abuse within 1 year prior to screening or use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs (such as cocaine, phencyclidine [PCP], and crack) within 1 year prior to screening.
- Participation in a clinical trial involving the administration of an investigational or marketed drug within 30 days (90 days for biologics) prior to the first dosing or concomitant participation in an investigational study involving no drug administration.
- Use of medication other than topical products without significant systemic absorption and hormonal contraceptives:
  - Prescription medication within 14 days prior to the first dosing;
  - OTC products including natural health products (e.g., food supplements and herbal supplements) within seven days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily);
  - Multivitamins or supplements containing vitamin B6 within 28 days prior to the first dosing;

    - A depot injection or an implant of any drug (other than hormonal contraceptives) within three months prior to the first dosing;
    - Monoamine oxidase (MAO) inhibitors within 30 days prior to the first dosing.
- Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing.
- Hemoglobin < 115 g/L and hematocrit < 0.32 L/L at screening.
- Breast-feeding subject.

Demographics of Subjects:
The mean age of the 48 subjects included in the PK analysis was 32 (range: 20-45 years) with a mean BMI of 24.6 kg/m^2 (range: 19.3-29.8 kg/m^2). Among the 48 females who were included in the PK analysis, 95.8% (46 subjects) were Caucasians and 4.2% (2 subjects) were African Americans.

Concomitant Medication and Diet Restrictions:
Prescription and OTC medications were prohibited throughout the study. No concomitant drug therapy was allowed during the study except one(s) required for the medical management of an AE. The use of hormonal contraceptives was allowed and documented. Any concomitant medication use other than the occasional use of acetaminophen was evaluated on a case-by-case basis by the principle investigator. All concomitant medication use was documented.

Subjects were required to abstain from:
- Food containing poppy seeds within 24 hours prior to the first admission of each period;
- Food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours prior to the first dosing until after the last PK blood sample collection of each period;
- Natural health products (including food supplements, herbal supplements, etc.) from 7 days prior to the first dosing until after the last PK blood sample collection of each period;
- Multivitamins containing vitamin B6 or B6 supplement from 28 days prior to the first dosing until after the last PK blood sample collection of the study;
- Food or beverages containing grapefruit, starfruit, pomegranate, pineapple, or pomelo from 7 days prior to the first dosing of each period until after the last PK blood sample collection of each period;
- Excessive consumption (e.g., more than once a day) of foods or beverages with high content of vitamin B6 (e.g., brewer's yeast, meat and poultry, liver, fish, spinach, peppers, squash, banana, unpeeled potatoes, nuts and seeds, whole-wheat) from 7 days prior to admission until after the last sample collection of each period;
- Soft or hard drugs during the study;
- Smoking from at least 2 hours prior to the first dosing until 5 hours post- dose. Subjects were not allowed to smoke more than nine cigarettes per day during the study;
- Alcohol-based products from 24 hours prior to admission until after the last PK sample collection of each period.

Reviewer's Comment: In order to minimize endogenous concentration of pyridoxine and its metabolites, study participants were asked to avoid consuming vitamin B6 supplements and foods with high content of vitamin B6 for appropriate periods of time before drug administration and during the study.

PK Characterization:

Blood samples for plasma (whole blood for pyridoxal) concentration measurements were collected as the following:

Doxylamine:

- At pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 60 hours post-dose (22 samples).

Pyridoxine:

- At pre-dose (-1, -0.5 hours, and -5 minutes) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, and 8 hours post-dose (24 samples).

Pyridoxal:

- At pre-dose (-1, -0.5 hours, and -5 minutes) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, and 16 post-dose (27 samples).

Pyridoxal 5′-phosphate:

- At pre-dose (-1, -0.5 hours, and -5 minutes) and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 48, and 72 hours post-dose (24 samples).

Reviewer's Comment: Sponsor employed different blood sampling schedules for each analyte but did not provide a rationale. Compared to Study 150033, more samples were collected during the early post-dose time period up to 6 hours post-dose.

Pyridoxine and its metabolites, pyridoxal and pyridoxal 5′-phosphate are endogenous compounds and needed to collect samples for baseline corrections. For baseline correction, for each subject and treatment period, the baseline value was defined as the mean of the -1, -0.5 hour, and within 5 minutes pre-dose samples obtained for that same subject and period on Day 1. The calculated mean baseline concentration was considered as the pre-dose value. The data for each subject and each treatment period was corrected for baseline by subtracting the mean baseline value from pre-dose and all post-dose values. If baseline-adjusted concentrations are negative, concentrations were to be set to zero. This study was conducted using a sampling truncated at 72 hours for pyridoxal-5′-phosphate. Whenever concentration data was missing for the last sampling time (i.e., 72 hours post-dose) for a subject, calculation of AUC(0-72) was not done. This subject was excluded from all analyses involving this specific AUC.

Non-compartment PK parameters including the following were calculated for plasma doxylamine, pyridoxine, and pyridoxal:

- AUC(0-t): area under the concentration-time curve from time zero to the last non-zero concentration
- AUC(0-inf): area under the concentration-time curve from time zero to infinity
- T_{max}: time of observed C_{max}
- C_{max}: maximum observed concentration

Non-compartment PK parameters including the following were calculated for plasma pyridoxal 5′-phosphate:

- AUC(0-72): area under the concentration-time curve from time zero to 72 hours post-dose
- T_{max}: time of observed C_{max}
- C_{max}: maximum observed concentration

Sample Size Determination:
Per Sponsor, based on the data from previous single-dose studies, the following was estimated:

- Intra-subject CV of doxylamine should be approximately 21% and 16% for AUC and C_{max}, respectively
- Intra-subject CV of baseline-corrected pyridoxal 5′-phosphate should be approximately 28% and 15% for both AUC and C_{max}, respectively

Thus, with these expected CVs and an expected ratio of AUC and C_{max} within 0.925 and 1.08, the study should have a power of at least 80% to show BE with 46 subjects. In order to account for possible dropouts, 52 subjects were included in the study.

Reviewer's Comment: The sample size of 52 appears to be adequate for BE assessment.

PK and Statistical Analyses:
PK and statistical analyses were performed using Pharsight® Knowledgebase Server™ (PKS) version 4.0.2 and Phoenix® WinNonlin® 6.4, which were validated for BE studies by (b) (4). These software perform non-compartmental analyses of PK parameters and statistical analyses (via SAS version 9.2) according to current regulatory recommendations. R (version 3.0.1 or higher) was used to generate plots of PK profiles.

Analysis of variance (ANOVA) was performed on the natural log-transformed PK parameters C_{max}, AUC(0-t), and AUC(0-inf) for doxylamine and on the natural log-transformed PK parameters C_{max} and AUC(0-72) for baseline-corrected pyridoxal 5′-phosphate. For these parameters, the 90% geometric CIs of the ratio (A/B) from the analysis of the ln-transformed C_{max}, AUC(0-t), AUC(0-inf), and AUC(0-72) must be within 80.00% to 125.00% to conclude BE for that parameter.

Safety Assessments:

- A urine pregnancy test was performed for all subjects at the time of screening and study exit procedures, and a serum pregnancy test was performed prior to drug administration in each period.
- Clinical laboratory tests (biochemistry, hematology, and urinalysis) were performed for each subject at the time of screening and study exit procedures.
- Physical examinations, ECGs measurements, and vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) were performed at the time of screening, only. In addition, menses last date were reported at screening, at check-in, and before discharge in each period.
- Throughout the study, subjects were monitored for AEs.

Bioanalytical Method:
Bioanalysis was conducted at the (b) (4). Study samples were analyzed using a LC-MS/MS method for the determination of doxylamine, pyridoxine, and pyridoxal 5′-phosphate concentrations in human plasma and for determination of pyridoxal concentrations in human whole blood. Study samples were stored in the freezer at -20°C for doxylamine, pyridoxine, pyridoxal, and at -80°C for pyridoxal 5′-phosphate until sample analysis. The analytes were extracted by protein precipitation. Carbinoxamine, pyridoxine-d_3, pyridoxal-d_3, and pyridoxal 5′-phosphate-d_3 were used as internal standards (ISs) for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate, respectively. After sample extraction, samples (i.e., 50 µL for pyridoxine, pyridoxal, and pyridoxal 5′-

phosphate and 100 µL for doxylamine) were injected for analysis. Sample analysis was performed using a triple quadrupole mass spectrometer following separation via the high pressure liquid chromatography (HPLC) system. The LC-MS/MS method was developed and validated with the dynamic range of 0.50-250 ng/mL for doxylamine, 0.25-100 ng/mL for pyridoxine, 0.5-400 ng/mL for pyridoxal, and 2-200 ng/mL for pyridoxal 5′-phosphate.

The stability of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate in human plasma samples was demonstrated during method validation. Doxylamine was stable in human plasma at room temperature for 24 hours and stable at -20ºC for approximately 507 days. Pyridoxine was stable in human plasma at room temperature for 22.5 hours and stable at -20ºC for approximately 166 days. Pyridoxal was stable in whole blood at 4ºC for 24 hours and stable at -20ºC for approximately 102 days. Pyridoxal 5′-phosphate was stable in human plasma at 4ºC for 27 hours and stable at -80ºC for approximately 289 days. The established long term stability was sufficient to cover the maximum storage period of 26 days for doxylamine, 22 days for pyridoxine, 28 days for pyridoxal, and 24 days for pyridoxal 5′-phosphate. Doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate were shown to be stable during 4 freeze-thaw cycles. Sample extracts for all four analytes were stable at room temperature for more than 95 hours.

Calibration standard and quality control (QC) working spiking solutions were prepared by diluting the analyte stock solutions. These working spiking solutions were then spiked in blank matrices to obtain calibration standards and QC samples. To maximize integrity of the matrix when preparing the calibration standards and QC samples, a maximum of 5% (v/v) of the working spiking solutions were added to the blank matrices. After preparation of the calibration standards and QC samples, those for pyridoxal 5′-phosphate were stored in the freezer at -80ºC and those for others were stored at -20ºC.

Accuracy during sample analysis was expressed as percent difference from theoretical concentration (i.e., %RE). Precision of the calibration standards and QC samples during sample analysis was expressed as the percent coefficient of variation (%CV).

Table A-1-1: Back Calculated Concentrations of Calibration Standards for Doxylamine in Human Plasma

Nominal Concentration (ng/mL)	0.5	1.0	10.0	25.0	50.0	100.0	200.0	250.0
Runs (n)	22	22	22	22	22	22	22	22
Mean Concentration (ng/mL)	0.51	0.96	10.0	24.6	50.3	98.8	201.5	258.7
Inter-run % CV	3.8	4.2	3.0	2.6	3.2	2.9	2.8	2.4
Inter-run % RE	2.0	-4.0	-0.1	-1.7	0.7	-1.2	0.8	3.5

Table A-1-2: Inter-run Accuracy and Precision of QC Samples for Doxylamine in Human Plasma

Nominal Concentration (ng/mL)	1.5	25.0	125.0	175.0
Runs (n)	32	32	32	32
Mean Concentration (ng/mL)	1.5	25.0	127.6	179.1
Inter-run % CV	4.1	3.2	3.3	2.7
Inter-run % RE	-1.3	-0.1	2.1	2.3

Table A-1-3: Back Calculated Concentrations of Calibration Standards for Pyridoxine in Human Plasma

Nominal Concentration (ng/mL)	0.25	0.5	3.0	10.0	20.0	40.0	80.0	100.0
Runs (n)	26	26	26	26	26	26	26	26
Mean Concentration (ng/mL)	0.25	0.49	3.1	10.1	20.3	40.0	79.3	97.7
Inter-run % CV	4.0	4.1	2.0	2.1	1.6	2.9	2.0	1.9
Inter-run % RE	0.0	-2.0	2.0	0.6	1.4	0.0	-0.9	-2.3

Table A-1-4: Inter-run Accuracy and Precision of QC Samples for Pyridoxine in Human Plasma

Nominal Concentration (ng/mL)	0.75	5.0	50.0	75.0
Runs (n)	38	38	38	38
Mean Concentration (ng/mL)	0.73	5.0	49.1	72.4
Inter-run % CV	2.7	2.4	2.3	2.3
Inter-run % RE	-2.7	-0.4	-1.9	-3.4

Table A-1-5: Back Calculated Concentrations of Calibration Standards for Pyridoxal in Human Whole Blood

Nominal Concentration (ng/mL)	0.5	1.0	10.0	24.96	40.0	80.0	160.0	320.0	400.0
Runs (n)	33	32	34	33	34	33	34	34	34
Mean Concentration (ng/mL)	0.5	1.0	10.0	25.4	40.5	81.1	158.9	313.9	394.1
Inter-run % CV	4.0	4.0	3.2	2.5	3.4	4.5	2.1	3.0	2.2
Inter-run % RE	0.0	-1.0	0.4	1.8	1.4	1.4	-0.7	-1.9	-1.5

Table A-1-6: Inter-run Accuracy and Precision of QC Samples for Pyridoxal in Human Whole Blood

Nominal Concentration (ng/mL)	1.84	21.34	101.84	201.34	301.34
Runs (n)	49	49	49	49	49
Mean Concentration (ng/mL)	1.89	20.4	96.0	191.1	285.4
Inter-run % CV	5.3	3.2	4.5	3.3	4.5
Inter-run % RE	2.7	-4.4	-5.8	-5.1	-5.3

Table A-1-7: Back Calculated Concentrations of Calibration Standards for Pyridoxal 5′-Phosphate in Human Plasma

Nominal Concentration (ng/mL)	2.0	4.0	10.0	16.0	20.0	40.0	80.0	160.0	200.0
Runs (n)	26	25	26	26	26	26	26	26	26
Mean Concentration (ng/mL)	2.0	4.0	10.1	16.0	20.2	40.2	79.9	158.1	198.6
Inter-run % CV	8.0	8.0	5.8	3.7	2.9	3.8	4.4	3.4	3.0
Inter-run % RE	0.0	-0.3	0.6	0.1	1.2	0.5	-0.2	-1.2	-0.7

Table A-1-8: Inter-run Accuracy and Precision of QC Samples for Pyridoxal 5′-Phosphate in Human Plasma

Nominal Concentration (ng/mL)	5.57	18.57	78.57	103.57	153.57
Runs (n)	39	39	39	39	39
Mean Concentration (ng/mL)	5.90	18.70	77.73	101.97	151.68
Inter-run % CV	29.7	4.1	3.5	4.3	3.4
Inter-run % RE	5.9	0.7	-1.1	-1.5	-1.2

Reviewer's Comment: While the cause has not been reported, one of the values from Run ID 5 on November 17, 2015 for the QC with the nominal concentration of 5.57 ng/mL was reported to be 16.34 ng/mL. This was the only outlier and if this concentration is excluded, other concentrations reported for this QC were in the acceptable concentration range.

Linearity during sample analysis was described as the mean r^2 of the standard curves. The mean r^2 values were ≥ 0.994 for doxylamine, ≥ 0.998 for pyridoxine, ≥ 0.996 for pyridoxal, and ≥ 0.990 for pyridoxal 5′-phosphate.

ISR was conducted on 6.9-7.3% of the total number of sample for each analyte. The percent (%) difference is defined as {(repeat – original) / [(repeat + original)/2]} x 100 and the percentage difference had to be within ± 20% for at least 67% of the ISR samples to be considered successful in confirming the reproducibility of the bioanalytical method.

Table A-1-9: Summary of ISR Results in Human Plasma (Study 150336)

Analyte	Total Number of Samples	Number of ISR Samples	Portion of ISR Samples (%)	Passing ISR Samples (%)
Doxylamine	2138	157	7.3	100
Pyridoxine	2343	168	7.2	98.2
Pyridoxal[a]	2633	182	6.9	98.4
Pyridoxal 5′-Phosphate	2333	167	7.2	95.8

[a] Matrix: Whole blood

Reviewer's Comment: It should be noted that for pyridoxal 5′-phosphate, ISR samples from Subjects 1 to 4 were reanalyzed twice by error. The total number of ISR samples including the duplicate samples was 199 and the ISR samples becomes 167 once the duplicates are removed. It should be noted that ISR results from Subject 3, Period 1, 14 hour post-dose sample had conflicting results as one of them had a percentage difference of -21.41% reported and was counted as a failure to meet ISR passing criteria.

While the Agency's Bioanalytical Method Validation Guidance recommends that the total number of ISR samples should be 7% of study sample size, it should be noted that the ISR samples for pyridoxal was 6.9%. Considering that the number of ISR samples is very close to the recommended 7% of study samples and considering that 98.4% of the ISR samples met the ISR acceptance criteria, the Sponsor's ISR results for pyridoxal is acceptable.

In summary, the acceptance criteria and assay performance for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate bioanalysis are in compliance with the Agency's Bioanalytical Method Validation Guidance and the bioanalytical methods are acceptable.

Disposition of Subjects:

There were 88 females screened and of these, 52 females were randomized and dosed. Forty eight (48) females completed all study periods. In accordance with the study protocol, data from all subjects who completed at least two periods, including one Test and one Reference, and for whom the PK profile could be adequately characterized were used for PK and statistical analyses (N=48). The following 4 subjects did not complete the study after receiving at least 1 dose of the study medication:

Table A-1-10: Summary of Subject Discontinuation

Subject Number	Reason for withdrawal (Date and time of withdrawal/last treatment received/reason)	Period of the last study drug administration	Replaced?	Replaced with
16	2015-11-02 10:14 / Test / Subject withdrew herself for personal reason	1	No	Not applicable
18	2015-11-04 08:39 / Test / Subject was withdrawn in Period 1 due to significant adverse event ("Pregnancy"; refer to Section 12.3.2, for details).	1	No	Not applicable
23	2015-10-17 11:04 / Reference / Subject was withdrawn for pharmacokinetic reasons (vomited within nine hours after dosing).	1	No	Not applicable
33	2015-11-13 17:57 / Reference / Subject withdrew herself for personal reason	1	No	Not applicable

Test (A)= Duchesnay, Inc., Canada, doxylamine-pyridoxine 1 x 20 mg-20 mg (b) (4) tablet.
Reference (B)= Duchesnay, Inc., Canada (Diclegis®), doxylamine-pyridoxine 2 x 10 mg-10 mg delayed-release tablets.

Protocol Deviations:
All enrolled subjects satisfied the entry criteria and received the correct treatment and dose. Non-scheduled concomitant medications were recorded. Ten subjects used wither acetaminophen or ibuprofen but no reports of protocol deviation regarding concomitant medications were reported. There were no deviations that affected subject safety or any of the outcomes of the study. A summary of protocol deviation can be found in Table A-1-11 below.

Table A-1-11: Summary of Protocol Deviation

Type	Subject Nos. (Test)	Subject Nos. (Ref.)
Study medication, Dosing, and Randomization		
In Period 2, two days after the dosing, two employees of inVentiv sent an email with confidential informations about this subject to other employees of inVentiv. This deviation is an important breach of confidentiality, since several details regarding subject's personal information were divulged. However, since each employee has to read and sign a Confidentiality Agreement that comes into effect at the date of entry to inVentiv, and since the information was not disclosed outside of inVentiv, to the Sponsor or a third party, there is no critical impact regarding this breach of confidentiality.	19	
Study Restrictions		
This subject did not use an acceptable method of contraception, condom with spermicide, as instructed. As a consequence, the subject obtained a positive pregnancy result with a home urine pregnancy test, approximately 13 days after the dosing in Period 1.There is no impact, as the safety profile of the study medication is well known, being used to prevent pregnancy nausea. Subject's safety was not compromised.	18	
Study Samples (PK)		
In Period 1, the samples of the 6.50-hour timepoint for pyridoxal-5'-phosphate of these subjects were stored in the -20°C freezer instead of -80°C freezer for approximately two hours. Even though there is no stability data at -20 °C, and because the samples were stored for only two hours at this temperature, there is no impact since their was a stability of 26 hours and 27 minutes at 4°C.	28, 30, 32, 35, 36, 37, 40, 42, 43, 45, 47, 49, 52	27, 29, 31, 33, 34, 38, 39, 41, 44, 46, 48, 50, 51
In Period 2, samples of pyridoxine of these subjects, centrifuged at 09:08 on November 14, 2015, were centrifuged for 10 non-consecutive minutes, because of a power outage. There is no impact since the separation was done adequately. In this case we are within the validated stabilities of 60 minutes in the whole blood and the 22,5 hours in matrix at room temperature.	27, 29, 31, 34, 38, 39, 41, 44, 46, 48, 50, 51	28, 30, 32, 35, 36, 37, 40, 42, 43, 45, 47, 49, 52
In Period 2, on November 14, 2015, the -20°C freezer failed because of a power outage. The samples of pyridoxal, doxylamine and pyridoxine for the 1.25- to 16.0-hours timepoints were stored to a -80°C freezer for approximately one day. There is no impact due to the following stabilities at -80°C: 95 days for pyridoxal, 371 days for doxylamine, and 100 days for pyridoxine.	27, 29, 31, 34, 38, 39, 41, 44, 46, 48, 50, 51	28, 30, 32, 35, 36, 37, 40, 42, 43, 45, 47, 49, 52

Test (A)= Duchesnay, Inc., Canada, doxylamine-pyridoxine 1 x 20 mg-20 mg (b) (4) tablet.
Reference (B)= Duchesnay, Inc., Canada (Diclegis®), doxylamine-pyridoxine 2 x 10 mg-10 mg delayed-release tablets.

Handling of Missing Samples:
Out of the 52 subjects enrolled, Subjects 16, 18, 23, and 33 were excluded from the PK analysis. For Subject 20, all pyridoxine concentrations were below limit of quantitation (BLQ) in Period 1 (Treatment B), thus the PK profile could not be adequately characterized. For this reason, Subject 20 was excluded from the PK population of pyridoxine. This subject was analyzed in Run 05ANHX with Subjects 18, 19, and 21. This run was investigated and no anomalies were found.

Except for the subjects mentioned above), other subjects with missing data were kept in the PK and statistical analyses as the PK parameters could be estimated using the remaining data points.

Reviewer's Comment: This reviewer concurs to the Investigator's/Sponsor's assessments and decisions made to either include or exclude these subjects/samples from the PK characterization and BE analysis.

PK and BE Assessment Results:

Reviewer's Comment: Sponsor performed their BE assessment based on doxylamine and pyridoxal 5′-phosphate. The Sponsor was asked to provide their rationale as to why the BE assessment was based on metabolite, pyridoxal 5′-phosphate rather than the parent drug, pyridoxine. In their March 24, 2016 response, the Sponsor provided the following rationale:

"While a BE assessment should always be performed on the active ingredient whenever possible, in this case pyridoxine acts as a pro-drug. Once phosphorylated, it crosses the membranes much easier and therefore, is absorbed very fast (i.e., less than 2.5 hrs in its DR form; the half-life is extremely fast, less than 15 mins). This type of kinetics makes it challenging to measure appropriately and furthermore because of the fast elimination there is no accumulation and therefore no steady state is reached and therefore no steady state value to compare.

Furthermore, the current formulation of Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) is ideal for the night dose (around 10 pm), in that the DR allows maximum concentrations of pyridoxine in the systemic circulation to be reached at around 2 am. Pyridoxine will be converted into pyridoxal by 3 am which will be then converted to pyridoxal 5'-phosphate which will reach maximum concentrations around 9 am. It is unlikely that pyridoxine and pyridoxal are the active vitamin B6 metabolites acting on morning nausea and vomiting of pregnancy (NVP) since by 8 am there is no pyridoxine in the systemic circulation due to a short half-life and pyridoxal concentrations are almost negligible. Therefore, pyridoxal 5'-phosphate is believed to be the most active component against NVP reaching peak concentrations at around 9 am."

While the mechanism of action is unknown, it appears that the Sponsor's rationale regarding T_{max} does not account for doxylamine while TRADENAME is a combination product of doxylamine and pyridoxine.

Vitamin B6 is a water-soluble vitamin present in 3 major forms: pyridoxine, pyridoxal, and pyridoxamine. These 3 forms are inter-convertible to their phosphorylated forms. As described in the current Diclegis® product label, pyridoxine is a pro-drug primarily metabolized in the liver. Once phosphorylated, it crosses the membranes much easier and therefore is absorbed very quickly and has an extremely short half-life of approximately 0.4 hours. The fast elimination makes it challenging to adequately characterize steady state and conduct BE assessment based on pyridoxine. In addition, its main active metabolite, pyridoxal 5′-phosphate is known to be the major active form in the blood, accounting for at least 60% of circulating vitamin B6 (Diclegis® product label).

Therefore, it appears to be a reasonable approach to conduct the BE assessment based on pyridoxal 5′-phosphate instead of pyridoxine.

It should be noted that the following comment was provided to the Sponsor via the Division's December 10, 2013 written response:

> *"… we recommend that you provide us with graphical comparisons of pyridoxal 5-phosphate and doxylamine PK at steady state for approved and proposed dosing regimen."*

Reference is made to Dr. Sayed Al Habet's Clinical Pharmacology review dated December 23, 2013 under NDA 021876 in DARRTS regarding the correspondence between the Division and the Sponsor on this matter prior to the submission of this NDA.

Based on the Sponsor's justification and the Division's advice provided to the Sponsor, the BE assessment in this review was based on doxylamine and pyridoxal 5′-phosphate. For pyridoxal 5′-phosphate, in order to minimize the contribution of endogenous concentration, baseline corrected pyridoxal 5′-phosphate concentrations were used for BE assessment.

Doxylamine

Mean (SD) plasma PK parameters of doxylamine are summarized in Table A-1-12.

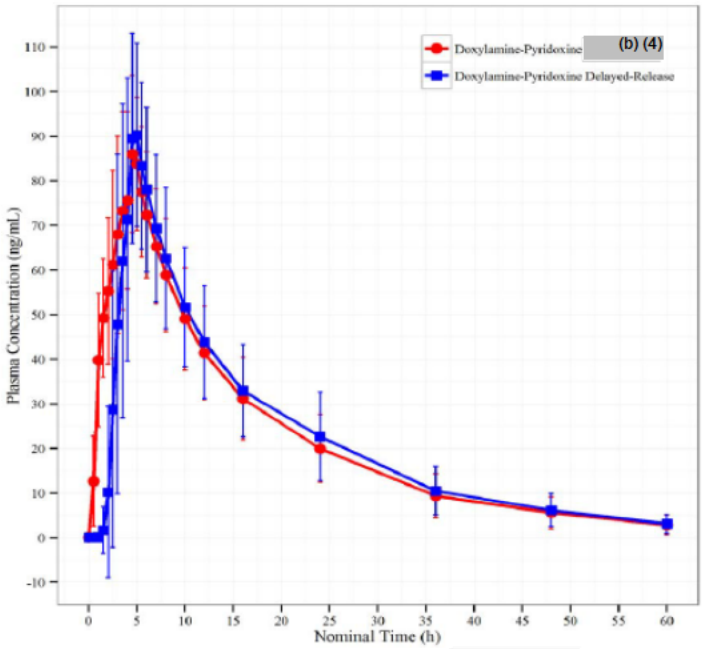
Table A-1-12: Mean (SD) Plasma PK Parameters of Doxylamine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference)

Parameter	Test (N=48)	Reference (N=48)
AUC(0-60) (ng·hr/mL)	1367.0 (356.7)	1340.0 (340.2)
AUC(0-inf) (ng·hr/mL)	1425.8 (405.1)	1400.8 (386.0)
C_{max} (ng/mL)	92.3 (15.7)	98.1 (17.2)
T_{max} (hr)[a]	4.5 (2.5-5.5)	4.5 (3.0-24.0)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Mean (±SD) concentration-time profiles for doxylamine for each treatment are shown in Figure A-1-1. It should be noted that the mean profiles for both the Test and Reference are plotted based on the mean plasma concentrations calculated per time point. Therefore, the maximum concentrations observed in the mean data figures may not reflect the mean C_{max}, as the C_{max} and the time of maximum concentration (T_{max}) vary between individuals.

Figure A-1-1: Mean (±SD) concentration-time profile for Doxylamine for each treatment



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to doxylamine for the parameters AUC(0-24) and C_{max} using natural log transformed data are summarized in Table A-1-13.

Table A-1-13: Summary of BE Analysis Results of Doxylamine PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) (N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-60) (ng·hr/mL)	1325.3	1301.4	102.0	98.4-105.7
AUC(0-inf) (ng·hr/mL)	1375.6	1353.9	101.7	98.1-105.5
C_{max} (ng/mL)	91.0	96.7	94.2	90.8-97.7

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Based on these results, the TRADENAME showed comparable rate and extent of exposure when compared to Diclectin®.

Pyridoxal 5′-phosphate

Mean (SD) plasma PK parameters of baseline corrected pyridoxal 5′-phosphate are summarized in Table A-1-14.

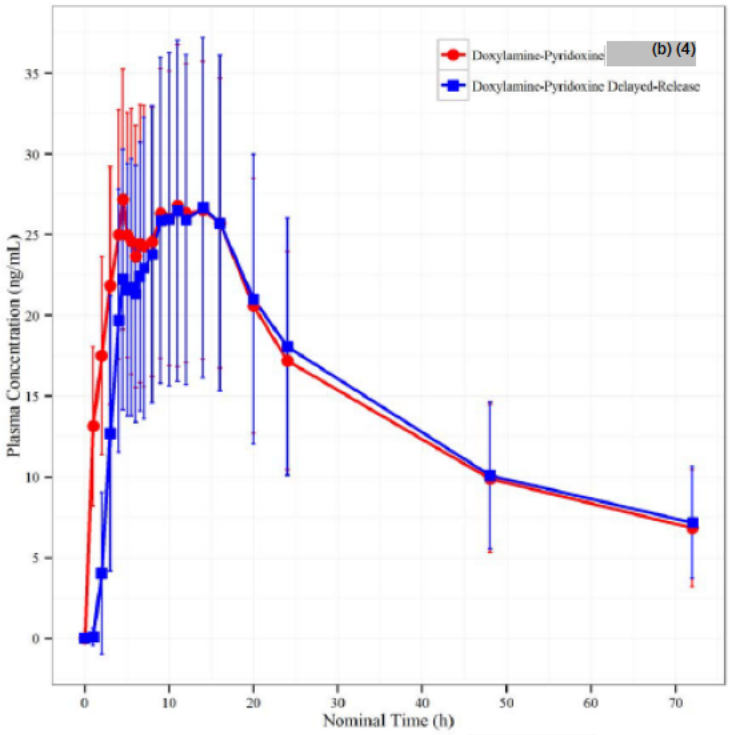
Table A-1-14: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference)

Parameter	Test (N=48)	Reference (N=48)
AUC(0-72) (ng·hr/mL)	1076.2 (382.2)	1037.9 (381.9)
C_{max} (ng/mL)	30.1 (9.2)	29.0 (9.9)
T_{max} (hr)[a]	9.0 (3.0-16.0)	11.0 (4.0-24.0)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Mean (±SD) concentration-time profiles for baseline corrected pyridoxal 5′-phosphate for each treatment are shown in Figure A-1-2. It should be noted that the mean profiles for both the Test and Reference are plotted based on the mean plasma concentrations calculated per time point. Therefore, the maximum concentrations observed in the mean data figures may not reflect the mean C_{max}, as the C_{max} and the time of maximum concentration (T_{max}) vary between individuals.

Figure A-1-2: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal 5′-Phosphate for each treatment



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Mean (SD) plasma PK parameters of baseline uncorrected pyridoxal 5′-phosphate are summarized in Table A-1-15.

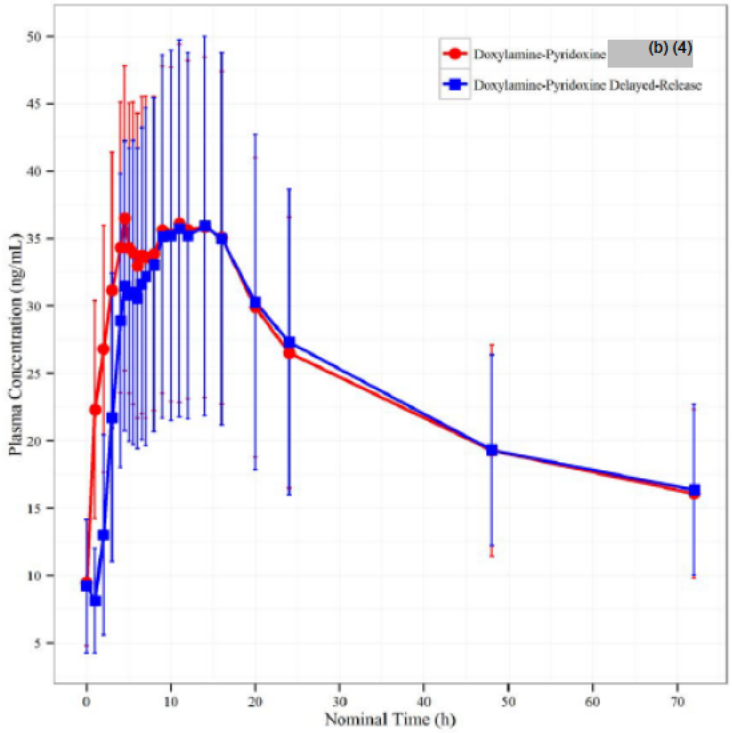
Table A-1-15: Mean (SD) Plasma PK Parameters of Baseline Uncorrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference)

Parameter	Test (N=48)	Reference (N=48)
AUC(0-72) (ng·hr/mL)	1742.7 (632.7)	1702.8 (622.7)
C_{max} (ng/mL)	39.3 (12.6)	38.3 (13.4)
T_{max} (hr)[a]	9.0 (3.0-16.0)	11.0 (4.0-24.0)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Mean (±SD) concentration-time profiles for baseline uncorrected pyridoxal 5′-phosphate for each treatment are shown in Figure A-1-3.

Figure A-1-3: Mean (±SD) concentration-time profile for Baseline Uncorrected Pyridoxal 5′-Phosphate for each treatment



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to pyridoxal 5′-phosphate for the baseline corrected parameters AUC(0-72) and C_{max} using natural log transformed data are summarized in Tables A-1-16.

Table A-1-16: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) (N=48)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-72) (ng·hr/mL)	1006.9	964.9	104.2	97.9-111.0
C_{max} (ng/mL)	28.8	27.5	104.8	101.1-108.7

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Based on these results, the TRADENAME showed comparable rate and extent of exposure when compared to Diclectin®.

Pyridoxine

Reviewer's Comment: For pyridoxine, since no pre-dose concentrations were detected for all subjects, the Sponsor did not perform any baseline adjustment on pyridoxine concentrations.

Mean (SD) plasma PK parameters of pyridoxine are summarized in Table A-1-17.

Table A-1-17: Mean (SD) Plasma PK Parameters of Pyridoxine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference)

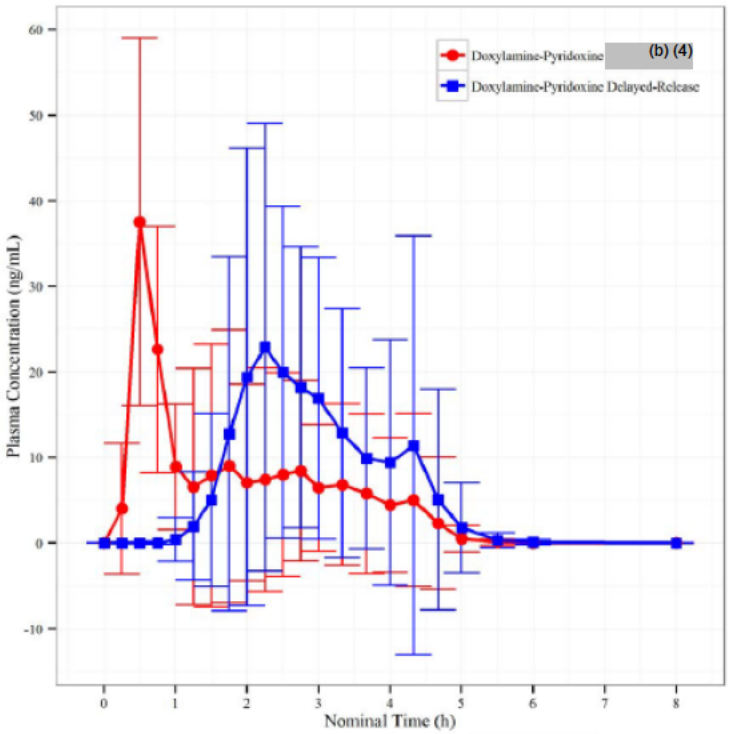
Parameter	Test (N=47)	Reference (N=47)
AUC(0-8) (ng·hr/mL)	42.3 (14.7)	49.0 (16.2)
AUC(0-inf) (ng·hr/mL)	42.5 (14.7)	49.2 (16.2)
C_{max} (ng/mL)	47.1 (18.7)	51.6 (24.4)
T_{max} (hr)[a]	0.5 (0.5-4.7)	2.5 (1.3-4.7)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Reviewer's Comment: For Subject 20, all pyridoxine concentrations were BLQ in Period 1 (Treatment B), thus the PK profile could not be adequately characterized. For this reason, Subject 20 was excluded from the PK population of pyridoxine.

Mean (±SD) concentration-time profiles for pyridoxine for each treatment are shown in Figures A-1-4.

Figure A-1-4: Mean (±SD) concentration-time profile for Pyridoxine for each treatment



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Pyridoxal

Mean (SD) whole blood PK parameters of baseline corrected pyridoxal are summarized in Table A-1-18.

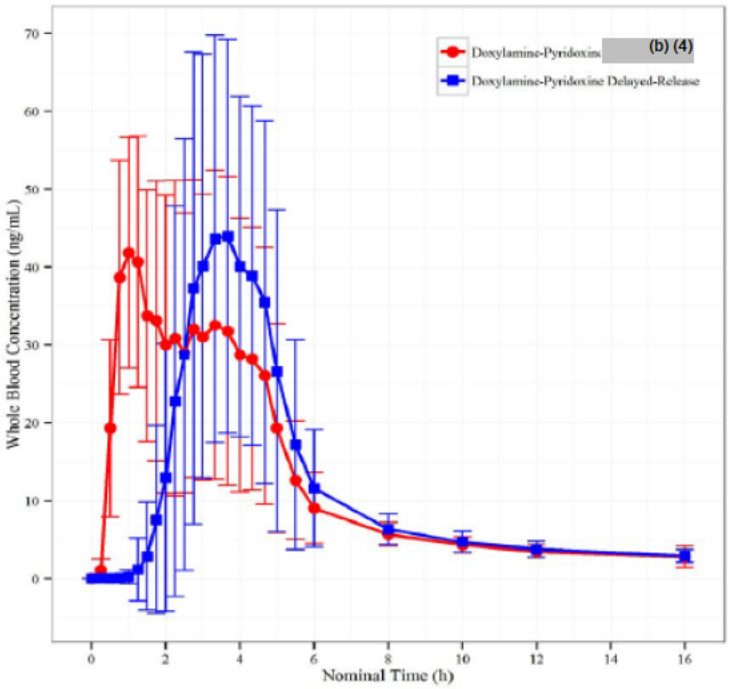
Table A-1-18: Mean (SD) Whole Blood PK Parameters of Baseline Corrected Pyridoxal Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference)

Parameter	Test (N=48)	Reference (N=48)
AUC(0-16) (ng·hr/mL)	203.7 (51.7)	182.3 (51.7)
AUC(0-inf) (ng·hr/mL)	213.6 (55.9)	218.8 (52.9)
C_{max} (ng/mL)	58.9 (17.0)	66.3 (21.6)
T_{max} (hr)[a]	3.0 (0.8-5.0)	3.5 (2.3-16.1)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Mean (±SD) concentration-time profiles for baseline corrected pyridoxal for each treatment are shown in Figure A-1-5.

Figure A-1-5: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal for each treatment



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Mean (SD) whole blood PK parameters of baseline uncorrected pyridoxal are summarized in Table A-1-19.

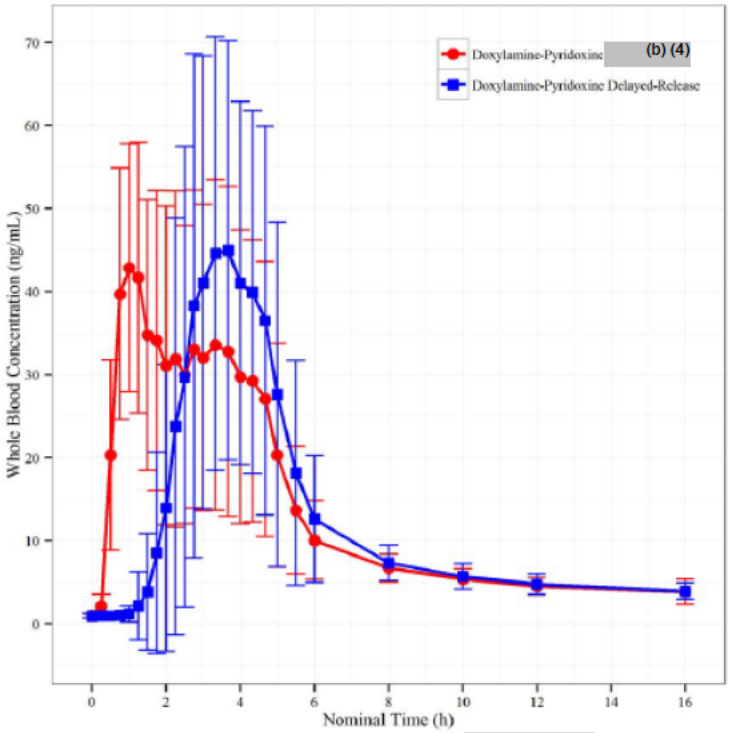
Table A-1-19: Mean (SD) Whole Blood PK Parameters of Baseline Uncorrected Pyridoxal Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference)

Parameter	Test (N=48)	Reference (N=48)
AUC(0-16) (ng·hr/mL)	219.8 (54.8)	198.0 (56.1)
C_{max} (ng/mL)	59.9 (17.2)	67.2 (21.7)
T_{max} (hr)[a]	3.0 (0.8-5.0)	3.5 (2.3-16.1)

Test: One TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride)
Reference: Two Diclegis® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride)
[a] Median (minimum-maximum)

Mean (±SD) concentration-time profiles for baseline uncorrected pyridoxal for each treatment are shown in Figure A-1-6.

Figure A-1-6: Mean (±SD) concentration-time profile for Baseline Uncorrected Pyridoxal for each treatment



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Safety Results:
Per Sponsor, a total of 36 treatment emergent adverse events (TEAEs) were reported by 23 of the 52 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 9 TEAEs reported by 20.0% (n=10) of the 50 subjects who received Test and 26 TEAEs reported by 36.0% (n=18) of the 50 subjects who received Reference.

The most commonly reported TEAEs were "headache" and "somnolence" reported by 13.5% (n=7) of subjects who constituted the safety population. All other TEAEs were reported by no more than 2 subjects.

> **Reviewer's Comment**: The Sponsor states that majority of the TEAEs reported were mild in severity and no safety concerns are expected.

Conclusion:
The results of this study indicates that BE is established for both doxylamine and baseline corrected pyridoxal 5′-phosphate based on AUC and C_{max} following a single dose of 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride. Both formulations were well tolerated, with no major AEs and no relevant differences in safety profiles were observed between the preparations

4.1.2 BE Study: Study 150033

Reviewer Comment: In the original NDA submission, the Sponsor did not submit the single dose BE Study 150336 that evaluated the BE of the starting dose of TRADENAME and Diclectin®. Instead, the original October 7, 2015 submission only included this multiple dose BE Study 150033 that assessed the BE between maximum daily doses of TRADENAME BID and Diclectin® TID (i.e., 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride per day) on Day 1 and Day 11. The single dose BE Study 150336 was submitted on June 13, 2016 and subsequently, the review clock was extended with a new user fee goal date of November 7, 2016 as it was considered to be a major amendment.

Title: Randomized, open-label, 3-way reference replicated crossover BE study of TRADENAME and Diclegis® (Reference) following single day and multiple day administrations in healthy subjects

Objectives: To compare the rate and extent of absorption of doxylamine, pyridoxine, and its metabolites following single and multiple day oral administration of a TRADENAME (Test) compared to Diclectin® (Reference) in healthy female subjects.

Clinical Study Center: InVentiv Health Clinique, Inc., Quebec, Canada
Clinical Study Period: March 8, 2015-June 14, 2015

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: June 5, 2015-July 14, 2015

Study Design, Treatments, and Drug Administration:
This was a single-center, open-label, randomized, 3-period, 3-sequence, reference replicated, crossover study conducted in 39 healthy premenopausal females (31 completed; 18-45 years of age) with a BMI within the range of 18.6-29.9 kg/m^2.

Subjects were confined to the clinical from evening of Day -1 until after the last blood draw on the morning of Day 12, in each period. The treatment phases were separated by washout periods of at least 28 days between the last dose of each period and the first dose of the subsequent period. Blood samples were collected pre-dose and through 24 hours post-dose on Days 1 and 11 for PK characterization (See *PK Characterization* section for details).

In each period, according to randomization schedule, all subjects received multiple oral doses of either Test or Reference study medication for 11 consecutive days as follow:

- Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride), BID (1 tablet each at 9 am and 9 pm)
- Reference: Diclectin® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet each at 9 am and 3 pm and 2 tablets at 9 pm)

All tablets were administered orally with 240 mL water. No food was allowed from at least 2.5 hours before until at least 2 hours after each dosing. Fluids were not permitted from 1 hour pre-dose and to 1 hour post-dose. Water was allowed *ad libitum* at all other times.

Reviewer's Comment: The approved starting dose is 2 tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, patients should continue taking 2 tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2,

patients should take the usual dose of 2 tablets at bedtime that night then take 3 tablets starting on Day 3 (i.e., 1 tablet in the morning and 2 tablets at bedtime). If these 3 tablets adequately control symptoms on Day 4, patients should continue taking 3 tablets daily. Otherwise, patients should take 4 tablets starting on Day 4 (i.e., 1 tablet in the morning, 1 tablet mid-afternoon, and 2 tablets at bedtime). The maximum recommended dose is 4 tablets daily. Diclegis® should be given on an empty stomach with a glass of water.

The proposed starting dose for the new formulation is one TRADENAME tablet orally at bedtime (Day 1). If the symptoms are controlled, patients should continue taking one TRADENAME tablet orally at bedtime every day. If symptoms persist (b) (4) take two tablets starting on Day (b) (4) (one tablet in the morning and one tablets at bedtime). Therefore, under the proposed new regimen, patients will start maximum daily dose of 40 mg doxylamine succinate and 40 mg pyridoxine hydrochloride from Day (b) (4) (b) (4) when symptoms are not controlled with the initial doses.

This study design was discussed in the Division's written responses to the Sponsor's questions provided on December 10, 2013 in lieu of the proposed Type C, Guidance meeting between the Division and the Sponsor. While the new formulation (TRADENAME), Test has a different dosing regimen from the Reference (i.e., twice daily dosing instead of three times per day dosing), the Sponsor evaluated the maximum daily dose of 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride. The following specific comment regarding the study design was conveyed to the Sponsor:

> *"We concur that a BE study, and single and multiple dose PK studies may be sufficient to bridge efficacy and safety information between this new formulation/regimen and the previously approved regimen. However, acceptability of these data will depend on the results and will be a review issue. For the BE study, we recommend using a single day crossover design as follows:*
>
> *Day 1:*
> *Treatment A (Twice Daily Arm): One tablet of test formulation (20 mg x 20 mg) given twice daily as follows: one on the morning and one at night*
> *Treatment B (Three Times Daily Arm): Reference formulation (10 mg x 10 mg) given three times daily as follows: one in the morning, one at 4 pm, and 2 tablets at night.*
>
> *Day 10:*
> *The same segment of a single day study described above can be repeated for the multiple doses segment on Day 10. In this case, BE can be assessed after single dose and multiple doses in one study in the same subjects.*
>
> *We also recommend that you conduct a fed/fasted BA study for the new formulation.*
>
> *In the absence of acceptable BE results, you will need clinical trial data to establish the efficacy and safety of your new formulation/regimen. In this situation, we would likely recommend that you conduct with the proposed new formulation (with IR and DR components), a randomized, placebo-controlled clinical trial, in pregnant adult women, 7 to 14 weeks gestation, with nausea and*

vomiting of pregnancy unresponsive to conservative management. This clinical trial should have the same study design that was conducted in support of the approval of Diclegis (10 mg doxylamine plus 10 mg pyridoxine) delayed-release product. Submit the protocol for such a trial with sufficient lead time to allow for our review and comment."

Reference is made to Dr. Sayed Al Habet's Clinical Pharmacology review dated December 23, 2013 and the official written responses dated December 10, 2013 under NDA 021876 in DARRTS regarding the correspondence between the Division and the Sponsor prior to the submission of this NDA.

Inclusion Criteria:

- Healthy, non-smoking or moderate smoking (i.e., < 10 cigarettes daily), premenopausal females of ages from 18 to 45 years.
- Females with BMI in the range of > 18.5 and < 30 kg/m².
- Females of childbearing potential who are sexually active with a male partner must be willing to use one of the following acceptable contraceptive methods throughout the study and for 30 days after the last study drug administration:
  - Intra-uterine contraceptive device placed at least 4 weeks prior to study drug administration;
  - Condom with intravaginally applied spermicide starting at least 14 days prior to study drug administration;
  - Hormonal contraceptives starting at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study;
  - Sterile male partner (vasectomized for at least 6 months).

Exclusion Criteria:

Subjects who had any of the following criteria were excluded from the study:

- Any clinically significant abnormality or abnormal laboratory test results found during medical screening or positive test for hepatitis B, hepatitis C, or HIV found during medical screening.
- Positive urine drug screen at screening.
- History of allergic reactions to doxylamine, other ethanolamine derivative antihistamines, pyridoxine, or other related drugs and any inactive ingredient in the Diclegis® formulation.
- Positive pregnancy test at screening.
- Any reason which, in the opinion of the Medical Sub-Investigator, would prevent the subject from participating in the study.
- Clinically significant ECG abnormalities or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at screening.
- History of significant alcohol abuse within 1 year prior to screening or regular use of alcohol within six months prior to the screening visit (more than 14 units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).
- History of significant drug abuse within 1 year prior to screening or use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs (such as cocaine, PCP, and crack) within 1 year prior to screening.
- Participation in a clinical trial involving the administration of an investigational or marketed drug within 30 days (90 days for biologics) prior to the first dosing or concomitant participation in an investigational study involving no drug administration.

- Use of medication other than topical products without significant systemic absorption and hormonal contraceptives:
  - Prescription medication within 14 days prior to the first dosing;
  - OTC products including natural health products (e.g., food supplements and herbal supplements) within seven days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily);
  - Multivitamins or supplements containing vitamin B6 within 28 days prior to the first dosing;
  - A depot injection or an implant of any drug (other than hormonal contraceptives) within three months prior to the first dosing;
  - MAO inhibitors within 30 days prior to the first dosing.
- Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing.
- Hemoglobin < 125 g/L and hematocrit < 0.32 L/L at screening.
- Breast-feeding subject.

Demographics of Subjects:
The mean age of the 37 subjects included in the PK analysis for Day 1 was 34 (range: 20-45 years) with a mean BMI of 24.0 kg/m^2 (range: 19.0-29.4 kg/m^2). All 39 females who were randomized and dosed were Caucasians.

Concomitant Medication and Diet Restrictions:
Prescription and OTC medications were prohibited throughout the study. No concomitant drug therapy was allowed during the study except one(s) required for the medical management of an AE. The use of hormonal contraceptives was allowed and documented. Any concomitant medication use other than the occasional use of acetaminophen was evaluated on a case-by-case basis by the principle investigator. All concomitant medication use was documented.

Subjects were required to abstain from:
- Food containing poppy seeds within 24 hours prior to the first admission of each period;
- Food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours prior to the first dosing until after the last PK blood sample collection of each period;
- Natural health products (including food supplements, herbal supplements, etc.) from 7 days prior to the first dosing until after the last PK blood sample collection of each period;
- Multivitamins containing vitamin B6 or B6 supplement from 28 days prior to the first dosing until after the last PK blood sample collection of the study;
- Food or beverages containing grapefruit, starfruit, pomegranate, pineapple, or pomelo from 7 days prior to the first dosing of each period until after the last PK blood sample collection of each period;
- Excessive consumption (e.g., more than once a day) of foods or beverages with high content of vitamin B6 (e.g., brewer's yeast, meat and poultry, liver, fish, spinach, peppers, squash, banana, unpeeled potatoes, nuts and seeds, whole-wheat) from 7 days prior to admission until after the last sample collection of each period;
- Soft or hard drugs during the study;
- Smoking from at least 2.5 hours prior to the first dosing until 6 hours post-morning-dose on Day 1 and 11. Subjects were not allowed to smoke more than nine cigarettes per day during the study;

- Alcohol-based products from 24 hours prior to admission until after the last PK sample collection of each period.

Reviewer's Comment: In order to minimize endogenous concentration of pyridoxine and its metabolites, study participants were asked to avoid consuming vitamin B6 supplements and foods with high content of vitamin B6 for appropriate periods of time before drug administration and during the study.

PK Characterization:
Blood samples for plasma (whole blood for pyridoxal) concentration measurements were collected as the following:

Doxylamine:
- Days 1 and 11: At pre-dose and at 1, 2, 3, 3.5, 4, 5, 6 (prior to dosing if applicable), 7, 8, 9, 10, 11, 12 (prior to dosing), 13, 14, 15, 15.5, 16, 17, 18, 19, 20, 21, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose.
- Days 3-10: Blood samples were collected prior to each morning's dose.

Pyridoxine:
- Days 1 and 11: At pre-dose (-1, -0.5 hours, and -10 minutes) and at 0.25, 0.5, 1, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6 (prior to dosing if applicable), 6.5, 7, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.5, 10, 10.5, 11, 11.5, 12 (prior to dosing), 12.5, 13, 13.5, 13.75, 14, 14.25, 14.5, 14.75, 15, 15.5, 16, 16.5, 17, 17.5, 18, 19, 20, 21, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose.
- Days 3-10: Blood samples were collected prior to each morning's dose.

Pyridoxal:
- Days 1 and 11: At pre-dose (-1, -0.5 hours, and -10 minutes) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 (prior to dosing if applicable), 7, 8, 9, 10, 11, 12 (prior to dosing), 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 19, 20, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose.
- Days 3-10: Blood samples were collected prior to each morning's dose.

Pyridoxal 5′-phosphate:
- Days 1 and 11: At pre-dose (-1, -0.5 hours, and -10 minutes) and at 1, 2, 3, 4, 5, 6 (prior to dosing if applicable), 7, 8, 9, 10, 11, 12 (prior to dosing), 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose.
- Days 3-10: Blood samples were collected prior to each morning's dose.

Reviewer's Comment: Sponsor employed different blood sampling schedules for each analyte but did not provide a rationale.

Pyridoxine and its metabolites, pyridoxal and pyridoxal 5′-phosphate are endogenous compounds and needed to collect samples for baseline corrections. For baseline correction, for each subject and treatment period, the baseline value was defined as the mean of the -1, -0.5 hour, and within 10 minutes pre-dose samples obtained for that same subject and period on Day 1. The calculated mean baseline concentration was considered as the pre-dose value. The data for each subject and each treatment period was corrected for baseline by subtracting the mean baseline value from pre-dose and all post-dose values. If baseline-adjusted concentrations are negative, concentrations

were to be set to zero. Pre-dose samples for the evaluation of steady-state attainment were collected at approximately the same time each day and within 10 minutes prior to dosing.

The following non-compartment PK parameters were calculated for plasma doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate:

- AUC(0-6), AUC(0-12), and AUC(0-24): (partial) area under the concentration-time curve
- T_{max}: time of observed C_{max}
- C_{max}: maximum observed concentration

Reviewer's Comment: While analyses for partial AUCs (e.g., AUC(0-12) and AUC(0-6)) were conducted, no analyses for partial C_{max} values were conducted.

Sample Size Determination:
Per Sponsor, based on the data from previous single-dose studies, the following was estimated:

- Intra-subject CV of doxylamine should be approximately 7% and 8% for both AUC and C_{max}, respectively
- Intra-subject CV of pyridoxine should be approximately 16% and 39% for AUC and C_{max}, respectively
- Intra-subject CV of baseline-corrected pyridoxal 5′-phosphate should be approximately 24% and 14% for both AUC and C_{max}, respectively

Thus, with these expected CVs and an expected ratio of AUC and C_{max} within 0.95 and 1.05, the study should have a power of at least 90% to show BE with 33 subjects. In order to account for possible dropouts, 39 subjects were included in the study.

Reviewer's Comment: The sample size of 39 appears to be adequate for BE assessment.

PK and Statistical Analyses:
PK and statistical analyses were performed using Pharsight® Knowledgebase Server™ (PKS) version 4.0.2 and Phoenix® WinNonlin® 6.4, which were validated for BE studies by (b) (4). These software perform non-compartmental analyses of PK parameters and statistical analyses (via SAS version 9.2) according to current regulatory recommendations. R (version 3.0.1 or higher) was used to generate plots of PK profiles.

ANOVA was performed on the natural log-transformed PK parameters C_{max} and AUC(0-24). For these parameters, the 90% geometric CIs of the ratio (A/B) from the analysis of the ln-transformed C_{max} and AUC(0-24) must be within 80.00% to 125.00% to conclude BE for that parameter.

Reviewer's Comment: It should be noted that ANOVA were not performed for partial C_{max} and AUC values.

Safety Assessments:

- A urine pregnancy test was performed for all subjects at the time of screening and study exit procedures, and a serum pregnancy test was performed prior to drug administration in each period.
- Clinical laboratory tests (biochemistry, hematology, and urinalysis) were performed for each subject at the time of screening and study exit procedures.
- Physical examinations, ECGs measurements, and vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) were performed at the time of screening, only. In

addition, menses last date were reported at screening, at check-in, and before discharge in each period.

- Throughout the study, subjects were monitored for AEs.

Bioanalytical Method:

Bioanalysis was conducted at the (b) (4) . Study samples were analyzed using a LC-MS/MS method for the determination of doxylamine, pyridoxine, and pyridoxal 5′-phosphate concentrations in human plasma and for determination of pyridoxal concentrations in human whole blood. Study samples were stored in the freezer at -20°C for doxylamine, pyridoxine, pyridoxal, and at -80°C for pyridoxal 5′-phosphate until sample analysis. The analytes were extracted from plasma by protein precipitation. Carbinoxamine, pyridoxine-d_3, pyridoxal-d_3, and pyridoxal 5′-phosphate-d_3 were used as ISs for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate, respectively. After sample extraction, samples (i.e., 50 µL for pyridoxine, pyridoxal, and pyridoxal 5′-phosphate and 100 µL for doxylamine) were injected for analysis. Sample analysis was performed using a triple quadrupole mass spectrometer following separation via the HPLC system. The LC-MS/MS method was developed and validated with the dynamic range of 0.50-250 ng/mL for doxylamine, 0.25-100 ng/mL for pyridoxine, 0.5-400 ng/mL for pyridoxal, and 2-200 ng/mL for pyridoxal 5′-phosphate.

The stability of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate in human plasma samples was demonstrated during method validation. Doxylamine was stable in human plasma at room temperature for 24 hours and stable at -20ºC for approximately 507 days. Pyridoxine was stable in human plasma at room temperature for 22.5 hours and stable at -20ºC for approximately 166 days. Pyridoxal was stable in whole blood at 4ºC for 24 hours and stable at -20ºC for approximately 127 days. Pyridoxal 5′-phosphate was stable in human plasma at 4ºC for 27 hours and stable at -80ºC for approximately 289 days. The established long term stability was sufficient to cover the maximum storage period of 122 days for doxylamine, 124 days for pyridoxine, 119 days for pyridoxal, and 105 days for pyridoxal 5′-phosphate. Doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate were shown to be stable during 4 freeze-thaw cycles. Sample extracts for all four analytes were stable at room temperature for more than 95 hours.

Calibration standard and QC working spiking solutions were prepared by diluting the analyte stock solutions. These working spiking solutions were then spiked in blank matrices to obtain calibration standards and QC samples. To maximize integrity of the matrix when preparing the calibration standards and QC samples, a maximum of 5% (v/v) of the working spiking solutions were added to the blank matrices. After preparation of the calibration standards and QC samples, those for pyridoxal 5′-phosphate were stored in the freezer at -80ºC and those for others were stored at -20ºC.

Accuracy during sample analysis was expressed as percent difference from theoretical concentration (i.e., %RE). Precision of the calibration standards and QC samples during sample analysis was expressed as the percent coefficient of variation (%CV).

Table A-2-1: Back Calculated Concentrations of Calibration Standards for Doxylamine in Human Plasma

Nominal Concentration (ng/mL)	0.5	1.0	10.0	25.0	50.0	100.0	200.0	250.0
Runs (n)	80	80	80	79	80	80	79	79
Mean Concentration (ng/mL)	0.50	0.98	10.43	24.74	49.60	99.67	198.15	250.24
Inter-run % CV	6.0	5.1	3.1	2.7	2.5	2.2	2.2	2.6
Inter-run % RE	0.0	-2.0	4.3	-1.0	-0.8	-0.3	-0.9	0.1

Table A-2-2: Inter-run Accuracy and Precision of QC Samples for Doxylamine in Human Plasma

Nominal Concentration (ng/mL)	1.5	25.0	125.0	175.0
Runs (n)	116	116	116	116
Mean Concentration (ng/mL)	1.45	24.05	120.64	168.82
Inter-run % CV	4.8	3.6	3.0	3.2
Inter-run % RE	-3.3	-3.8	-3.5	-3.5

Table A-2-3: Back Calculated Concentrations of Calibration Standards for Pyridoxine in Human Plasma

Nominal Concentration (ng/mL)	0.25	0.5	3.0	10.0	20.0	40.0	80.0	100.0
Runs (n)	144	144	144	142	144	143	144	144
Mean Concentration (ng/mL)	0.25	0.50	3.0	10.2	20.1	41.1	78.2	97.2
Inter-run % CV	4.0	4.0	4.3	3.6	3.9	3.2	3.2	3.7
Inter-run % RE	0.0	0.0	0.0	1.9	0.7	2.8	-2.2	-2.9

Table A-2-4: Inter-run Accuracy and Precision of QC Samples for Pyridoxine in Human Plasma

Nominal Concentration (ng/mL)	0.75	5.0	50.0	75.0
Runs (n)	205	205	205	205
Mean Concentration (ng/mL)	0.75	5.00	49.42	73.02
Inter-run % CV	4.0	4.0	3.9	5.5
Inter-run % RE	0.0	0.0	-1.2	-2.6

Table A-2-5: Back Calculated Concentrations of Calibration Standards for Pyridoxal in Human Whole Blood

Nominal Concentration (ng/mL)	0.5	1.0	10.0	24.96	40.0	80.0	160.0	320.0	400.0
Runs (n)	81	81	82	81	82	78	82	82	82
Mean Concentration (ng/mL)	0.5	0.99	10.16	24.72	40.54	80.57	160.02	316.47	395.85
Inter-run % CV	4.0	4.0	2.3	1.7	2.0	2.3	1.8	2.0	2.2
Inter-run % RE	0.0	-1.0	1.6	-0.96	1.4	0.7	0.0	-1.1	-1.0

Table A-2-6: Inter-run Accuracy and Precision of QC Samples for Pyridoxal in Human Whole Blood

Nominal Concentration (ng/mL)	1.62	1.67	21.65	201.65	301.65
Runs (n)	75	45	120	120	120
Mean Concentration (ng/mL)	1.72	1.87	21.96	201.11	300.97
Inter-run % CV	3.5	3.7	4.1	2.8	2.7
Inter-run % RE	6.2	12.0	1.3	-0.3	-0.2

Reviewer's Comment: Sponsor reported that a second preparation of QC of 1.62 ng/mL was done on June 19, 2015 because the one (1.67 ng/mL) prepared on March 20, 2015 showed a significant (but still acceptable) positive bias of 11.98%.

Table A-2-7: Back Calculated Concentrations of Calibration Standards for Pyridoxal 5′-Phosphate in Human Plasma

Nominal Concentration (ng/mL)	2.0	4.0	10.0	15.0	20.0	40.0	80.0	160.0	200.0
Runs (n)	74	74	76	76	76	76	76	76	76
Mean Concentration (ng/mL)	2.02	3.93	9.87	15.27	20.15	40.38	79.81	159.02	199.33
Inter-run % CV	5.5	4.6	3.2	3.0	2.4	2.0	1.7	1.8	1.8
Inter-run % RE	1.0	-1.8	-1.3	1.8	0.8	1.0	-0.2	-0.6	-0.3

Table A-2-8: Inter-run Accuracy and Precision of QC Samples for Pyridoxal 5′-Phosphate in Human Plasma

Nominal Concentration (ng/mL)	5.98	18.98	103.98	153.98
Runs (n)	112	112	112	112
Mean Concentration (ng/mL)	5.84	18.68	102.60	151.42
Inter-run % CV	5.0	4.1	3.6	3.8
Inter-run % RE	-2.3	-1.6	-1.3	-1.7

Linearity during sample analysis was described as the mean r^2 of the standard curves. The mean r^2 values were ≥ 0.998 for doxylamine, ≥ 0.994 for pyridoxine, ≥ 0.997 for pyridoxal, and ≥ 0.994 for pyridoxal 5′-phosphate.

ISR was conducted on 5.6-5.8% of the total number of sample for each analyte. The percent (%) difference is defined as {(repeat – original) / [(repeat + original)/2]} x 100 and the percentage difference had to be within ± 20% for at least 67% of the ISR samples to be considered successful in confirming the reproducibility of the bioanalytical method.

Table A-2-9: Summary of ISR Results in Human Plasma (Study 150033)

Analyte	Total Number of Samples	Number of ISR Samples	Portion of ISR Samples (%)	Passing ISR Samples (%)
Doxylamine	6424	370	5.8	100
Pyridoxine	11971	668	5.6	96.1
Pyridoxal[a]	8271	471	5.7	96.2
Pyridoxal 5′-Phosphate	6208	362	5.8	97.8

[a] Matrix: Whole blood

An OSIS consult requesting inspections of the clinical and bioanalytical sites of this pivotal BE study was made on January 4, 2016. An OSIS memorandum was issued on February 22, 2016 with a recommendation to accept the data without on-site inspection. Details of the OSIS recommendations can be found in Shila Nkah's OSIS memorandum dated February 22, 2016 in DARRTS. See Appendix Section 4.2 of this review.

> **Reviewer's Comment**: While the Agency's Bioanalytical Method Validation Guidance recommends that the total number of ISR samples should be 7% of study sample size, it should be noted that ISR was conducted on 5.6-5.8% of the total number of sample for each analyte. Although the ISR samples were less than the recommended 7% of study samples, considering that 96.1-100% of the ISR samples met the ISR acceptance criteria, the performance of the Sponsor's bioanalytical method appears to be reliable.
>
> The acceptance criteria and assay performance for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate bioanalysis are in compliance with the Agency's Bioanalytical Method Validation Guidance and the bioanalytical methods are acceptable.

Disposition of Subjects:

There were 77 females screened and of these, 39 females were randomized and dosed. Thirty one (31) females completed all study periods. In accordance with the study protocol, data from all subjects who completed at least two periods, including one Test and one Reference, and for whom the PK profile could be adequately characterized were used for PK and statistical analyses (N=37 for Day 1 analysis and N=34 for Day 11 analysis). The following 8 subjects did not complete the study after receiving at least 1 dose of the study medication:

Table A-2-10: Summary of Subject Discontinuation

Subject Number	Reason for withdrawal (Date and time of withdrawal/last treatment received/reason)	Period of the last study drug administration	Replaced?	Replaced with
06	2015-04-24 22:40 / Test / Subject elected to withdraw for personal reasons. Subject came back in Period 3.	2	No	Not applicable
06	2015-05-24 09:56 / Reference / Subject elected to withdraw for personal reasons.	3	No	Not applicable
07	2015-04-25 15:44 / Reference / Subject elected to withdraw for personal reasons.	2	No	Not applicable
14	2015-04-15 19:15 / Test / Subject did not show-up at check-in in Period 2.	1	No	Not applicable
16	2015-03-16 19:00 / Test / Subject was withdrawn due to significant adverse event (Vomiting; refer to Section 12.3.2 for details).	1	No	Not applicable
19	2015-05-24 08:52 / Reference / Subject withdrawn due to significant adverse event (Hemoglobin decreased) at check-in in Period 3.	2	No	Not applicable
20	2015-03-16 21:38 / Reference / Subject withdrawn from Period 1 due to significant adverse event (Visual impairment, refer to Section 12.3.2 for details). Subject came back in Periods 2 and 3.	1	No	Not applicable
29	2015-04-28 10:44 / Reference / Subject elected to withdraw for personal reasons. Subject came back in Period 3.	2	No	Not applicable
29	2015-06-07 14:32 / Test / Subject elected to withdraw for personal reasons.	3	No	Not applicable
30	2015-06-14 11:33 / Reference / Subject elected to withdraw for personal reasons.	3	No	Not applicable

Test (A)= Duchesnay, Inc., Canada, doxylamine-pyridoxine 20 mg-20 mg (b) (4) tablet on a BID dosing regimen (total dose 40 mg-40 mg daily) for 11 consecutive days.
Reference (B)= Duchesnay, Inc., Canada, (Diclegis®), doxylamine-pyridoxine 10mg-10 mg delayed-release tablet on a TID dosing regimen (total dose 40 mg-40 mg daily) for 11 consecutives days.

Protocol Deviations:

All enrolled subjects satisfied the entry criteria and received the correct treatment and dose. No use of concomitant medications was reported. There were no deviations that affected subject safety or any of the outcomes of the study. Subjects were confined to the clinical facility and monitored from the evening of Day -1 until after the last scheduled blood draw on the morning of Day 12, in each period. During the confinements, subjects were under constant surveillance by the clinical staff to ensure that they respected the protocol restrictions. A summary of protocol deviation can be found in Table A-2-11 below.

Table A-2-11: Summary of Protocol Deviation

Type	Subject Nos. (Test)	Subject Nos. (Ref.)
Study medication, Dosing, and Randomization		
Due to adverse events or difficulty with pre-dose blood collection, the following subjects were dosed more than 10 minutes from scheduled time: - Subject No. 07 was dosed 12 minutes 11 seconds late on the morning of Day 5 and 12 minutes 14 seconds late on the evening of Day 5 in Period 1; - Subject No. 13 was dosed 6 minutes 3 seconds late on the afternoon of Day 7 and 6 minutes 5 seconds late on the evening of Day 7 in Period 1; - Subject No. 16 was dosed 7 minutes 3 seconds late on the morning of Day 9 in Period 1; - Subject No. 22 was dosed at 09:38, 15:38, and 21:38 on Day 1 and 2 in Period 1, but starting on Day 3 she was dosed 26 minutes earlier (09:02, 15:02 and 21:02) to facilitate study procedures. This subject was also dosed 4 minutes 2 seconds late on the morning of Day 6 in Period 3; - Subject No. 31 was dosed 8 minutes 43 seconds late on the morning of Day 3 and 8 minutes 1 second late on the morning of Day 4 in Period 3. These dosing times deviations were low in magnitude and should not have significantly impacted the steady state attainment. Moreover, no PK evaluation was performed on the days these deviations occurred.	07, 16, 22	13, 22, 31
Eligibility		
At screening, a breast exam was performed in error for seven volunteers; of these three were enrolled and dosed in this study. These subjects' safety was however not affected by this deviation nor the integrity of the data.	Not applicable	Not applicable
Study Restrictions		
In Period 1, the tobacco restriction was not respected for the following instances: - On Day 1, Subject No. 06 and 08 respectively smoked a cigarette 5 minutes 34 seconds and 51 seconds after the beginning of the restriction. - On Day 11, Subject No. 07 smoked a cigarette 9 minutes 34 seconds after the beginning of the restriction. There should be no impact on the study results since the tobacco restriction was followed from more than two hours before dosing until six hours after dosing. In addition, doxylamine and pyridoxine are not metabolized by CYP1A2.	07	06, 08
The following subjects left the clinical facilities before the end of their confinement period: Subject No. 06 left on Day 9 in Period 2 and on Day 1 of Period 3 for personal reasons; Subject No. 07 left on Day 10 of Period 2 for personal reasons; Subject No. 20 left on Day 11 of Period 1 since she was withdrawn due to adverse events; Subject No. 29 left on Day 2 of Period 2 and on Day 4 of Period 3 for personal reasons; Subject No. 30 left on Day 11 of Period 3 for personal reason. No impact on safety: attending physician judged that subjects 06, 07, 20 and 30 were Ok to leave. Subject 29 in Period 3 was assessed as OK to	06, 29	06, 07, 20, 29 30

leave and in her premature departure in Period 2 was later judged as having no impact on safety. There should be no impact on study results obtained before the end of their confinement since subjects followed study restrictions. Therefore, if these subjects completed at least two periods, including one Test and one Reference, and their pharmacokinetic profile can be adequately characterised, then they may be included in the pharmacokinetic population.		
Subject No. 26 on the evening of Day 10 in Period 2, Subject No. 33 on the morning of Day 4 in Period 3, and Subject Nos. 34 and 35 on the evening of Day 2 in Period 2, drank less then 30 mL of water during the water restriction to swallow medication needed for the treatment of advere events. The ingestion of such a small quantity of water few minutes from dosing should not have any impact on drug absortption.		26, 33, 34, 35
On Day 1 in Period 3, this subject smoked 10 cigarettes even if she was not allowed to smoke more than nine cigarettes per day. Since the subject respected the smoking restriction time and since doxylamine or pyridoxine are not metabolized by CYP1A2, there should be no impact on study results.	08	
Due to a conditioning issue with the food delivered by the caterer for the diner of Day 8 in Period 3, these subjects ate a slice of vegetarian pizza in addition to their regular evening snack. Since excessive consumption of food or beverages with high content of vitamin B6 was avoided, there should not have any impact on study results.	02, 03, 08, 10, 15, 18	01, 04, 05, 09, 11, 12, 13, 17, 20
On Day 2 in Period 3, this subject drank approximately 240 mL of water six minutes after the start of the water restriction (54 minutes prior to dosing). However, such a small time deviation should have no impact on the study results.	03	
Study Samples		
In Period 1, these subjects' samples collected 14.5 hours post-dose on Day 1 for pyridoxal analysis were centrifuged in error. There is however no impact on sample integrity since they were inverted 20 times before processing.	01, 07, 12, 14, 16, 19	02, 03, 04, 06, 08, 09, 10, 11, 13, 15, 17, 18, 20
These subjects pre-dose samples were collected more than 10 minutes prior to dosing: - Subject No. 07, on Day 5 in Period 1, sample for pyridoxal and doxylamine was collected 9 minutes 11 seconds early; - Subject No. 14, on Day 3 in Period 1, sample for pyridoxal and doxylamine was collected 2 minutes 13 seconds early and sample for P5P and pyridoxine was collected 2 minutes 7 seconds early; - Subject No. 16, on Day 9 in Period 1, sample for pyridoxal and doxylamine was collected 1 minute 57 seconds early and sample for P5P and pyridoxine was collected 1 minute 25 seconds early; - Subject No. 22, on Day 6 in Period 3, sample for pyridoxal and doxylamine was collected 8 minutes 13 seconds early. Since the samples were collected before dosing, there is no impact on the PK characterization.	07, 14, 16, 22	
A clot was found in the following blood samples prior to centrifugation: <u>In Period 1, for pyridoxine:</u> - Subject No. 01, 8.50-hours post-dose on Day 1 and 10.5- and 14.0-hours post-dose on Day 11; - Subject No. 04, 8.25- and 18.0-hours post-dose on Day 11; - Subject No. 06, 7.75-hours post-dose on Day 1; - Subject No. 07, 8.25-hours post-dose on Day 1 and 6.50-, 10.5-, and 11.5-hours post-dose on Day 11; - Subject No. 13, 8.75-hours post-dose on Day 1; - Subject No. 14, 11.5-hours post-dose on Day 11; - Subject No. 39, 8.25-hours post-dose on Day 11.	01, 07, 14, 30, 39	04, 06, 13, 18, 33

In Period 1, for P5P: - Subject No.01, 14.0-hours post-dose on Day 11; - Subject No. 04, 18.0-hours post-dose on Day 11; In Period 2, for pyridoxine: - Subject No. 18, 8.50-hours post-dose on Day 11; - Subject No. 30, 0.250-hour post-dose on Day 11; - Subject No. 33, 21.0-hours post-dose on Day 1. In Period 2, for P5P: - Subject No. 33, 21.0-hours post-dose on Day 11. Since the matrix could not be confirmed for these samples, no value were reported and they were not included in the PK analysis.		
The blood sample collected for P5P and pyridoxine 8.00-hours post-dose on Day 1 in Period 1 and prior to dosing on Day 3 in Period 3 were collected in the wrong collection tube and were consequently discarded and recorded as missing. However, one missing sample on Day 1 should have no impact on the PK profile and one missing sample on Day 3 should have no impact on the steady state attainment.		30
The following blood sample collected for P5P and pyridoxine, had to be performed twice because the first sample was collected in the wrong type of tube: - Subject No. 01 (pyridoxine only), 14.25-hours post-dose on Day 1 in Period 2; - Subject No. 10, 22.0-hours post-dose on Day 11 in Period 1; - Subject No. 22, 17.0-hours post-dose on Day 1 in Period 2; - Subject No. 33, 16.0-hours post-dose on Day 1 in Period 2; - Subject No. 21, 2.00-hours post-dose on Day 11 in Period 3. There is however no impact on these subject's safety since the total volume of blood collected for the whole study did not exceed the maximum blood volume allowed.		01, 10, 21, 22, 33
On Day 7 in Period 2, the pre-dose sample for doxylamine and pyridoxal for these subjects were unlabelled and it was consequently impossible to determine which sample belongs to which subject. Both of these sample were then discarded and recorded as missing. However, a missing pre-dose sample on Day 7 should have a minimal impact on the steady-state attainment calculation.		05, 07
The following blood samples collected for doxylamine analysis were left at room temperature in error before centrifugation: Subject No. 13, 16.0-hours post-dose on Day 2 in Period 3, sample was left at room temperature for approximately six minutes; Subject No. 29, 19.0-hours post-dose on Day 1 in Period 1, sample was left at room temperature for approximately 12 minutes; Subject No. 39, 3.50-hours post-dose on Day 11 in Period 1, sample was left at room temperature for approximately five minutes. Upon notification, these samples were immediately put in an ice/water bath and they were processed and stored according to the Analytical Methodology Information Sheet requirements. Since the stability in whole blood at room temperature is not validated for this analyte, the concentration for these samples was not reported and was excluded from the analysis.	39	13, 29
On Day 11, in Period 3, the blood sample collected 1.00-hour post-dose for P5P and pyridoxine analysis was left at room temperature for approximately 10 minutes after centrifugation.However,there is no impact on sample integrity since a short term stability was validated for these analytes.		20
On Day 4, in Period 3, pre-dose blood samples were not collected for this subject, due to difficulty with blood draw. However, a missing sample on Day 4 will have no impact on the steady state atteintment calculation.		31
On Period 3, Day 11, this subject's 16.5 hour post-dose samples collected for the analysis of pyridoxal and pyridoxine were not included in the PK statistics. These samples were analyzed but due to a problem of communication between departments, were erroneously judged invalid for	22	

statistical analyses. However, the analytes pyridoxine and pyridoxal are presented as supportive information only thus this deviation as no impact on the outcome of the study. Moreover,these samples were only one missing sample for this subject period and day regarding each analyte, thus no impact on the pk characterization of pyridoxine and pyridoxal was identified.		
Safety measurements		
At discharge, it was ommited to document the menses last date for Subject Nos. 16 and 20 in Period 1 and for Subject No. 29 in Period 3. There is no impact on the study results since this information was required as additional information only.	16, 29	20
On Day 1 following the first dosing of Period 3, this subject withdrew her consent for the rest of the study for personal reasons. She left before having performed the study exit procedures and before having reported her menses. Moreover, the subject refused to be contacted for any further study procedures. These deviations should have minimal impact since the subject was under close medical supervision during her confinement and she had no ongoing adverse event when she left the clinical facility.		06 (Study exit)
This subject did not show up in Periods 2 and 3. Many attemps to reach the subject were performed in order to get information regarding her participation in the study and to scheduled her study exit procedures but they were unsuccessful. There is however no impact on subject's safety since she had no ongoing adverse events when she left the clinical facility after Period 1 and it is very unlikely that study exit procedures would have revealed safety issue.		14 (Study exit)

CYP: Cytochrome P450; P5P: Pyridoxal 5'-phosphate; PK: Pharmacokinetic.
Test (A)= Duchesnay, Inc., Canada, doxylamine-pyridoxine 20 mg-20 mg (b) (4) tablet on a BID dosing regimen (total dose 40 mg-40 mg daily) for 11 consecutive days.
Reference (B)= Duchesnay, Inc., Canada, (Diclegis®), doxylamine-pyridoxine 10 mg-10 mg delayed-release tablet on a TID dosing regimen (total dose 40 mg-40 mg daily) for 11 consecutives days.

Handling of Missing Samples:
The following subjects were set as missing for PK and statistical analyses:

- On Day 11, Subject 04 in Period 1 had too many missing samples, thus the PK profile could not be adequately characterized. For this reason this subject was excluded from the PK population of Day 11 Period 1.
- On Day 11, Subject 37 in Period 3 had too many missing samples, thus the PK profile could not be adequately characterized. For this reason this subject was excluded from the PK population of Day 11 Period 3.

Except for Subjects 04 and 37 (as mentioned above), other subjects with missing data were kept in the PK and statistical analyses as the PK parameters could be estimated using the remaining data points.

Reviewer's Comment: This reviewer concurs to the Investigator's/Sponsor's assessments and decisions made to either include or exclude these subjects/samples from the PK characterization and BE analysis.

PK and BE Assessment Results:

Reviewer's Comment: As indicated in Table A-1-10, Subjects 14 and 16 discontinued and did not have adequate data for BE assessment for Day 1 and were excluded from data analysis (N=39 enrolled - 2 subjects = 37 subjects). In addition, Subjects 6, 7, and 29 discontinued the study and did not have adequate data for BE assessment on Day 11, These 3 subjects were additionally excluded from data analysis for Day 11 (N=37 subjects analyzed for Day 1 - 3 subjects = 34 subjects).

Doxylamine

Mean (SD) plasma PK parameters of doxylamine are summarized in Tables A-2-12 and A-2-13.

Table A-2-12: Mean (SD) Plasma PK Parameters of Doxylamine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 1

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	1421.7 (271.7)	1041.1 (273.5)	1049.6 (286.7)
AUC(0-12) (ng·hr/mL)	614.1 (143.7)	287.5 (137.7)	300.3 (105.1)
AUC(0-6) (ng·hr/mL)	321.0 (72.2)	105.8 (59.1)	106.1 (44.0)
C_{max} (ng/mL)	94.5 (20.7)	125.9 (35.7)	116.5 (29.5)
T_{max} (hr)[a]	20.0 (2.2-23.0)	22.0 (15.5-23.9)	22.0 (15.5-23.9)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days

Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days

Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study. There were different number of subjects from whom data were available between Reference 1 and Reference 2.

[a] Median (minimum-maximum)

Table A-2-13: Mean (SD) Plasma PK Parameters of Doxylamine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 11

Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	2879.4 (696.0)	2813.6 (767.2)	3016.0 (647.2)
AUC(0-12) (ng·hr/mL)	1573.2 (406.5)	1437.6 (426.7)	1550.9 (373.5)
AUC(0-6) (ng·hr/mL)	883.6 (228.5)	767.5 (217.2)	827.4 (205.1)
C_{max} (ng/mL)	173.6 (45.5)	159.6 (37.0)	168.9 (34.5)
T_{max} (hr)[a]	3.5 (1.0-20.0)	19.5 (0.0-24.0)	21.0 (3.0-23.0)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days

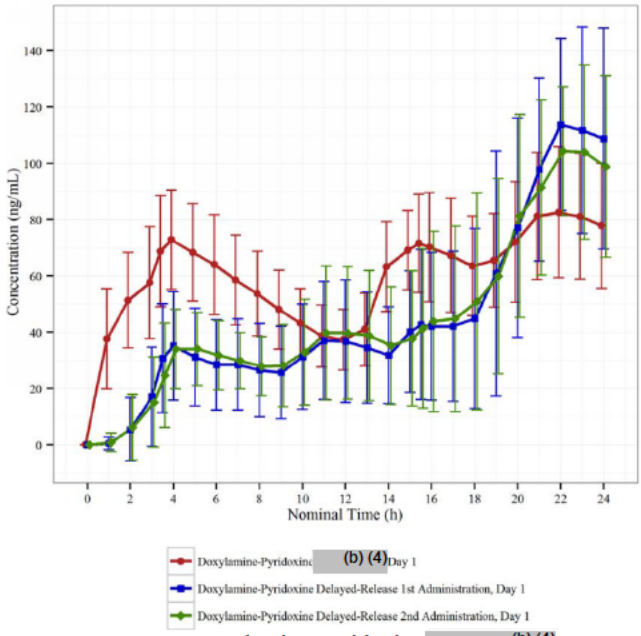
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days

Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study. There were different number of subjects from whom data were available between Reference 1 and Reference 2.

[a] Median (minimum-maximum)

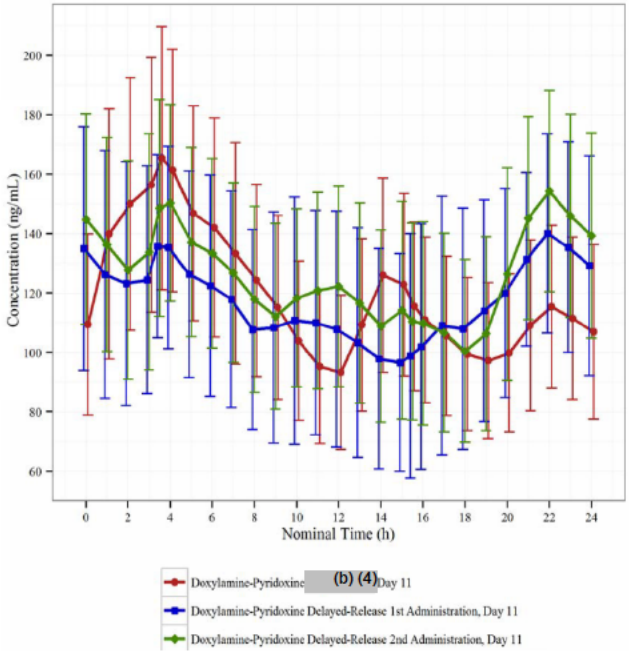
Mean (±SD) concentration-time profile for doxylamine for each treatment on Days 1 and 11 are shown in Figures A-2-1 and A-2-2. It should be noted that the mean profiles for both the Test and Reference are plotted based on the mean plasma concentrations calculated per time point. Therefore, the maximum concentrations observed in the mean data figures may not reflect the mean C_{max}, as the C_{max} and the time of maximum concentration (T_{max}) vary between individuals.

Figure A-2-1: Mean (±SD) concentration-time profile for Doxylamine for each treatment on Day 1



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure A-2-2: Mean (±SD) concentration-time profile for Doxylamine for each treatment on Day 11



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to doxylamine for the parameters AUC(0-24) and C_{max} on Days 1 and 11 using natural log transformed data are summarized in Tables A-2-14 and A-2-15.

Table A-2-14: Summary of BE Analysis Results of Doxylamine PK Parameters
Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 1 (N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	1397.1	1010.6	140.0	130.2-150.6
C_{max} (ng/mL)	92.3	117.0	79.6	76.1-83.2

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
[a] Median (minimum-maximum)

Table A-2-15: Summary of BE Analysis Results of Doxylamine PK Parameters
Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 11 (N=34)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	2802.2	2720.4	99.1	95.7-102.5
C_{max} (ng/mL)	168.3	155.6	105.3	100.9-109.9

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
[a] Median (minimum-maximum)

For TRADENAME, the least-squares means ratios (Day 11/Day 1) of ln-transformed AUC(0-24) and C_{max} were 196.7% and 179.2%, respectively, for doxylamine.

Based on these results, the TRADENAME showed greater rate and extent of exposure on Day 11 when compared to Day 1. Indeed, the mean accumulation index was 2.0 for doxylamine.

Pyridoxal 5′-phosphate

Mean (SD) plasma PK parameters of baseline corrected pyridoxal 5′-phosphate are summarized in Tables A-2-16 and A-2-17.

Table A-2-16: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 1

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	680.5 (230.1)	423.4 (136.7)	425.9 (138.1)
AUC(0-12) (ng·hr/mL)	245.2 (85.2)	116.1 (64.2)	110.1 (48.2)
AUC(0-6) (ng·hr/mL)	101.9 (36.8)	34.2 (20.9)	31.7 (20.6)
C_{max} (ng/mL)	44.9 (15.1)	43.2 (19.5)	41.7 (11.7)
T_{max} (hr)[a]	21.0 (15.0-23.9)	22.0 (10.0-23.9)	21.5 (18.0-23.9)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

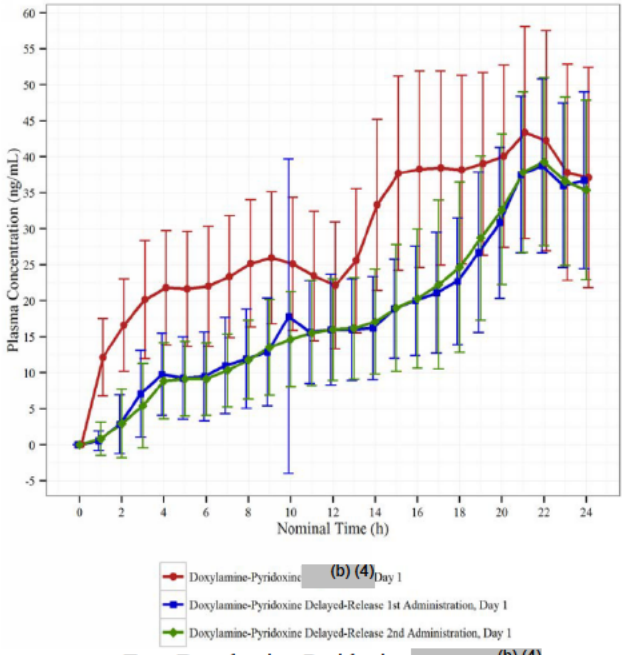
Table A-2-17: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 11

Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	1742.3 (554.3)	1722.6 (517.8)	1773.7 (571.3)
AUC(0-12) (ng·hr/mL)	831.7 (274.5)	835.1 (266.1)	843.4 (296.3)
AUC(0-6) (ng·hr/mL)	426.2 (144.0)	418.6 (134.7)	420.1 (153.1)
C_{max} (ng/mL)	85.9 (26.2)	82.6 (23.4)	87.7 (26.2)
T_{max} (hr)[a]	15.0 (2.0-24.0)	21.0 (0.0-24.0)	19.0 (4.0-24.0)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

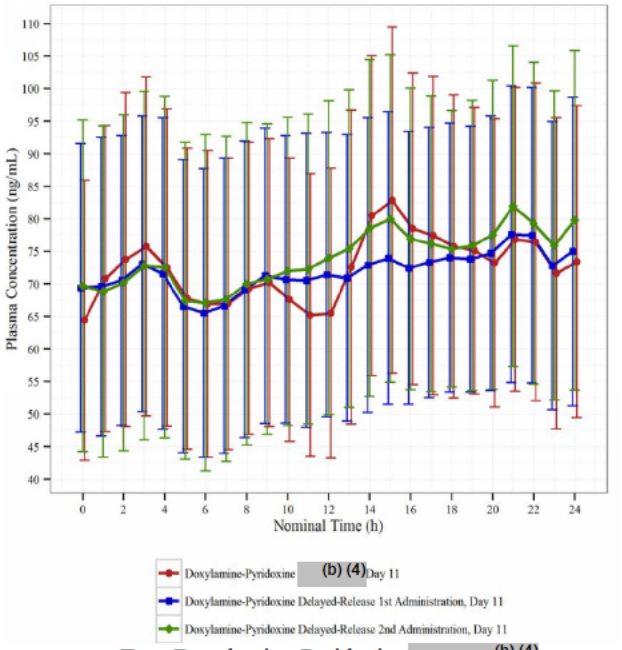
Mean (±SD) concentration-time profile for baseline corrected pyridoxal 5′-phosphate for each treatment on Days 1 and 11 are shown in Figures A-2-3 and A-2-4. It should be noted that the mean profiles for both the Test and Reference are plotted based on the mean plasma concentrations calculated per time point. Therefore, the maximum concentrations observed in the mean data figures may not reflect the mean C_{max}, as the C_{max} and the time of maximum concentration (T_{max}) vary between individuals.

Figure A-2-3: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal 5′-Phosphate for each treatment on Day 1



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure A-2-4: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal 5′-Phosphate for each treatment on Day 11



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Mean (SD) plasma PK parameters of baseline uncorrected pyridoxal 5′-phosphate are summarized in Tables A-2-18 and A-2-19.

Table A-2-18: Mean (SD) Plasma PK Parameters of Baseline Uncorrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 1

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	947.0 (395.3)	625.8 (249.3)	673.9 (244.2)
AUC(0-12) (ng·hr/mL)	379.1 (177.1)	217.5 (116.6)	234.2 (107.1)
AUC(0-6) (ng·hr/mL)	168.8 (80.7)	84.6 (46.8)	93.4 (50.1)
C_{max} (ng/mL)	56.0 (21.4)	51.7 (23.0)	52.1 (15.5)
T_{max} (hr)[a]	21.0 (15.0-23.9)	22.0 (10.0-23.9)	21.5 (18.0-23.9)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

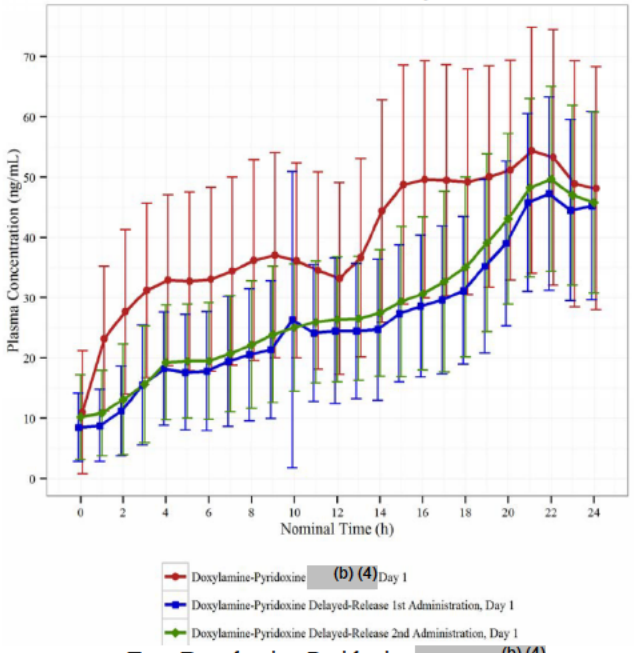
Table A-2-19: Mean (SD) Plasma PK Parameters of Baseline Uncorrected Pyridoxal 5′-Phosphate Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 11

Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	2022.9 (653.3)	1929.4 (585.6)	2034.6 (643.6)
AUC(0-12) (ng·hr/mL)	971.8 (325.4)	938.5 (300.4)	973.8 (332.6)
AUC(0-6) (ng·hr/mL)	496.3 (168.9)	470.3 (151.9)	485.3 (171.2)
C_{max} (ng/mL)	97.5 (30.3)	91.2 (26.2)	90.7 (28.9)
T_{max} (hr)[a]	15.0 (2.0-24.0)	21.0 (0.0-24.0)	19.0 (4.0-24.0)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

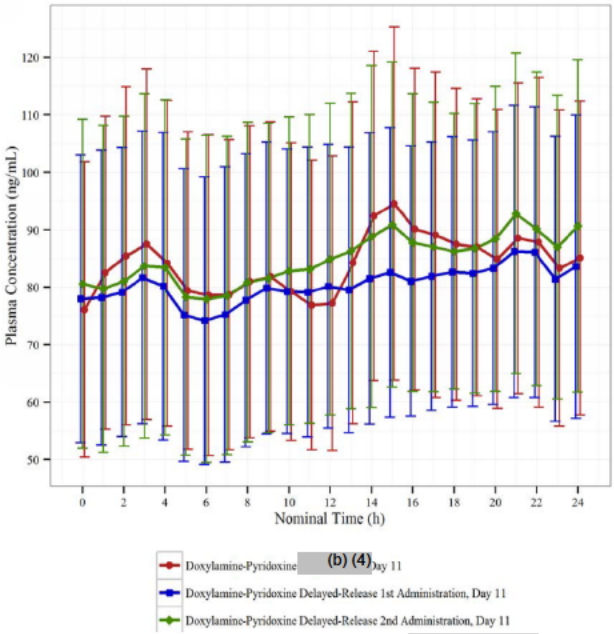
Mean (±SD) concentration-time profile for baseline uncorrected pyridoxal 5′-phosphate for each treatment on Days 1 and 11 are shown in Figures A-2-5 and A-2-6.

Figure A-2-5: Mean (±SD) concentration-time profile for Baseline Uncorrected Pyridoxal 5′-Phosphate for each treatment on Day 1



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure A-2-6: Mean (±SD) concentration-time profile for Baseline Uncorrected Pyridoxal 5′-Phosphate for each treatment on Day 11



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

The point estimates and 90% CIs for the difference between the Test and Reference with respect to pyridoxal 5′-phosphate for the baseline corrected parameters AUC(0-24) and C_{max} on Days 1 and 11 using natural log transformed data are summarized in Tables A-2-20 and A-2-21.

Table A-2-20: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 1 (N=37)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	644.8	406.1	161.5	147.6-176.7
C_{max} (ng/mL)	42.5	40.4	105.6	99.6-112.0

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
[a] Median (minimum-maximum)

Table A-2-21: Summary of BE Analysis Results of Baseline Corrected Pyridoxal 5′-Phosphate PK Parameters Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 11 (N=34)

Parameter	Geometric Mean		Point estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-24) (ng·hr/mL)	1661.5	1657.4	100.1	95.8-104.5
C_{max} (ng/mL)	82.2	81.4	100.8	96.7-105.0

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
[a] Median (minimum-maximum)

For TRADENAME, the least-squares means ratios (Day 11/Day 1) of ln-transformed AUC(0-24) and C_{max} were 254.8% and 191.2%, respectively, for baseline corrected pyridoxal 5'-phosphate.

Based on these results, the TRADENAME showed greater rate and extent of exposure on Day 11 when compared to Day 1. Indeed, the mean accumulation index was 2.6 for baseline corrected pyridoxal 5'-phosphate.

Reviewer's Comment: The Sponsor concludes that BE is established for both doxylamine and pyridoxal 5′-phosphate based on AUC(0-24) and C_{max} on Day 11 but not for Day 1.

However, while this study assessed the BE between the maximum daily doses of TRADENAME BID and Diclectin® TID (i.e., 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride per day) on Day 1 and Day 11, it lacks the bridging for the proposed starting dose of TRADENAME (i.e., one 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride tablet given at bedtime) to the currently approved starting dose for Diclegis® (i.e., two 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride tablets given at bedtime).

The BE between the starting dose of TRADENAME and Diclegis® was established in the new BE Study 150336 submitted on June 13, 2016.

It should be noted that the currently approved intermediate daily dose of 30 mg doxylamine succinate / 30 mg pyridoxine hydrochloride for Diclegis® will not be available via the new formulation, TRADENAME.

Pyridoxine

Reviewer's Comment: For pyridoxine, baseline-uncorrected and baseline-corrected data were to be presented as per protocol. However, since no pre-dose concentrations were detected for all subjects, the Sponsor did not perform any baseline adjustment on pyridoxine concentrations.

Mean (SD) plasma PK parameters of pyridoxine are summarized in Tables A-2-22 and A-2-23.

Table A-2-22: Mean (SD) Plasma PK Parameters of Pyridoxine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 1

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	68.8 (20.4)	88.8 (35.3)	85.6 (27.9)
AUC(0-12) (ng·hr/mL)	32.8 (12.1)	19.1 (10.9)	19.4 (10.1)
AUC(0-6) (ng·hr/mL)	32.7 (12.1)	11.9 (6.9)	11.4 (4.8)
C_{max} (ng/mL)	37.7 (14.7)	41.9 (25.6)	40.0 (18.9)
T_{max} (hr)[a]	1.5 (0.5-20.0)	19.0 (1.0-22.0)	18.0 (1.0-22.0)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

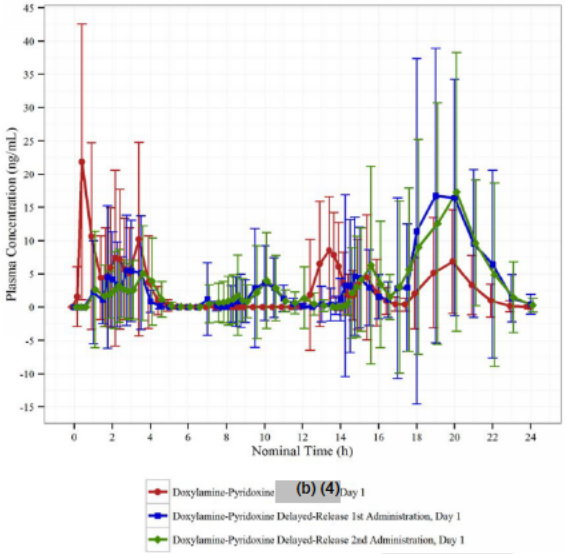
Table A-2-23: Mean (SD) Plasma PK Parameters of Pyridoxine Following Doses of TRADENAME Tablets (Test) or Diclectin® Tablets (Reference) on Day 11

Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	80.0 (22.7)	98.7 (29.9)	104.3 (39.2)
AUC(0-12) (ng·hr/mL)	46.3 (15.4)	39.4 (16.2)	37.2 (10.5)
AUC(0-6) (ng·hr/mL)	45.3 (16.3)	23.2 (7.4)	21.5 (9.5)
C_{max} (ng/mL)	48.2 (23.7)	42.7 (18.3)	45.1 (27.1)
T_{max} (hr)[a]	1.5 (0.3-16.5)	10.3 (1.5-22.0)	19.0 (1.8-21.0)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

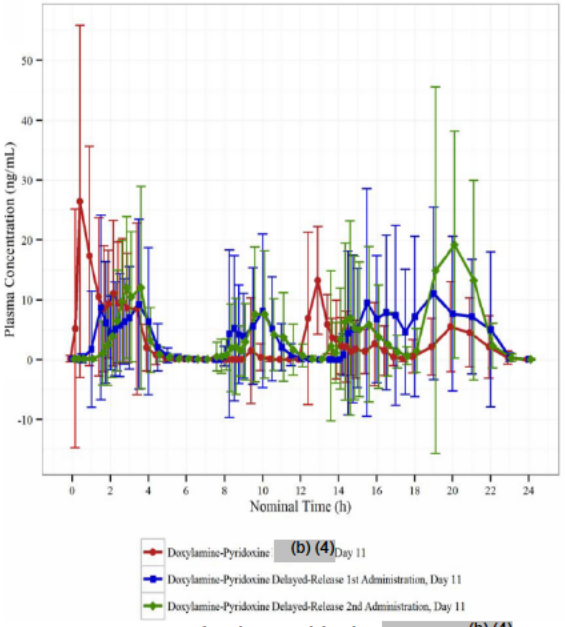
Mean (±SD) concentration-time profile for pyridoxine for each treatment on Days 1 and 11 are shown in Figures A-2-7 and A-2-8.

Figure A-2-7: Mean (±SD) concentration-time profile for Pyridoxine for each treatment on Day 1



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure A-2-8: Mean (±SD) concentration-time profile for Pyridoxine for each treatment on Day 11



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Pyridoxal

Mean (SD) whole blood PK parameters of baseline corrected pyridoxal are summarized in Tables A-2-24 and A-2-25.

Table A-2-24: Mean (SD) Whole Blood PK Parameters of Baseline Corrected Pyridoxal Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 1

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	542.9 (167.6)	456.7 (150.3)	479.8 (134.9)
AUC(0-12) (ng·hr/mL)	224.0 (84.7)	101.1 (63.9)	112.1 (55.6)
AUC(0-6) (ng·hr/mL)	182.0 (68.2)	55.4 (33.2)	58.1 (32.5)
C_{max} (ng/mL)	76.1 (25.0)	96.4 (34.7)	99.9 (36.2)
T_{max} (hr)[a]	4.0 (1.0-22.0)	20.0 (15.0-22.0)	20.0 (15.5-22.1)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

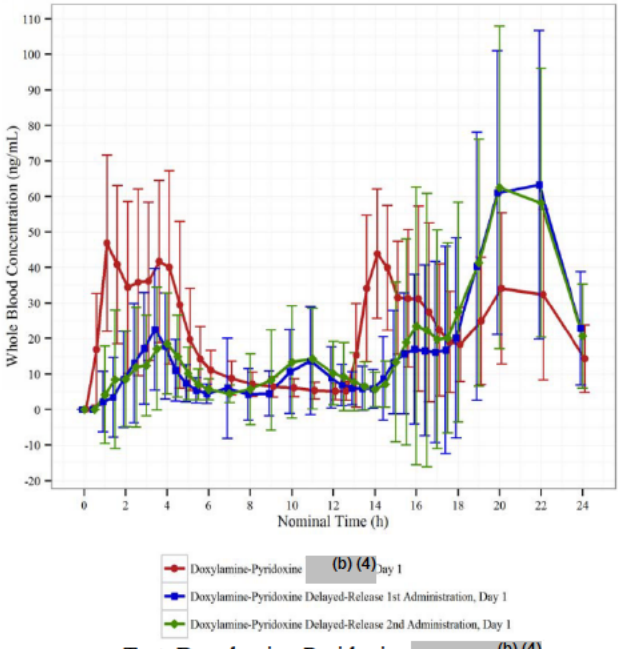
Table A-2-25: Mean (SD) Whole Blood PK Parameters of Baseline Corrected Pyridoxal Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 11

Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	1511.4 (300.0)	1542.7 (392.4)	1542.5 (275.3)
AUC(0-12) (ng·hr/mL)	848.1 (183.6)	679.1 (216.8)	669.8 (131.2)
AUC(0-6) (ng·hr/mL)	647.2 (149.6)	392.1 (125.5)	382.6 (93.9)
C_{max} (ng/mL)	189.6 (48.3)	193.0 (53.0)	185.5 (42.6)
T_{max} (hr)[a]	3.0 (2.0-15.0)	20.0 (2.5-22.2)	20.0 (3.0-22.3)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

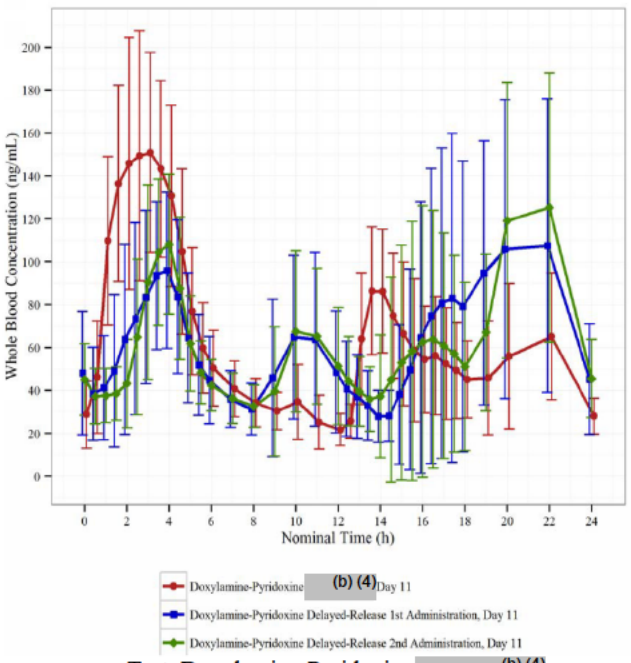
Mean (±SD) concentration-time profile for baseline corrected pyridoxal for each treatment on Days 1 and 11 are shown in Figures A-2-9 and A-2-10.

Figure A-2-9: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal for each treatment on Day 1



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure A-2-10: Mean (±SD) concentration-time profile for Baseline Corrected Pyridoxal for each treatment on Day 11



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Mean (SD) whole blood PK parameters of baseline uncorrected pyridoxal are summarized in Tables A-2-26 and A-2-27.

Table A-2-26: Mean (SD) Whole Blood PK Parameters of Baseline Uncorrected Pyridoxal Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 1

Parameter	Test (N=37)	Reference 1 (N=37)	Reference 2 (N=34)
AUC(0-24) (ng·hr/mL)	587.6 (199.9)	491.4 (161.3)	523.4 (156.2)
AUC(0-12) (ng·hr/mL)	246.5 (100.1)	118.4 (70.4)	133.8 (62.4)
AUC(0-6) (ng·hr/mL)	193.3 (75.3)	64.0 (36.2)	68.9 (37.5)
C_{max} (ng/mL)	78.0 (26.0)	97.8 (34.9)	101.7 (36.8)
T_{max} (hr)[a]	4.0 (1.0-22.0)	20.0 (15.0-22.0)	20.0 (15.5-22.1)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

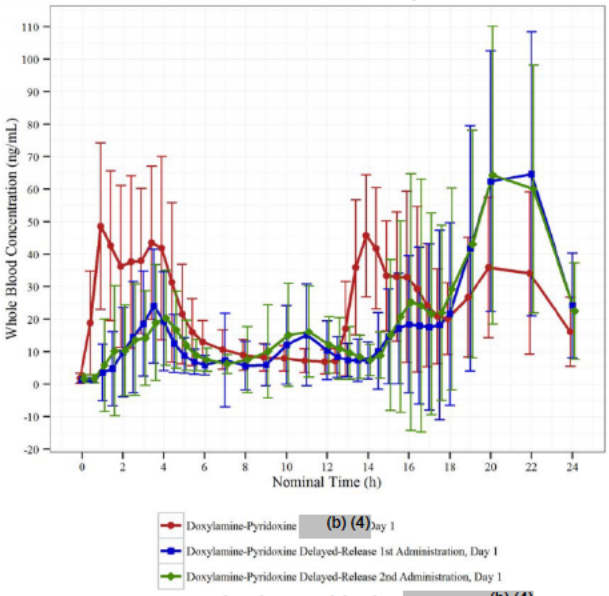
Table A-2-27: Mean (SD) Whole Blood PK Parameters of Baseline Uncorrected Pyridoxal Following Doses of TRADENAME Tablets (Test) or Diclegis® Tablets (Reference) on Day 11

Parameter	Test (N=34)	Reference 1 (N=32)	Reference 2 (N=31)
AUC(0-24) (ng·hr/mL)	1558.2 (311.0)	1578.3 (397.2)	1588.1 (276.3)
AUC(0-12) (ng·hr/mL)	871.5 (189.6)	696.9 (218.2)	692.6 (131.1)
AUC(0-6) (ng·hr/mL)	658.9 (152.9)	401.0 (126.7)	394.0 (93.2)
C_{max} (ng/mL)	191.5 (48.8)	194.5 (53.4)	47.4 (18.0)
T_{max} (hr)[a]	3.0 (2.0-15.0)	20.0 (2.5-22.2)	20.0 (3.0-22.3)

Test: TRADENAME tablet (20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride) BID (1 tablet at 9 am and 9 pm) for 11 consecutive days
Reference: Diclegis® tablet (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride) TID (1 tablet at 9 am and 3 pm and 2 tablets at 9 pm) for 11 consecutive days
Reference 1 and Reference 2 are replicates of the Reference treatment as this study is a Reference replicated study.
[a] Median (minimum-maximum)

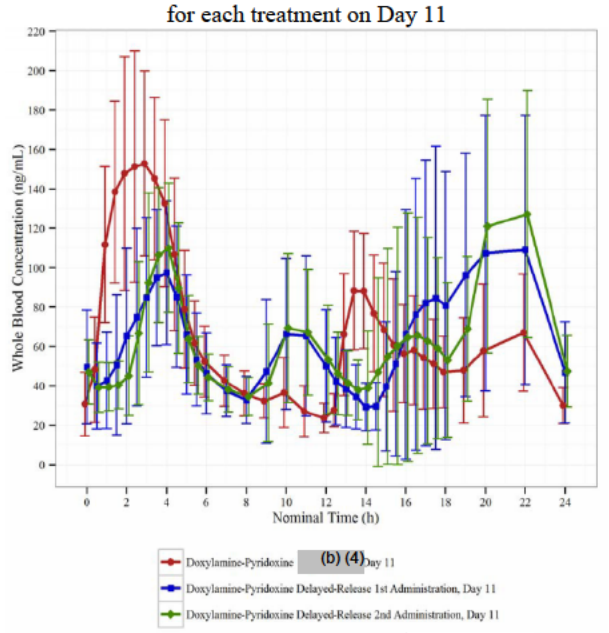
Mean (±SD) concentration-time profile for baseline uncorrected pyridoxal for each treatment on Days 1 and 11 are shown in Figures A-2-11 and A-2-12.

Figure A-2-11: Mean (±SD) concentration-time profile for Baseline Uncorrected Pyridoxal for each treatment on Day 1



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Figure A-2-12: Mean (±SD) concentration-time profile for Baseline Uncorrected Pyridoxal for each treatment on Day 11



Test: Doxylamine-Pyridoxine (b) (4)
Reference: Doxylamine-Pyridoxine Delayed-Release

Safety Results:

Per Sponsor, a total of 126 TEAEs were reported by 34 of the 39 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as

follows: 59 TEAEs reported by 48.7% (n=19) of the 39 subjects who received Test and 67 TEAEs reported by 86.5% (n=32) of the 37 subjects who received Reference.

The most commonly reported TEAEs were "headache" reported by 30.8% (n=12) of subjects who constituted the safety population, "dizziness" reported by 15.4% (n=6) of subjects who constituted the safety population, and "constipation", "nausea", "fatigue", and "somnolence" reported by 12.8% (n=5) of subjects who constituted the safety population.

> **Reviewer's Comment**: The Sponsor reports that majority of the TEAEs reported were mild in severity and no safety concerns are expected. Since this study used a 3-way reference-replicated design in which the Reference was administered twice and Test once, it was expected that a higher number of subjects experienced TEAE following administration with Reference.

Conclusion:
The results of this study indicates that BE is established for both doxylamine and baseline corrected pyridoxal 5′-phosphate based on AUC(0-24) and C_{max} on Day 11 but not for Day 1.

This study assessed the BE between the maximum daily doses of TRADENAME BID and Diclectin® TID (i.e., 40 mg doxylamine succinate / 40 mg pyridoxine hydrochloride daily) on Day 1 and Day 11 but it lacks the bridging for the proposed starting dose of TRADENAME (i.e., one 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride tablet) to the currently approved starting dose for Diclegis® (i.e., two 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride tablets).

4.1.3 Food Effect Study: Study 140115

Title: Randomized, Open-label, 2-way Crossover Comparative BA Food Effect Study of Doxylamine-Pyridoxine 20 mg/20 mg [redacted] Tablet Following A 20 mg/20 mg Dose in Healthy Subjects

Objective: To evaluate the effect of food on the PK of 20 mg doxylamine / 20 mg pyridoxine tablet

Clinical Study Center: inVentiv Health Clinique Inc., Quebec, Canada
Clinical Study Period: October 14-November 8, 2014

Bioanalytical Study Center: [redacted]
Bioanalysis Period: October 14 - November 25, 2014

Study Design, Treatments, and Drug Administration:
This single-center, open-label, randomized, 2-way crossover food-effect study was conducted in 24 healthy premenopausal females (age: 18-45 years; BMI: > 18.5 and < 30.0 kg/m^2). All subjects received the following Test and Reference treatments orally with 240 mL ambient-temperature water following an overnight fasting of at least 10 hours:

- Test: One TRADENAME (20 mg doxylamine / 20 mg pyridoxine) tablet under fed condition
- Reference: One TRADENAME (20 mg doxylamine / 20 mg pyridoxine) tablet under fasting condition

Subjects reported to the clinic at least 11 hours prior to study drug administration and remained in house until 36 hours post-dose. Outpatient visits were at 48, 60, and 72 hours post-dose in each treatment period. There was a washout period of at least 21 days between treatment periods.

Subjects assigned to the Test treatment received a standardized high-fat (approximately 50% of total caloric content of the meal), high-calorie (800-1,000 calories) breakfast 30 minutes before drug administration, and it was consumed completely in a period of 30 minute period. This meal derived approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The breakfast consisted of two eggs fried in butter, two slices of toast with butter, two strips of bacon, approximately 128 g of hash brown potatoes, and 200 mL of whole milk. All subjects were served a controlled meal not less than 4 hours post-dose and at appropriate times thereafter, in each period. Subjects were served standardized post-dose meals similar in composition in each period. All meals served on study had a low content in vitamin B6 (e.g., no tuna, chicken, turkey, cod, salmon, beef tenderloin, or banana was served). Except for fluids provided with breakfast (Test) and 240 mL water given with study medication, no fluids were allowed from 1 hour before dosing until 1 hour post-dose. Water was provided *ad libitum* at all other times.

Inclusion Criteria:

- Healthy, premenopausal, non-smoking or moderate smoking (i.e., < 9 cigarettes daily) females between ages of 18-45 years at screening.
- Females with BMI of > 18.5 and < 30.0 kg/m².
- Females of childbearing potential who are sexually active with a male partner must be willing to use one of the following acceptable contraceptive method throughout the study and for 30 days after the last study drug administration:

- Intra-uterine contraceptive device placed at least 4 weeks prior to study drug administration;
- Condom with intravaginally applied spermicide starting at least 14 days prior to study drug administration;
- Hormonal contraceptives starting at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study;
- Sterile male partner (vasectomized since at least 6 months).

Exclusion Criteria:
Subjects who had any of the following criteria were excluded from the study:

- Pregnant or lactating females
- Positive pregnancy test at screening.
- Any clinically significant abnormality or abnormal laboratory test results found during medical screening or positive test for hepatitis B, hepatitis C, or HIV found during medical screening.
- History of allergic reactions to doxylamine, other ethanolamine derivative antihistamines, pyridoxine, or other related drugs and any inactive ingredient in the Diclectin®/Diclegis® formulation.
- ECG abnormalities or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at screening.
- History or presence of alcoholism or drug abuse within 1 year prior to screening or regular use of alcohol (more than 14 units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]) within 6 months prior to screening.
- Use of medication other than topical products without significant systemic absorption and hormonal contraceptives:
  - Prescription medication within 14 days prior to the first dosing;
  - OTC products including natural health products (e.g., food supplements and herbal supplements) within 7 days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily);
  - Multivitamins or supplements containing vitamin B6 within 28 days prior to the first dosing;
  - A depot injection or an implant of any drug (other than hormonal contraceptives) within three months prior to the first dosing;
  - MAO inhibitors within 30 days prior to the first dosing.
- Participation in a clinical trial involving the administration of an investigational or marketed drug within 30 days (90 days for biologics) prior to the first dosing or concomitant participation in an investigational study involving no drug administration.
- Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the first dosing.
- Hemoglobin < 115 g/L and hematocrit < 0.32 L/L at screening.

Demographics of Subjects:
Twenty four (24) subjects were randomized and dosed in this study; all of these subjects completed the study. Subject 20 had many consecutive missing samples in Period 2 (Fed). Because this subject's PK profile could not be adequately characterized, she was excluded from the PK population.

The mean age of the 23 subjects included in the PK analysis was 32 (range: 18-44 years) with a mean BMI of 24.2 kg/m^2 (range: 19.0-28.8 kg/m^2). There were 22 Caucasians (95.7%) and 1 Black or African American (4.3%).

Concomitant Medication and Diet Restrictions:
Prescription and OTC medications were prohibited throughout the study. No concomitant drug therapy was allowed during the study except one(s) required for the medical management of an AE. The use of hormonal contraceptive was allowed and documented. Any concomitant medication use other than the occasional use of acetaminophen was evaluated on a case-by-case basis by the QI or a physician. All concomitant medication use was documented.

Subjects were required to abstain from:

- Food containing poppy seeds within 24 hours prior to admission of each period;
- Food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours prior to dosing until after the last PK blood sample collection of each period;
- Natural health products (including food supplements, herbal supplements, etc.) from seven days prior to each dosing until after the last PK blood sample collection of each period;
- Multivitamins containing vitamin B6 or B6 supplement from 28 days prior to the first dosing until after the last PK blood sample collection of the study;
- Food or beverages containing grapefruit, starfruit, pomegranate, pineapple, or pomelo from seven days prior to each dosing until after the last PK blood sample collection of each period;
- Excessive consumption (e.g., more than once a day) of foods or beverages with high content of vitamin B6 (e.g., brewer's yeast, meat and poultry, liver, fish, spinach, peppers, squash, banana, unpeeled potatoes, nuts and seeds, whole-wheat) from seven days prior to admission until after the last sample collection of each period;
- Soft or hard drugs during the study;
- Smoking from at least two hours prior to dosing until 10 hours post-dose for Test (Fed), and five hours post-dose for Reference (Fasting). Subjects were not allowed to smoke more than nine cigarettes per day;
- Alcohol-based products from 24 hours prior to admission until after the last PK sample collection of each period.

PK Characterization:
Blood samples for plasma (whole blood for pyridoxal) concentration measurements were collected as the following:

Doxylamine:

- Fed: At pre-dose and at 1, 2, 3, 3.5, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 16, 20, 24, 36, 48, and 72 hours post-dose.
- Fasting: At pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 5.5, 6, 7, 7.5, 8, 10, 12, 16, 24, 36, 48, and 60 hours post-dose.

Pyridoxine:

- Fed: At pre-dose (-1, -0.5 hours, and -5 minutes) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24 hours post-dose.
- Fasting: At pre-dose (-1, -0.5 hours, and -5 minutes) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, and 8 hours post-dose.

Pyridoxal:

- Fed: At pre-dose (-1, -0.5 hours, and -5 minutes) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 30 hours post-dose.
- Fasting: At pre-dose (-1, -0.5 hours, and -5 minutes) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, and 16 hours post-dose.

Pyridoxal 5′-phosphate:

- Fed: At pre-dose (-1, -0.5 hours, and -5 minutes) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 18, 20, 22, 24, 30, 36, 48, and 72 hours post-dose.
- Fasting: At pre-dose (-1, -0.5 hours, and -5 minutes) and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 48, and 72 hours post-dose.

Reviewer's Comment: The Sponsor stated the following in their study report:
"Considering that pyridoxine reaches maximum concentrations relatively rapidly under fasting conditions, and that it is also eliminated rapidly, intensive sample collection was done within the first hours for this analyte in order to get a good characterization of their PK profile."

Pyridoxine and its metabolites, pyridoxal and pyridoxal 5′-phosphate are endogenous compounds and needed to collect samples for baseline corrections. Pre-dose samples for the baseline correction were collected at -1, -0.5 hours, and -5 minutes of the scheduled dose time.

For baseline correction for each subject and treatment period, the baseline value was defined as the mean of the -1, -0.5 hour, and within 5 minutes pre-dose samples obtained for that same subject. The calculated mean baseline concentration was considered as the pre-dose value. The data for each subject and each treatment period was corrected for baseline by subtracting the mean baseline value from pre-dose and all post-dose values. If baseline-adjusted concentrations are negative, concentrations were to be set to zero.

The following non-compartment PK parameters were calculated for plasma doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate:

- AUC(0-t): area under the concentration-time curve from zero to the last non-zero concentration
- AUC(0-inf): area under the concentration-time curve from zero to infinity (extrapolated)
- C_{max}: maximum observed concentration
- T_{max}: time of observed C_{max}
- $t_{½}$: elimination half-life

Sample Size Determination:
Sponsor stated that a total of 24 subjects were judged to be sufficient to meet the study objectives. No additional information on sample size determination was provided in the application.

Reviewer's Comment: The sample size of 24 appears to be adequate for food effect assessment.

Statistical Analysis for Food Effect Assessment:
Individual and mean plasma concentrations versus time curves were presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, SD, CV (%), minimum,

maximum, and median) of the plasma concentrations versus time were presented as well for the PK parameters. For doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate, using general linear model (GLM) procedures in Statistical Analysis System® (SAS®), ANOVA were performed on untransformed T_{max}, K_{el}, and $t_{½}$ and on ln-transformed AUC(0-t), AUC(0-inf), AUC(0-72) (for pyridoxal 5′-phosphate) and C_{max} at the alpha level of 0.05. Factors incorporated in the model included: Sequence, Subject (Sequence), Period, and Treatment. The Fed-to-Fasted ratio of means (A/B) and 90% geometric CI for the ratio of means, based on least-squares means from the ANOVA of the ln-transformed data, were calculated for AUC(0-t), AUC(0-inf), and C_{max}. For pyridoxine, pyridoxal, and pyridoxal 5′-phosphate, both baseline-uncorrected and baseline-corrected data were presented. For baseline-uncorrected data, analyses were performed on ln-transformed AUC(0-t) and C_{max} only.

No food effect was to be concluded if the 90% geometric CIs of the ratio (A/B: fed conditions/fasting conditions) of least-squares means from the ANOVA of the ln-transformed AUC(0-t), AUC(0-inf), and C_{max} were within 80.00% to 125.00%.

Safety Assessments:

- A urine pregnancy test was performed for all subjects at the time of screening and study exit procedures, and a serum pregnancy test was performed prior to drug administration in each period.
- Clinical laboratory tests (biochemistry, hematology, and urinalysis) were performed for each subject at the time of screening and study exit procedures.
- Physical examinations, ECGs measurements, and vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) were performed at the time of screening, only.
- Throughout the study, subjects were monitored for AEs.

Bioanalytical Method:

Bioanalysis was conducted at the (b) (4) . Human plasma samples were analyzed using a LC-MS/MS method for the determination of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate concentrations. Plasma samples were stored in the freezer at -20°C for doxylamine, pyridoxine, pyridoxal, and at -80°C for pyridoxal 5′-phosphate until sample analysis. The analytes were extracted from plasma by protein precipitation. Carbinoxamine, pyridoxine-d_3, pyridoxal-d_3, and pyridoxal 5′-phosphate-d_3 were used as ISs for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate, respectively. After sample extraction, samples (i.e., 50 µL for pyridoxine, pyridoxal, and pyridoxal 5′-phosphate and 100 µL for doxylamine) were injected for analysis. Sample analysis was performed using a triple quadrupole mass spectrometer following separation via the HPLC system. The LC-MS/MS method was developed and validated with the dynamic range of 0.50-250 ng/mL for doxylamine, 0.25-100 ng/mL for pyridoxine, 0.5-200 ng/mL for pyridoxal, and 2-200 ng/mL for pyridoxal 5′-phosphate.

The stability of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate in human plasma samples was demonstrated during method validation. Doxylamine was stable in human plasma at room temperature for 24 hours and stable at -20ºC for approximately 507 days. Pyridoxine was stable in human plasma at room temperature for 22.5 hours and stable at -20ºC for approximately 166 days. Pyridoxal was stable in whole blood at 4ºC for 24 hours and stable at -20ºC for approximately 127 days. Pyridoxal 5′-phosphate was stable in human plasma at 4ºC for 27 hours and stable at -80ºC for approximately 289 days. The established long term stability was sufficient to cover the maximum storage period of 122 days for doxylamine, 124 days for pyridoxine, 119 days for pyridoxal, and 105 days for pyridoxal 5′-phosphate. Doxylamine, pyridoxine, pyridoxal,

and pyridoxal 5′-phosphate were shown to be stable during 4 freeze-thaw cycles. Sample extracts for all four analytes were stable at room temperature for more than 95 hours.

Calibration standard and QC working spiking solutions were prepared by diluting the analyte stock solutions. These working spiking solutions were then spiked in blank matrices to obtain calibration standards and QC samples. To maximize integrity of the matrix when preparing the calibration standards and QC samples, a maximum of 5% (v/v) of the working spiking solutions were added to the blank matrices. After preparation of the calibration standards and QC samples, those for pyridoxal 5′-phosphate were stored in the freezer at -80ºC and those for others were stored at -20ºC.

Accuracy during sample analysis was expressed as percent difference from theoretical concentration (i.e., %RE). Precision of the calibration standards and QC samples during sample analysis was expressed as the percent coefficient of variation (%CV).

Table A-3-1: Back Calculated Concentrations of Calibration Standards for Doxylamine in Human Plasma

Nominal Concentration (ng/mL)	0.5	1.0	10.0	25.0	50.0	100.0	200.0	250.0
Runs (n)	14	14	14	14	14	14	14	14
Mean Concentration (ng/mL)	0.5	1.0	10.4	25.1	49.4	97.6	198.2	251.6
Inter-run % CV	4.0	5.0	3.1	2.4	2.8	3.0	3.8	4.7
Inter-run % RE	0.0	0.0	4.1	0.2	-1.3	-2.4	-0.9	0.6

Table A-3-2: Inter-run Accuracy and Precision of QC Samples for Doxylamine in Human Plasma

Nominal Concentration (ng/mL)	1.5	25.0	125.0	175.0
Runs (n)	20	20	20	20
Mean Concentration (ng/mL)	1.5	24.8	124.4	174.4
Inter-run % CV	8.0	3.5	4.5	5.0
Inter-run % RE	0.0	-1.0	-0.5	-0.4

Table A-3-3: Back Calculated Concentrations of Calibration Standards for Pyridoxine in Human Plasma

Nominal Concentration (ng/mL)	0.25	0.5	3.0	5.0	10.0	20.0	40.0	80.0	100.0
Runs (n)	17	18	18	17	18	18	18	18	18
Mean Concentration (ng/mL)	0.25	0.51	2.96	4.99	10.01	20.64	39.88	79.08	99.23
Inter-run % CV	4.0	3.9	2.0	2.4	3.1	3.9	3.7	3.7	2.7
Inter-run % RE	0.0	2.0	-1.3	-0.2	0.1	3.2	-0.3	-1.2	-0.8

Table A-3-4: Inter-run Accuracy and Precision of QC Samples for Pyridoxine in Human Plasma

Nominal Concentration (ng/mL)	0.75	5.0	50.0	75.0
Runs (n)	22	22	22	22
Mean Concentration (ng/mL)	0.75	4.98	49.26	72.49
Inter-run % CV	4.0	4.4	3.2	4.2
Inter-run % RE	0.0	-0.4	-1.5	-3.4

Table A-3-5: Back Calculated Concentrations of Calibration Standards for Pyridoxal in Human Whole Blood

Nominal Concentration (ng/mL)	0.5	1.0	5.0	20.0	40.0	80.0	160.0	200.0
Runs (n)	26	25	26	26	25	26	25	24
Mean Concentration (ng/mL)	0.50	0.99	5.08	20.31	40.14	79.40	157.39	198.93
Inter-run % CV	8.0	5.1	4.3	3.3	3.3	4.1	4.4	5.2
Inter-run % RE	0.0	-1.0	1.6	1.6	0.4	-0.8	-1.6	-0.5

Table A-3-6: Inter-run Accuracy and Precision of QC Samples for Pyridoxal in Human Whole Blood

Nominal Concentration (ng/mL)	1.95	11.93	101.93	151.93
Runs (n)	26	26	26	26
Mean Concentration (ng/mL)	1.75	10.87	93.80	137.05
Inter-run % CV	8.0	4.1	4.8	3.7
Inter-run % RE	-10.3	-8.9	-8.0	-9.8

Table A-3-7: Back Calculated Concentrations of Calibration Standards for Pyridoxal 5′-Phosphate in Human Plasma

Nominal Concentration (ng/mL)	2.0	4.0	10.0	20.0	30.0	40.0	80.0	160.0	200.0
Runs (n)	13	14	14	14	14	14	14	14	14
Mean Concentration (ng/mL)	2.00	4.02	9.87	19.76	31.99	39.69	79.79	157.21	196.94
Inter-run % CV	7.0	6.2	3.4	3.3	3.6	3.5	2.4	2.9	2.0
Inter-run % RE	0.0	0.5	-1.3	-1.2	6.6	-0.8	-0.3	-1.7	-1.5

Table A-3-8: Inter-run Accuracy and Precision of QC Samples for Pyridoxal 5′-Phosphate in Human Plasma

Nominal Concentration (ng/mL)	6.07	19.07	74.07	154.07
Runs (n)	20	20	20	20
Mean Concentration (ng/mL)	6.11	18.44	73.35	145.30
Inter-run % CV	6.9	6.3	3.1	6.2
Inter-run % RE	0.7	-3.3	-1.0	-5.7

Linearity during sample analysis was described as the mean r^2 of the standard curves. The mean r^2 values were ≥ 0.998 for doxylamine, ≥ 0.994 for pyridoxine, ≥ 0.997 for pyridoxal, and ≥ 0.0994 for pyridoxal 5′-phosphate.

ISR was conducted on 5.6-5.8% of the total number of sample for each analyte. The percent (%) difference is defined as {(repeat - original) / [(repeat + original)/2]} x 100 and the percentage difference had to be within ± 20% for at least 67% of the ISR samples to be considered successful in confirming the reproducibility of the bioanalytical method.

Table A-3-9: Summary of ISR Results in Human Plasma (Study 140115)

Analyte	Total Number of Samples	Number of ISR Samples	Portion of ISR Samples (%)	Passing ISR Samples (%)
Doxylamine	1245	113	9.1	100
Pyridoxine	1221	111	9.1	93.7
Pyridoxal[a]	1319	116	8.8	89.7
Pyridoxal 5′-Phosphate	1195	110	9.2	93.6

[a] Matrix: whole blood

> **Reviewer's Comment**: Acceptance criteria and assay performance for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate bioanalysis are in compliance with the Agency's Bioanalytical Method Validation Guidance and the bioanalytical method are acceptable.

Disposition of Subjects:
Twenty four (24) healthy, premenopausal females were randomized, dosed, and completed the study. Subject 20 had many consecutive missing samples in Period 2 (Test) and she was excluded from the PK population for all analytes because it was not possible to adequately characterize her PK profiles.

Treatment Compliance:
Measurements of treatment compliance were 100%, as subjects were dosed under direct supervision, subject identification was verified and cross-checked with the pre-dispensed medication, and a mouth (using a tongue depressor and a flashlight) and hand check was performed to ensure subjects had swallowed the study medication.

Protocol Deviations:
Table A-3-10 provides a summary of protocol deviation.

Table A-3-10: Summary of Protocol Deviations

Type	Subject Nos. (Test)	Subject Nos. (Ref.)
Study Restrictions		
In Period 2, this subject left the clinical facilities approximately six hours before the end of the scheduled confinement period for personal reasons. The subject was informed of the possible risks related to this premature departure and was instructed to contact the clinical project coordinator if she experienced any adverse events. The subject came back for the scheduled return visits and her safety was not jeopardized.	14	
In Period 2, the subject drank three beers (500 mL each) approximately 41 hours following administration of Treatment A. There is no impact on study results since doxylamine, pyridoxine and its metabolites do not share the same metabolic pathway than ethanol.	01	
In Period 2, this subject ate a small piece of chocolate approximately 23 hours prior to administration of Treatment B. Based on caffeine half-life of four to five hours, more than 96% of the ingested caffeine was already eliminated when the subject was dosed. There is consequently no impact on study results.		15
Study Samples (Pharmacokinetic)		
In Period 2, during the bagging process, the frozen 10 hours post-dose sample for doxylamine (aliquot 1 of 2) was accidently left at room temperature for approximately 15 minutes and put back in the freezer at -20°C. The sample was thawed at this time. There is no impact on sample integrity since the short term in matrix validated for doxylamine is 24 hours at room temperature with four freeze/thaw cycles.	24	

Type	Subject Nos. (Test)	Subject Nos. (Ref.)
In Period 2, micro coagulation was observed in the following blood samples: samples collected 8.00, 8.50, 9.00, 13.0, 14.0, 16.0, 20.0, 24.0 and 36.0 hours post-dose for doxylamine analysis; samples collected 8.00, 9.00, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0, 21.0, 22.0, 23.0 and 24.0 hours post-dose for pyridoxine analysis; samples collected 8.00, 9.00, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 19.0, 20.0, 21.0, 22.0, 23.0, 24.0 and 30.0 hours post-dose for pyridoxal analysis; samples collected 8.00, 9.00, 10.0, 11.0, 12.0, 14.0, 15.0, 16.0, 18.0, 20.0, 22.0, 24.0, 30.0 and 36.0 hours post-dose for pyridoxal 5'-phosphate analysis. These samples were analyzed based on client request but were excluded from the statistical analysis since the analytical methods used for the four analytes were not validated in human serum and the micro coagulation could have an impact on the distribution of the medication in plasma.	20	
In Period 2, the blood sample collected nine hours post-dose for doxylamine and pyridoxal analysis was directly exposed to ambiant light for a few seconds after collection. Doxylamine is not light sensitive, there is consequently no impact for this analyte. However, since pyridoxal is light sensitive, this sample was analyze based on client request, but was excluded from the statistical analysis.	20	
In Period 1, the blood samples collected 1.25 hour post-dose for pyridoxal analysis were centrifuged at 3000 rpm for 10 minutes at 4°C in error. There is no impact on samples integrity since the tubes were remixed after centrifugation and whole blood were transferred into the aliquots as requested.		13, 14, 19, 20, 22 and 24

Test (A)= Duchesnay, Inc., Canada, doxylamine-pyridoxine 1 x 20 mg-20 mg (b) (4) tablet, administred under fed conditions.
Reference (B)= Duchesnay, Inc., Canada, doxylamine-pyridoxine 1 x 20 mg-20 mg (b) (4) tablet, administred under fasting conditions.

Reviewer's Comment: This reviewer concurs to the Investigator's/Sponsor's assessments and decisions made to either include or exclude these subjects/samples from the PK characterization and BE analysis.

PK and Food Effect Assessment Results:

Mean (SD) PK parameters of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate obtained following administration of a TRADENAME tablet with food (Test) or without food (Reference) are summarized in Tables A-3-11, A-3-12, A-3-13, A-3-14, A-3-15, and A-3-16.

Table A-3-11: Mean (SD) Plasma PK Parameters of Doxylamine Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	1242.8 (254.0)	1273.7 (276.2)
AUC(0-inf) (ng·hr/mL)	1281.4 (282.9)	1321.9 (315.5)
C_{max} (ng/mL)	64.5 (15.2)	85.9 (10.6)
T_{max} (hr)[a]	6.5 (2.0-24.0)	3.5 (2.5-5.5)
$t_{½}$ (hr)	12.7 (2.6)	11.9 (2.2)

[a] Median (minimum-maximum)
t=72 hr (Test) and 60 hr (Reference)

Table A-3-12: Mean (SD) Plasma PK Parameters of Pyridoxine Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	22.8 (9.9)	34.7 (10.6)
AUC(0-inf) (ng·hr/mL)	27.0 (10.1)[b]	35.1 (8.5)[b]
C_{max} (ng/mL)	12.7 (5.7)	38.9 (19.3)
T_{max} (hr)[a]	8.0 (1.0-21.0)	0.75 (0.3-4.3)
$t_{½}$ (hr)	1.2 (2.4)[b]	0.4 (0.2)[b]

[a] Median (minimum-maximum)
[b] n=12, For Subjects 3, 4, 7, 8, 15, 17, 18, 21, 22, 23, and 24, AUC(0-inf) and $t_{½}$ could not be properly estimated due to an insufficient number of detectable concentrations in the terminal elimination phase and these subjects were excluded from all analyses involving AUC(0-inf) and $t_{½}$.
t=24 hr (Test) and 8 hr (Reference)

Reviewer's Comment: All pre-dose pyridoxine concentrations were below the LLOQ for all subjects and therefore, no baseline adjustments were performed on pyridoxine concentrations.

Table A-3-13: Mean (SD) Whole Blood PK Parameters of Baseline Uncorrected Pyridoxal Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	238.1 (32.2)	227.1 (33.0)
C_{max} (ng/mL)	34.2 (6.2)	63.1 (18.0)
T_{max} (hr)[a]	6.0 (1.0-21.0)	2.3 (0.8-5.0)

[a] Median (minimum-maximum)
t=30 hr (Test) and 16 hr (Reference)

Table A-3-14: Mean (SD) Whole Blood PK Parameters of Baseline Corrected Pyridoxal Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	204.2 (25.7)	209.4 (30.0)
AUC(0-inf) (ng·hr/mL)	249.2 (43.0)	244.0 (32.5)
C_{max} (ng/mL)	33.1 (6.2)	62.0 (17.8)
T_{max} (hr)[a]	6.0 (1.0-21.0)	2.3 (0.8-5.0)
$t_{½}$ (hr)	12.5 (7.6)	8.0 (1.7)

[a] Median (minimum-maximum)
t=30 hr (Test) and 16 hr (Reference)

Table A-3-15: Mean (SD) Plasma PK Parameters of Baseline Uncorrected Pyridoxal 5′-phosphate Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	1638.6 (529.6)	1624.9 (526.2)
C_{max} (ng/mL)	38.2 (11.8)	35.8 (10.9)
T_{max} (hr)[a]	16.0 (6.0-22.0)	5.0 (3.0-71.8)

[a] Median (minimum-maximum); t=72 hr (Test and Reference); AUC(0-inf) was not determined

Table A-3-16: Mean (SD) Plasma PK Parameters of Baseline Corrected Pyridoxal 5′-phosphate Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (Study 140115; N=23)

Parameter	Test	Reference
AUC(0-t) (ng·hr/mL)	1064.6 (386.9)	1021.7 (318.5)
C_{max} (ng/mL)	30.2 (10.0)	27.4 (7.7)
T_{max} (hr)[a]	16.0 (6.0-22.0)	5.0 (3.0-71.8)

[a] Median (minimum-maximum); t=72 hr (Test and Reference); AUC(0-inf) was not determined

The mean concentration-time profiles for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5′-phosphate obtained following administration of a TRADENAME tablet with food (Test) or without food (Reference) are shown in Figures A-3-1, A-3-2, A-3-3, A-3-4, A-3-5, and A-3-6, respectively.

Figure A-3-1: Mean Plasma Concentration-Time Profiles of Doxylamine Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

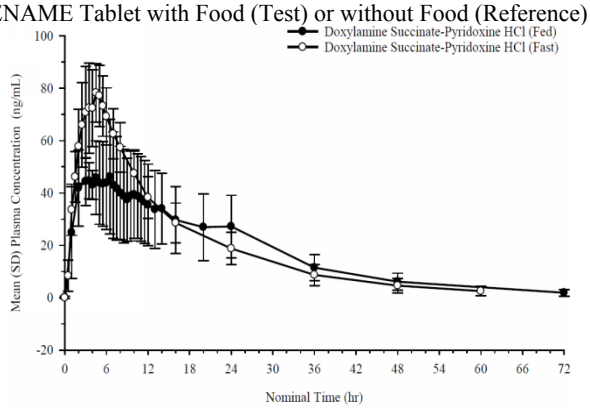


Figure A-3-2: Mean Plasma Concentration-Time Profiles of Pyridoxine Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

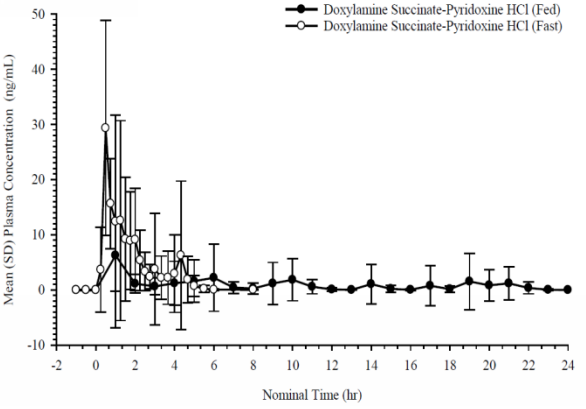


Figure A-3-3: Mean Whole Blood Concentration-Time Profiles of Baseline Uncorrected Pyridoxal Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

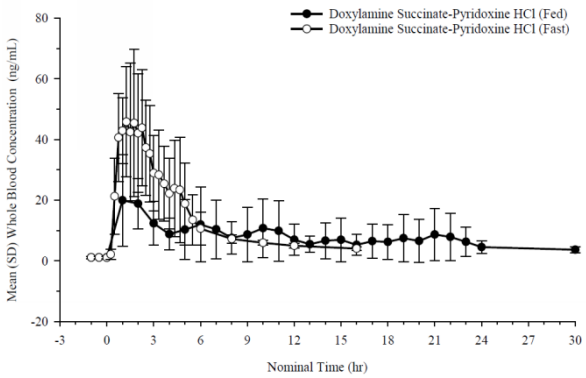


Figure A-3-4: Mean Plasma Concentration-Time Profiles of Baseline Corrected Pyridoxal Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

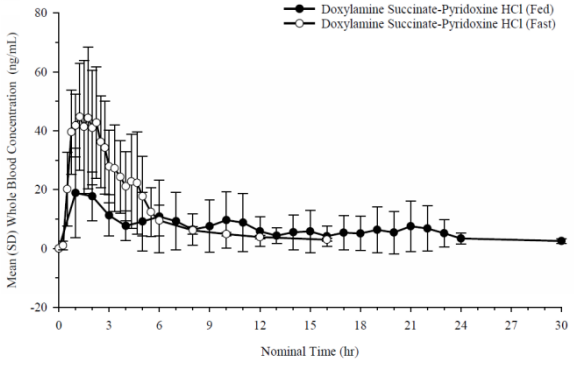


Figure A-3-5: Mean Plasma Concentration-Time Profiles of Baseline Uncorrected Pyridoxal 5′-phosphate Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

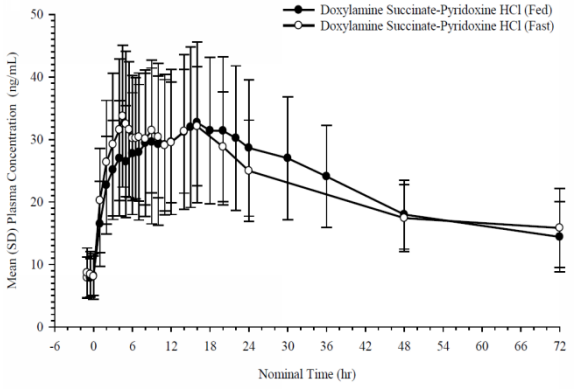


Figure A-3-6: Mean Plasma Concentration-Time Profiles of Baseline Corrected Pyridoxal 5′-phosphate Following a Single Dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

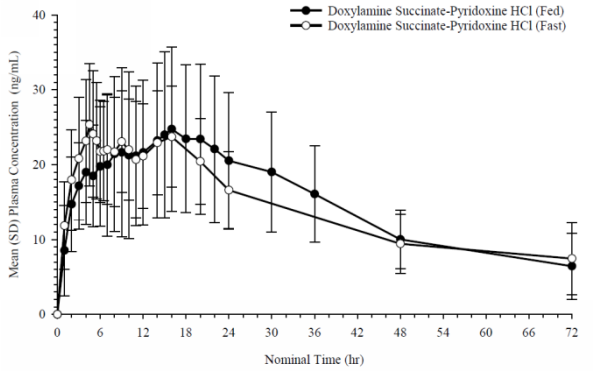


Table A-3-17: Summary of Geometric Means, Point Estimates, and 90% CI of Doxylamine PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	1219.1	1247.0	97.6	93.6-101.7
AUC(0-inf) (ng·hr/mL)	1253.5	1289.1	97.0	92.9-101.3
C_{max} (ng/mL)	62.7	85.3	73.6	68.0-79.8

Table A-3-18: Summary of Geometric Means, Point Estimates, and 90% CI of Pyridoxine PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	20.6	33.1	62.8	54.5-72.3
AUC(0-inf) (ng·hr/mL)	25.3	34.2	70.7	53.8-92.9
C_{max} (ng/mL)	11.4	35.1	32.7	26.9-39.6

Table A-3-19: Summary of Geometric Means, Point Estimates, and 90% CI of Baseline Uncorrected Pyridoxal PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	236.0	224.9	105.1	100.1-110.5
C_{max} (ng/mL)	33.7	60.8	55.1	49.5-61.4

Table A-3-20: Summary of Geometric Means, Point Estimates, and 90% CI of Baseline Corrected Pyridoxal PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	202.5	207.4	97.9	93.4-102.6
AUC(0-inf) (ng·hr/mL)	245.4	242.0	101.8	96.2-107.8
C_{max} (ng/mL)	32.6	59.7	54.2	48.6-60.5

Table A-3-21: Summary of Geometric Means, Point Estimates, and 90% CI of Baseline Uncorrected Pyridoxal 5′-phosphate PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	1562.1	1546.4	100.8	94.8-107.1
C_{max} (ng/mL)	36.5	34.2	106.6	102.6-110.9

Table A-3-22: Summary of Geometric Means, Point Estimates, and 90% CI of Baseline Corrected Pyridoxal 5′-phosphate PK Parameters following a Single dose of TRADENAME Tablet with Food (Test) or without Food (Reference) (N=23)

Parameter	Geometric Mean		Point Estimate (%) (Test/Reference)	90% CI
	Test	Reference		
AUC(0-t) (ng·hr/mL)	1005.4	975.1	103.4	95.6-111.8
C_{max} (ng/mL)	28.7	26.4	109.3	103.4-115.5

Reviewer's Comment: For doxylamine, food decreased the mean C_{max} by 26.4% but not AUCs. Food delayed the median T_{max} from 3.5 hours to 6.5 hours. For pyridoxine, food decreased the mean C_{max} by 67.3%, AUC(0-t) for 37.2%, and AUC(0-inf) for 29.3%. It should be noted that only 12 subjects were included in the calculation of AUC(0-inf) as stated in Table A-3-12,. Food delayed the median T_{max} for from 0.8 hours to 8.0 hours.

While the Sponsor considered doxylamine and pyridoxine as primary analytes for food effect assessment, data for pyridoxal and pyridoxal 5′-phosphate were also submitted. For baseline corrected pyridoxal, food decreased the mean C_{max} by 45.8% but not AUCs. Food delayed the median T_{max} from 2.3 hours to 6.0 hours. For baseline corrected pyridoxal 5′-phosphate, food did not affect the mean C_{max} and AUCs but delayed the median T_{max} from 5.0 hours to 16.0 hours.

Based on this study results, this reviewer recommends TRADENAME tablets to be administered under fasting conditions to avoid food affecting the extent of exposure (i.e., C_{max} and AUC) and rate of absorption (i.e., T_{max}).

Safety Results:
Per Sponsor, no deaths, serious or significant AEs were reported during this study. A total of 24 TEAEs were recorded by 11 subjects during the study: 11 TEAEs reported by 29.2% of subjects following administration of under fed state and 13 TEAEs reported by 29.2% of subjects following administration of fasting state. One subject had abnormal urinalysis results at the time of study exit procedures; however, available data (including clinical laboratory tests) confirmed the absence of significant changes in the subject's state of health.

Reviewer's Comment: It appears that both treatments had similar safety profiles.

Conclusion:
When TRADENAME tablets were administered with a high fat and high calorie meal, food caused a delay in the median T_{max} of doxylamine, pyridoxine, baseline corrected pyridoxal, and baseline corrected pyridoxal 5′-phosphate to 6.5, 8.0, 6.0, and 16.0 hours, respectively. In addition, food decreased the C_{max} of doxylamine, pyridoxine, and baseline corrected pyridoxal for 26.4%, 77.3%, and 45.8%, respectively and AUC(0-t) of pyridoxine for 37.2%.

Therefore, TRADENAME tablets should be administered under fasting conditions to avoid food affecting the rate of absorption (i.e., T_{max}) and extent of exposure (i.e., C_{max} and AUC).

4.2 Office of Study Integrity and Surveillance Consult Report

MEMORANDUM

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

DATE: 1/28/2016

TO: Division of Anesthesia Analgesia and Addiction Products
Office of Drug Evaluation II

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

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 021876/S-0010

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

Although the last inspection was classified as a VAI, based on the nature of the findings from the last inspection, and our recommendation to the review division, an inspection of the site will not be needed at this time.

Requested Site Inspection

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

MEMORANDUM

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

DATE: 1/28/2016

TO: Division of Anesthesia Analgesia and Addiction Products
Office of Drug Evaluation II

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

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 021876/S-0010

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. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	inVentiv Health Clinique Inc.	2500, Rue Einstein, Québec, Canada, G1P 0A2

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

/s/

SHILA S NKAH
02/22/2016

4.3 Clinical Pharmacology Filing Memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA Number	021876	**SDN**	467
Applicant	Duchesnay Inc.	**Submission Date**	October 7, 2015
Generic Name	Doxylamine Succinate, Pyridoxine Hydrochloride	**Brand Name**	Diclegis®
Drug Class	Doxylamine succinate is an antihistamine and pyridoxine hydrochloride is a vitamin B6 analog		
Indication	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management		
Dosage Regimen	One tablet daily at bedtime, if not effective, one tablet in the morning and one tablet at bedtime		
Dosage Form	(b) (4) tablet	**Route of Administration**	Oral
OCP Division	DCP3	**OND Division**	DBRUP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Li Li (CDER)	Myong Jin Kim	
Pharmacometrics	N/A	N/A	
Genomics	N/A	N/A	
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/6/2015	**74-Day Letter Date**	12/20/2015
Review Due Date	6/7/2016	**PDUFA Goal Date**	8/7/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain: clinical and analytical site inspection for bioequivalence study (Study 150033)

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

1

☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☐ Relative Bioavailability		
☑ Bioequivalence	1	Diclegis (b) (4) vs Dicleigs® (currently approved product)
☑ Food Effect	1	Effect of food on the PK of Diclegis (b) (4)
☐ Other		
Human Pharmacokinetics		
Healthy Subjects ☐ Single Dose		
Healthy Subjects ☐ Multiple Dose		
Patients ☐ Single Dose		
Patients ☐ Multiple Dose		
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	2
Total Number of Studies to be Reviewed				2

2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☑No ☐N/A	BE study: the PK parameters for each study subject were submitted, but individual concentration data were not submitted
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

3

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☑No ☐N/A	BE study: the PK parameters for each study subject were submitted, but individual concentration data were not submitted
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Introduction:

The Sponsor has submitted a supplemental New Drug Application (sNDA) for a new strength/regimen/formulation for Diclegis®, which will reduce the maximum number of tablets taken by patients from 4 tablets per day to 2 tablets per day (i.e., 1 tablet in the morning and 1 tablet at bedtime). These new strength and dosing regimen are in line with the currently recommended maximum dose of doxylamine succinate 40 mg / pyridoxine hydrochloride 40 mg.

Diclegis® is a fixed dose combination drug product containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. It was approved for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management under NDA 021876 on April 8, 2013. The approved starting dose is 2 tablets orally at bedtime (Day 1). If symptoms persist on Day 2, take one tablet in the morning and 2 tablets at bedtime on Day 3. If symptoms still not be adequately controlled, take 4 tablets per day on Day 4, i.e., 1 tablet in the morning, 1 tablet mid-afternoon and 2 tablets at bedtime.

The proposed new formulation, named as Diclegis (b) (4) contains 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. Diclegis® (b) (4) consists of an immediate release (IR) portion in addition to the delayed-release (DR) tablet core. (b) (4) The Sponsor (b) (4) The proposed new dosing regimen will be 1 Diclegis (b) (4) tablet orally at bedtime (Day 1). If symptoms persist (b) (4) take 2 tablets starting on Day (b) (4) (one tablet in the morning and one tablets at bedtime). Therefore, under the proposed new regimen, patients will start maximum daily dose of 40 mg/ 40 mg from Day (b) (4) (b) (4) In addition, the new dosing regimen does not have the 30 mg/ 30 mg daily dose.

Per Sponsor, the advantages of this new Diclegis (b) (4) regimen/formulation include:

- reduced variation of doxylamine and pyridoxal 5'-phosphate plasma concentrations at steady state
- improved patient compliance by reducing the number of tablets from four to two tablets daily

In support of this sNDA, the Sponsor conducted two clinical pharmacology studies. Specifically, Study 150033 evaluated the bioequivalence (BE) between the proposed Diclegis (b) (4) formulation (twice per day/BID) and the approved Diclegis® formulation (three times per day/TID) at a total daily dose of 40 mg/ 40 mg of doxylamine and pyridoxine. Study 140115 evaluated the effect of food on the pharmacokinetics (PK) of Diclegis (b) (4) formulation.

Regulatory History

The Sponsor requested a type C guidance meeting with DBRUP seeking advice on the reformulation of the tablets to decrease the total number of tablets to two per day. The Division responded to the Sponsor via a written response (DARRTS on December 10, 2013) and agreed with the Sponsor that "*a bioequivalence comparison study between Diclegis 10 mg/10 mg delayed release tablet and 20 mg /20 mg* (b) (4) *tablet formulations in healthy adult female volunteers may be sufficient to support the efficacy and safety of the new formulation.*"

The WR also stated that "*For the bioequivalence study, we recommend using a single day crossover design as*

follows:

Day 1:

- *Treatment A (Twice Daily Arm): One tablet of test formulation (20 mg x 20 mg) given twice daily as follows: one on the morning and one at night*
- *Treatment B (Three Times Daily Arm): Reference formulation (10 mg x10 mg) given three times daily as follows: one in the morning, one at 4 PM, and 2 tablets at night (as approved).*

Day 10:
The same segment of a single day study described above can be repeated for the multiple doses segment on Day 10. In this case, bioequivalence can be assessed after single dose and multiple doses in one study in the same subjects.

The Sponsor was advised that in the absence of acceptable bioequivalence results, the Sponsor will need clinical trial data to establish the efficacy and safety of your new formulation/regimen. In addition, the Sponsor was advised to conduct a fed/fasted bioavailability study for the new formulation.

(Detailed information can be found in Dr. Sayed Habet's Clinical Pharmacology review in DARRTS dated on December 23, 2013).

Clinical Development of Diclegis® (b) (4)
In this sNDA, two clinical pharmacology studies were submitted to support the approval of the new formulation.

- BE study (Study 150033)
  Study Design
  This is an open label, randomized, multiple-dose, 3-way reference-replicated crossover study comparing the rate and extent of absorption of Diclegis (b) (4) (test) and Diclegis® (reference) in 39 healthy female subjects under fasting conditions. In each period, subjects were administered multiple oral dose of either the Test or Reference study medication for 11 consecutive days as follow:
  - Treatment A (Test): Diclegis (b) (4) (20 mg/20 mg (b) (4) elease tablet) BID, i.e., 1 tablet at 09:00 and 1 tablet at 21:00 for 11 consecutive days
  - Treatment B (Reference): Diclegis® (10 mg/10 mg DR tablet) TID, i.e., 1 tablet at 09:00, 1 tablet at 15:00 and 2 tablets at 21:00 for 11 consecutive days

  The treatment periods were separated by washout periods of at least 28 days. Blood samples were collected at pre-dose and up to 24 hour post-dose on day 1 and day 11 for measurements of plasma concentrations of doxylamine, pyridoxine and pyridoxal 5'-phosphate and blood concentrations of pyridoxal. Regarding baseline correction for the endogenous concentrations of pyridoxine and metabolites, the baseline value was defined as the mean of the -1.00 hour, -0.500 hour, and within 10 minutes pre-dose samples obtained for that same subject and period on Day 1.

  Standard for BE assessment for doxylamine and baseline-corrected pyridoxal 5'-phosphate:
  If CV_{WR} was <30% for a primary parameter such as AUC_{0-24}, $AUC_{0-24\ ss}$, C_{max}, $C_{max\ ss}$, $C_{min\ ss}$), then the 90% geometric confidence intervals of the mean ratio (A/B) based on the ln-transformed data must be within 80.00-125.00% to conclude BE for that parameter. If CV_{WR} was ≥30% for a primary parameter (AUC_{0-24}, AUC_{0-24ss}, Cmax, Cmaxss, Cminss), then 1) the point estimate of the test-to-reference ratio

was within 80.00-125.00% and 2) the 95% upper confidence bound for the scaled average BE criteria was ≤ 0 to conclude BE for that parameters. Criteria for average BE for baseline uncorrected pyridoxal-5-phosphate, pyridoxine and pyridoxal were calculated and presented as supportive data. Repeated measures analysis were carried out on ln-transformed pre-dose concentrations (on Days 9 to 11) to determine attainment of steady-state.

Study Results

The study showed that following the administration of a total dose of 40 mg doxylamine/40 mg pyridoxine for 11 consecutive days under fasting conditions, the 90% geometric confidence intervals of test-to-reference geometric mean ratios (GMR) on AUC_{0-24} and Cmax for doxylamine and baseline-corrected pyridoxal 5'-phosphate were within 80.00% to 125.00% (**Table 1, Figure 1** and **Figure 2**). For pyridoxine, BE on AUC_{0-24} was not met for both day 1 and day 11 (**Table 2** and **Figure 3**).

Table 1 Test-to Reference GMR and 90% confidence interval on AUC_{0-24} and C_{max} for doxylamine and baseline-corrected pyridoxal 5'-phosphate

		Parameters	Ratio[1]	90% Confidence Intervals[2]
Doxylamine	Day 1	AUC_{0-24}	140.04%	130.24% – 150.58%
		C_{max}	79.57%	76.11% – 83.19%
	Day 11	AUC_{0-24}	99.05%	95.73% - 102.49%
		C_{max}	105.26%	100.84% - 109.88%
Pyridoxal-5-Phosphate (baseline -corrected)	Day 1	AUC_{0-24}	161.49%	147.58% -176.71%
		C_{max}	105.64%	99.64% - 112.00%
	Day 11	AUC_{0-24}	100.08%	95.82% - 104.53%
		C_{max}	100.76%	96.68% - 105.00%

Figure 1 Mean (±SD) concentration-time profiles for doxylamine for each treatment on Day 1 (left panel) and Day 11 (Right panel)

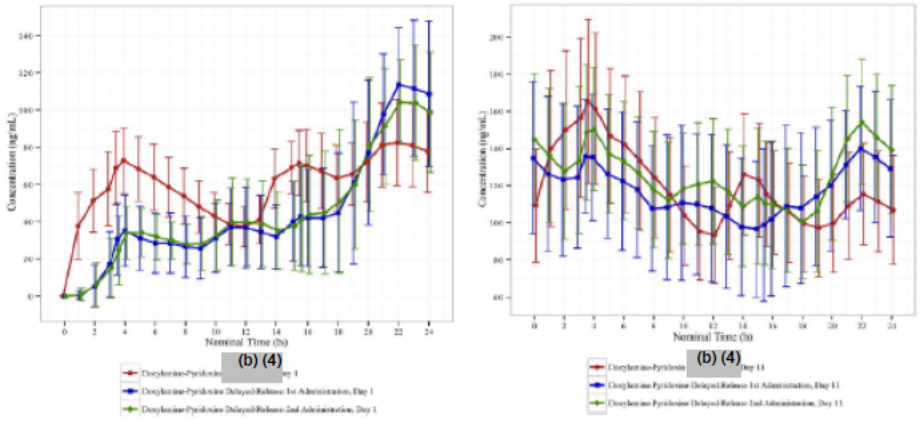


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Figure 2 Mean (±SD) concentration-time profiles for baseline-corrected pyridoxal 5'-phosphate for each treatment on Day 1 (left panel) and Day 11 (Right panel)

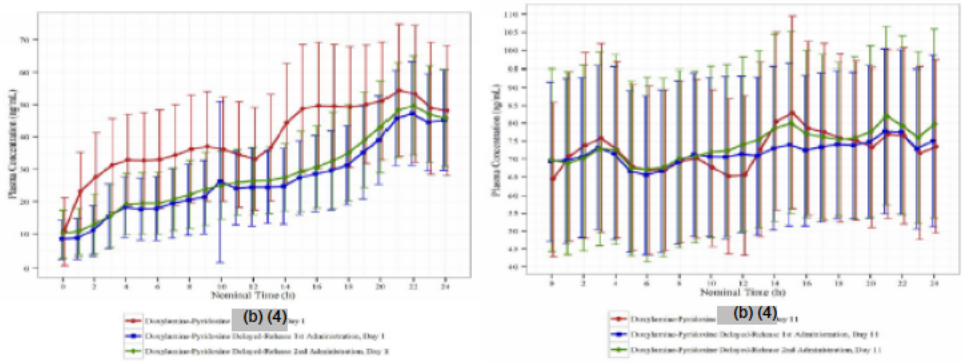
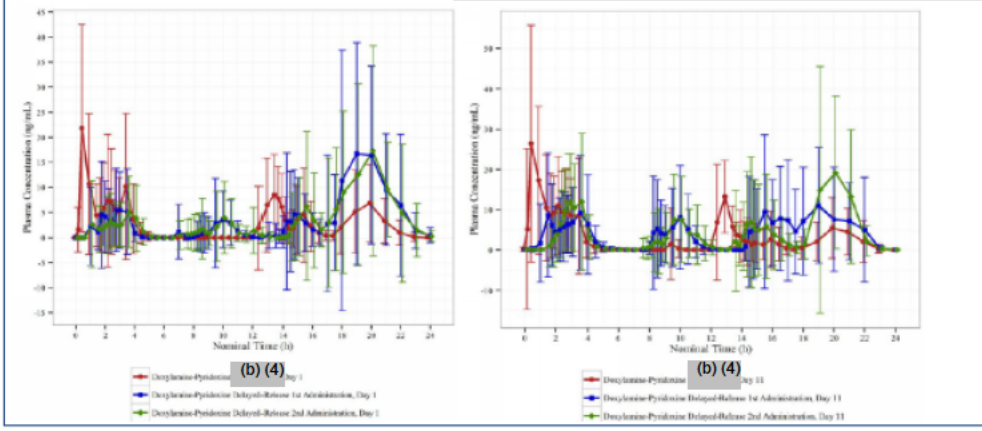


Table 2 Test-to Reference GMR and 90% confidence interval on AUC_{0-24} and Cmax for pyridoxine

	Parameters	Ratio[1]	95% Upper Confidence Bound[2]	90% Confidence Intervals[3]	CV_{WR}
Day 1	AUC_{0-24}	80.79%	-	75.69% - 86.24%	26.14%
	C_{max}	98.21%	- 0.1373	-	53.37%
Day 11	AUC_{0-24}	80.53%	-	74.72% - 86.80%	19.95%
	C_{max}	108.66%	- 0.0288	-	33.33%

1 Point estimate of the geometric mean ratio (A/B)
2 Reference-scaled average bioequivalence approach
3 90% Geometric Confidence Interval using ln-transformed data

Figure 3 Mean (±SD) concentration-time profiles for pyridoxine for each treatment on Day 1 (left panel) and Day 11 (Right panel)



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- Food Effect Study (Study 140115)
  This was a randomized, open-label, 2-way crossover study comparing the bioavailability of doxylamine and pyridoxine in 24 healthy female subjects taking a single dose of Diclegis® (b) (4) under fasting and fed conditions. The study results showed that food delayed the absorption of doxylamine by 3 hours (median Tmax). The Cmax of doxylamine was decreased by 26% while the AUC remained unchanged and the Cmax and AUCs of pyridoxine were decreased respectively by 67% and up to 37%.

Diclegis DUAL Formulation:
The new formulation, Diclegis (b) (4) consists of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride, including an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. Diclegis (b) (4) contains an IR portion in addition to the DR tablet core. (b) (4) To this core, an IR (b) (4) coating of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride was added. The composition of proposed Diclegis (b) (4) formulation is depicted in the Table below:

Table 3 Composition of proposed Diclegis (b) (4) formulation

Component and Quality Standard (and Grade, if applicable)	Function	20 mg/20 mg Delayed-Release Tablets
		Quantity per unit (mg)
Doxylamine Succinate, USP	API	(b) (4)
Pyridoxine HCl, USP	API	
Microcrystalline Cellulose (b) (4) 102, NF	(b) (4)	
Magnesium Trisilicate, USP		
Croscarmellose Sodium, NF		
Magnesium Stearate, NF		
Colloidal Silicone Dioxide, NF		
(b) (4)		
Triethyl Citrate, NF		

APPEARS THIS WAY ON ORIGINAL

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Simethicone	(b) (4) USP (b) (4)	(b) (4)	(b) (4)
Carnauba Wax Powder, NF			
(b) (4)		(b) (4)	
(b) (4)	Pink, In-house	Printing ink	trace
OVERALL TABLET TOTAL			*232.6*

Absorption, Distribution and Elimination (ADE):
Specific studies describing the ADE of Diclegis (b) (4) were not conducted. The Sponsor is proposing to use the available information of Diclegis®.

Drug-Drug Interactions (DDIs): No DDI studies were conducted with Diclegis (b) (4)

Specific Populations:

- Pediatric use: The Sponsor requested a waiver for pediatric (b) (4) females < (b) (4) years of age, as these populations are not at risk of pregnancy. The Sponsor (b) (4) (b) (4) Currently, the approved product, Diclegis® is under PREA commitment with the Agency to conduct a pediatric assessment for pregnancy adolescents aged 12 to 17 years. The planned clinical study completion date is January 2018.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments.

Bioanalytical Method:
For Study 140115 and Study 150033, plasma concentrations of doxylamine, pyridoxine, pyridoxal and and blood concentrations of pyridoxal 5'-phosphate was measured using validated high performance liquid chromatographic method or Liquid chromatography–mass spectrometry method. The analytical methods validation reports are summarized in **Table 4**.

Table 4 Summary of Clinical Study Analytical Method Validation Reports

Report Number*	Substance	Matrix	Applicable to Study Reports	
			140115	150033
125031AFLO	Pyridoxine	Human NaF/$K_2C_2O_4$ Plasma	x	x
65187OBT	Doxylamine	Human EDTA Plasma	x	x
135110ALEG	Pyridoxal-5-Phosphate	Human NaF/$K_2C_2O_4$ Plasma	x	x
125040AFZQ	Pyridoxal	Human EDTA K_2 Whole Blood	x	-
115018AMBI	Pyridoxal	Human EDTA K_2 Whole Blood	-	x

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Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 021876 is not fileable for the following reasons:

- Per FDA BA BE guidance, single dose BE study is the most sensitive way to assess the similarity between formulations. However, the submitted data showed that single dose BE was not met for the proposed formulation. As conveyed to the Sponsor in the WR, clinical trial data to establish the efficacy and safety of the new formulation/regimen will be needed in the absence of acceptable BE results. As there is no clinical trial data in the current submission, we deem this submission incomplete.
- In the proposed label for Diclegis (b) (4) subjects will start with a 20 mg/ 20 mg daily dose (one tablet at bedtime) and may remain with this regimen if symptoms are adequately controlled. Per survey results for Diclegis® (provided by the Sponsor in the meeting package submitted in 2013), about 20% of study subjects may stay at 20-20 mg daily dose. However, no BE assessment was conducted for this dosing regimen. Therefore, whether safety and efficacy of Diclegis (b) (4) will be similar to those of Diclegis® at dosing regimen of 20 mg/ 20 mg is not known.

During the internal discussion with DBRUP on December 1st, 2015, the review team is in the opinion that failed single dose BE (Day 1 of study 150033) is a review issue and this sNDA is fileable.

Office of Study Integrity and Surveillance Inspection Request

- Considering Study 150033 is a pivotal BE study, an inspection on clinical and analytical site will be requested. (b) (4) (b) (4)

Review Issues comments to be forwarded to the Applicant in the 74-day letter

- Safety and efficacy of Diclegis (b) (4) at dosing regimen of 20 mg doxylamine succinate /20 mg pyridoxine hydrochloride per day
  In the proposed label for Diclegis (b) (4) the subjects will start with a 20 mg/ 20 mg daily dose (one tablet at bedtime) and may remain with this regimen if symptoms are adequately controlled. Per survey results for Diclegis® (provided by the Sponsor in the meeting package submitted in 2013), about 20% of study subjects may stay at 20-20 mg daily dose. However, no BE assessment was conducted for this dosing regimen. Therefore, the safety and efficacy of Diclegis (b) (4) t daily dose of 20 mg/ 20 mg will be a review issue.

- Study 150033:
  - Bioequivalence (BE) of doxylamine, pyridoxine and its metabolites (baseline corrected and uncorrected) on Day 1 and Day 11 at 40 mg/40 mg daily dose between Diclegis (b) (4) and Diclegis® formulations will be a review issue.
  - Clinical relevance of failed BE on Day 1 will be a review issue.
  - Different PK profiles of Diclegis (b) (4) and Diclegis® on Day 11
    Although BE appears to have met for doxylamine and baseline-corrected pyridoxal 5'-phosphate on Day 11 of 40-40 mg daily dosing, the PK profiles of Diclegis (b) (4) and Diclegis® are different. Specifically, time to reach peak concentration (Tmax) of doxylamine from Diclegis®

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is around early morning, which is clinically relevant to the treatment of morning sickness, whereas Tmax of doxylamine from Diclegis (b) (4) is around noon, which may lead to more sedation issues. Therefore, whether difference in the PK profiles between the test and reference products implies different clinical response as the reference product will be a review issue (see FDA BA BE Guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf)

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Information Requests to be forwarded to the Applicant in the 74-day letter

- Submit the supporting information that safety and efficacy of Diclegis (b) (4) will be similar to those of Diclegis ® at the dosing regimen of 20-20 mg daily dose.
- Submit the supporting information that different shapes of PK profiles on Day 11 following multiple doses of Diclegis (b) (4) and Diclegis® administration will not significantly affect the safety and efficacy of the drug product. If available, submit the dose-response or concentration-response data to support your justification.
- Provide justification on why BE assessment was based on metabolite pyridoxine-5-phophate, rather than parent drug pyridoxine.
- Submit datasets for individual concentration-time data from Study 150033
- Submit the SAS code for the BE analysis

Reviewer's Notes

- Per Sponsor, "Data from a previous multi-dose study with Diclegis® demonstrate that steady-state is attained after 9-10 days of consecutive dosing."
- Per FDA BA BE guidance, "*In some cases, conclusions of BE based on the peak drug concentration (Cmax) and area under the plasma concentration time curve (AUC) between the test product and the reference product may be insufficient to demonstrate that there is no difference in safety or efficacy if the systemic concentration time profiles of the test product and the reference product are different (e.g., time to reach peak drug concentration (Tmax) is different). For example, differences in the shape of the systemic concentration profile between the test and reference products could imply that the test product may not produce the same clinical response as the reference product. In such cases, additional data analysis (e.g., partial AUCs), exposure-response evaluation, or clinical studies may be recommended to evaluate the BE of the two products.*"
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf

- Per FDA BA BE Guidance, "*Measurement of the active ingredient or the active moiety, rather than metabolites, is generally recommended for BE studies because the concentration-time profile of the active ingredient or the active moiety is more sensitive to changes in formulation performance than that of the metabolite*".

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/s/

LI LI
12/04/2015

MYONG JIN KIM
12/04/2015

EDWARD D BASHAW
12/04/2015

Given the status of this as a supplement for a new formulation to a 505(b)(2) application-one that was approved without a direct pk link to the original Bendectin formulation, the finding of a lack of single dose BE between the two formulations should necessitate that the sponsor conduct the head to head clinical trial as discussed previously with the sponsor. I fully support the reviewers findings in this filing memo and agree that from a Clinical Pharmacology standpoint that this application should be "refused to file" for the reasons contained in this review.

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/s/

CHONGWOO YU
10/14/2016

EDWARD D BASHAW
10/14/2016