Clinical Pharmacology Review

NDA/eCTD #:	207,960/0000
Proposed Brand Name:	Quillichew ER
Generic Name:	Methylphenidate HCl
Dosage Form:	Extended-Release Chewable Tablet
Dosage Strength:	20 mg, 30 mg, 40 mg
Indication:	Attention Deficit Hyperactive Disorder (ADHD)
Sponsor:	Pfizer/NextWave Pharmaceuticals
Submission Type:	505(b)(2)
Submission Date:	February 4, 2015
OCP Reviewers:	Huixia Zhang, PhD; Hao Zhu, PhD

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1. EXECUTIVE SUMMARY

Methylphenidate (MPH) is a prescription stimulant commonly used to treat Attention Deficit Hyperactive Disorder (ADHD). MPH is currently available in the market as immediate release (IR) solution, IR tablet, IR chewable tablet, extended release (ER) tablet, ER capsule, ER suspension, and ER transdermal patch.

In this submission, Pfizer is seeking approval of Quillichew ER, methylphenidate (MPH) HCl Extended-Release Chewable Tablets (ERCT) for the treatment of ADHD in patients aged 6 years and older, via 505b (2) approach. The reference listed drug (RLD) for this application is the orally administered Methylin® (methylphenidate HCl) Immediate Release Chewable Tablet (Methylin IRCT, NDA 21,475), which was initially approved by demonstrating bioequivalence to Ritalin tablet (505(b)(2)) in 2003. In this review, Quillichew and MPH ERCT are used interchangeably.

MPH ERCT comprises of (b) (4) This formulation utilizes the same drug release mechanism as MPH ER powder for oral suspension (Quillivant XR®), which is a (b) (4) extended-release (b) (4) formulation (20% IR and 80% ER) of MPH HCl (NDA202,100, approved in 2011 and owned by the same sponsor of MPH ERCT now). MPH ERCT serves as an alternative formulation for patients with ADHD who are unable or unwilling to swallow tablets or capsules to allow for improved medication compliance.

The efficacy of MPH ERCT in ADHD children (6 to 12 years of age) was demonstrated in a double-blind, placebo-controlled laboratory classroom study (B7491005). The primary efficacy endpoint was the average of all post-dose SKAMP-Combined scores measured on the full laboratory classroom day. The onset of efficacy was determined to be 2 hours post-dose and efficacy was maintained through the 8 hour time point (refer to the medical review). Relative bioavailability of MPH ERCT compared to Methylin IRCT (RLD), and food effect was evaluated in healthy adults (B7491004). The sponsor also conducted two studies using pilot formulations (prototype 1 and prototype 2) to evaluate the relative bioavailability to Quillivant XR oral suspension and the effect of chewing.

OCP's major findings are summarized as follows:

1. An adequate link has been established between MPH ERCT and Methylin IRCT, the reference listed product, through a relative bioavailability study.
2. Different onset and duration of clinical responses are expected upon product switching from Methylin IRCT to MPH ERCT or from MPH ER powder for oral suspension (Quillivant XR®) to MPH ERCT.
3. ADHD indication in adolescents and adults can be extrapolated from the efficacy findings from children 6-12 years of age without additional controlled trials.
4. The pharmacokinetic profile of MPH ERCT is consistent with the expectation for an extended-release formulation and is sufficient to support a once daily dosing regimen. Following multiple-dosing of MPH ERCT, no significant accumulation is anticipated.
5. MPH ERCT can be taken chewed or swallowed as whole.

6. MPH ERCT may be given with or without food.
7. Patients should avoid alcohol while taking MPH ERCT.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of MPH ERCT. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreements with the sponsor
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	One positive registration trial in 6-12 years; efficacy bridged from all available information for >13 years.
Proposed dose for general patients	☒ Yes ☐ No ☐ NA	Sponsor proposed a starting dose of 20 mg; maximum dose of 60mg/day.
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with sponsor

1.2 Phase IV Commitments

Office of Clinical Pharmacology proposes the following post-marketing study.

PMC or PMR	Key Drug Development Question	Rationale	Design Summary (TBD)
☐ PMC ☒ PMR	What are the PK properties of Quillichew ER in male or female children (4 to less than 6 years of age) with ADHD?	Concentration time profile of methylphenidate determines the onset and duration of the clinical response. It is valuable to assess the PK profile in ADHD patients 4-5 years old and ensure it is similar to that in older patients. This information can be used to support the clinical efficacy and safety trial design.	Study population: ADHD patients 4-5 years old Study design: single dose/multiple dose, open label (b) (4) [redacted]

2. QUESTION BASED REVIEW

2.1 Specific Questions

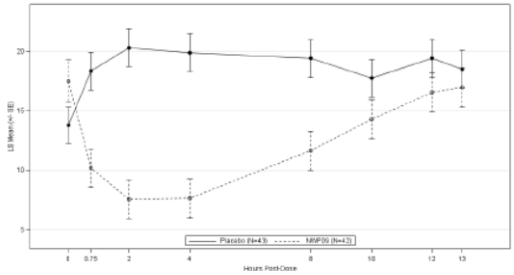
2.1.1 Are there evidence of effectiveness for Quillichew in pediatric patients aged 6-12 years?

Yes. The efficacy of Quillichew in pediatric patients with ADHD (6 to 12 years of age) was demonstrated in study B7491005.

Study B7491005 was a randomized, double-blind, placebo-controlled, cross-over, multicenter, laboratory classroom study. In the open-label dose optimization phase (6 weeks), the initial methylphenidate dose for all subjects was 20 mg once daily in the morning. The dose was titrated weekly in increments of 10 or 20 mg until an optimal dose or the maximum dose (60 mg/day) was reached. After 6 weeks of dose-optimization, subjects were randomized to receive either methylphenidate (with the optimal dose that was established in the open-label, optimization phase) or placebo for one week. Subjects were evaluated for ADHD symptoms and signs using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale in a laboratory classroom setting at multiple time points during an abbreviated laboratory classroom day.

The primary efficacy endpoint was the average of all post-dose SKAMP-Combined scores measured on the full laboratory classroom day, and this endpoint was met. The onset of efficacy was determined to be 2 hours post-dose, and efficacy was maintained through 8-hour time point.

Figure 1: SKAMP-combined scores over time (LS mean±SE) by treatment group



-source: B7491005 CSR Figure 14.2.1

2.1.2 Can Quillichew be approved without designated efficacy study in adolescents and adults?

Yes, Quillichew can be approved for adolescents and adults in the treatment of ADHD.

MPH has been shown to be safe and efficacious in children (6-12 years), adolescents (13-17 years), and adults in the concentration range that Quillichew targets. It is generally believed that a strong PK-effectiveness relationship exists for MPH. Thus, multiple MPH ER products are developed to generate specific time courses of pharmacodynamic effects through their unique shapes of pharmacokinetic profiles. For a specific product, it is essential to demonstrate that the unique shape of pharmacokinetic profile in patients across different age groups

(children, adolescents, and adults) is consistent, so that similar onset and duration of the treatment effect is expected in patients across different age groups.

For Quillichew, similar pharmacokinetic profiles in children, adolescents, and adults are expected, even though no direct comparison for the pharmacokinetic profiles can be performed. In the development program for Quillichew, pharmacokinetic data were only obtained in adults. No pharmacokinetic information was obtained in children or adolescents. However, Quillichew formulation (b) (4) . The absorption of (b) (4) is expected to be similar with Methylin IRCT in patients across different age groups. It is known Methylin IRCT is approved in pediatric patients and adults. Likewise, the (b) (4) in Quillichew is similar to the Quillivant XR®, a product now owned by Pfizer (the same sponsor for Quillichew), with the same release mechanism. Quillivant XR® was also approved in patients 6 years and above with similar pharmacokinetic profiles shown in children, adolescents, and adults. In combination with the findings from Methylin IRCT and Quillivant XR®, similar shapes of pharmacokinetic profiles in children, adolescents, and adults are expected for Quillichew.

It has been shown that Quillichew is efficacious between 2-8 hours postdose in patients 6-12 years of age in the pivotal efficacy and safety trial. In addition, similar pharmacokinetic profiles are expected in children, adolescents, and adults. Hence, the efficacy findings from children can be extended to adolescents and adults.

2.1.3 Can the same clinical response be expected when patients switch from Quillivant XR suspension to Quillichew of the same dose?

No. Different clinical response may be expected when patients switch from Quillivant XR suspension to Quillichew of the same dose with small difference in exposure profile and clinical efficacy difference based on label.

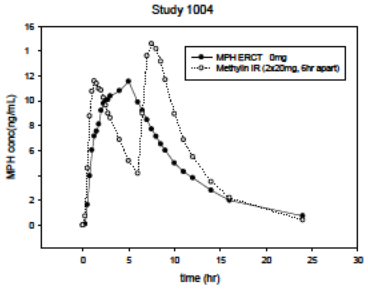
According to the label, Quillivant XR suspension showed efficacy at 0.75, 2, 4, 8, 10, and 12 hours post-dosing, while Quillichew only demonstrated efficacy at 2 hours post-dose and sustained effect through 8 hour but not 10, and 12 hours post-dose time points. So a later onset and shorter treatment duration is demonstrated for Quillichew.

2.1.4 Can Quillichew be directly switched from the Methyline IRCT with the same daily dose?

No. Patients currently using IRCT cannot be switched to the same total daily dose of Quillichew.

It is a general belief that clinical response is highly correlated with concentration time curves for MPH products. As shown in Figure 2, MPH demonstrated distinct concentration time curves after administration of MPH ERCT compared to administration of equivalent dose of MPH IRCT. Different clinical response is expected for the two products, and they cannot be switched interchangeably with the same daily dose.

Figure 2: Mean plasma methylphenidate concentration versus time by treatment after single dose under fasted conditions



2.1.5 Can Quillichew be taken chewed or swallowed as whole?

Yes. Quillichew can be taken chewed or swallowed as whole.

Results from a relative BA study showed that there is no significant difference in the PK of MPH when a ERCT prototype 1 tablet was chewed for 20 seconds before swallowing, or the tablet was swallowed as whole (Table 1). Cmax, AUC_{inf} and all relevant partial AUCs all met bioequivalence criteria after the tablet was given with or without chewing. Shape of PK profiles was also similar.

Table 1: Pharmacokinetic parameters (mean±sd) of methylphenidate after oral administration of 40 mg MPH ERCT chewed or swallowed as whole under fasting conditions

Parameters	TrtA (n=12)	TrtB (n=11)	Geomean ratio (%, TrtA/TrtB, 90% CI)
C_{max} (ng/mL)	12.4±3.4	11.9±2.1	1.06 (0.99, 1.13)
AUC_{inf} (hr*ng/mL)	102.6±29.9	107.1±27.4	1.00 (0.92, 1.08)
AUC_{0-3} (hr*ng/mL)	15.8±7.3	17.2±6.7	0.91 (0.92, 1.08)
AUC_{3-7} (hr*ng/mL)	40.7±12.2	38.7±8.6	1.09 (0.98, 1.20)
AUC_{7-12} (hr*ng/mL)	24.6±7.9	25.6±7.6	1.02 (0.89, 1.16)

Trt A: 40 mg MPH ERCT (chewed for 20 seconds) under fasting conditions
Trt B: 40 mg MPH ERCT (swallowed whole) under fasting conditions

It is noted that the formulation used in this relative BA study was the prototype 1 formulation, not the To-Be-Marketed (TBM) formulation. TBM formulation has (b) (4) (Table 2). Chewing is not anticipated to change the dissolution of the free drug. Theoretically, grinding force from chewing might (b) (4) increase drug release. The increase in drug release from th (b) (4) might change the PK profile. If this assumption is correct, the change in pharmacokinetic profile would be more apparent in a formulation with (b) (4) , such as the prototype 1 tablet, than in a formulation with (b) (4) such as the TBM formulation. In reality, no meaningful difference in PK profiles and major PK parameters in the comparison study with or without chewing was identified even using the prototype 1 tablet. Therefore, a meaningful change in PK profiles and major PK parameters is unlikely after the TBM product is administered with or without chewing.

In addition, the grinding force on drug release was further assessed through an in vitro dissolution study. The dissolution profiles are found to be similar independent of the grinding force (please refer to ONDP review), which further supports that chewing will unlikely change the PK profile in a meaningful way as compared to swallowing for the TBM formulation.

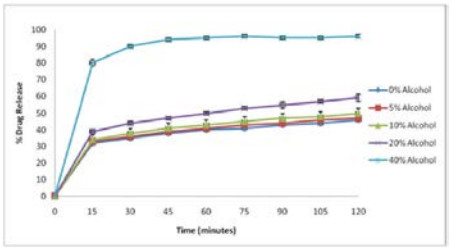
Table 2: Formulation comparison between Prototype 1 and TBM formulation of Quillichew

Composition	Prototype 1	TBM Formulation
	(b) (4)	

2.1.6 Can MPH ERCT be given with alcohol?

No. Based on in vitro studies, about 90% of the drug was released at 30 min time point in 40% alcohol (Figure 4) (For detailed review of the in vitro assays, please refer to ONDP review). Also, alcohol is known to impair CNS function, which might lead to pharmacodynamic interaction with MPH. Therefore, patients should be advised to avoid alcohol.

Figure 4: Dissolution profiles of 40 mg MPH ERCT in 0.1N HCl with different percentage of alcohol



-Source: \\CDSESUB1\EVSPROD\MF025909 Module 3.2.P.2 Pharmaceutical Development/Dissolution Method Development Report

2.2 Standard Questions

2.2.1 What's the relative bioavailability of MPH ERCT?

Pharmacokinetic parameters and profiles of MPH after administration of 40 mg MPH ERCT or Methylin IRCT (2x20mg, 6hr apart) are compared in Table 3 and Figure 2, respectively. Overall, MPH ERCT had about 11% lower AUC_{inf} of MPH compared to administration of equivalent dose of MPH IRCT. Comparison of partial AUCs indicated that at the earlier (0-3 hr) and late phases (7-12 hr) of the curves, MPH ERCT had 25-46% lower exposure compared to Methylin IRCT (Table 3).

Table 3: Comparison of Partial AUCs (mean±sd) of MPH after administration of 40 mg MPH ERCT or Methylin IR chewable tablet (20mg*2, 6hr apart)

Parameters	Treatment A (n=31)	Treatment C (n=29)	Geomean ratio (trtA/trtC, 90% CI)
T_{max} (hr)*	5 (2.5, 6.5)	7.5(0.75, 8.75)	-
AUC_{0-3} (hr*ng/mL)	19.7±8.5	25.7±8.1	0.75 (0.70, 0.80)
AUC_{3-7} (hr*ng/mL)	41.6±11.0	27.5±8.3	1.52 (1.46, 1.58)
AUC_{7-12} (hr*ng/mL)	28.5±9.2	51.7±13.7	0.54 (0.51, 0.57)
AUC_{inf} (hr*ng/mL)	118.1±36.1	132.3±39.8	0.89 (0.87, 0.91)
$T_{1/2}$(hr)	5.1 ± 0.8	3.3 ±0.7	-

Treatment A: Methylphenidate ERCT - Fasting
Treatment C: Methylin IRCT – Fasting
**Median (range)*

The link between MPH ERCT and Methylin IRCT, the reference listed product, has been adequately established through a relative bioavailability study under fasted conditions. As shown in Figure 2, the mean pharmacokinetic profile of MPH ERCT is consistent with the expectations for an extended release formulation and is sufficient to support a once daily dosing.

Because of its half-life (~5 hr) and once daily dosing regimen, the first dose is almost completely eliminated from the body by the end of 24-hr period, and no significant accumulation of methylphenidate is expected.

2.2.2 Does food affect the bioavailability of MPH ERCT?

High-fat meal increased systemic exposure (AUC_{inf}) of MPH ERCT by ~ 20%, and C_{max} by ~ 4%. The magnitude of increase in exposure is not expected to have a large effect on the efficacy or safety of the product.

Table 4: Pharmacokinetic parameters (mean±sd) of MPH after oral administration of 40 mg MPH ERCT under fed or fasting conditions

Parameters	Treatment B (n=31)	Treatment A (n=31)	Geomean ratio (90% CI)
C_{max} (ng/mL)	13.0±3.7	12.5 ±3.7	1.04 (0.99, 1.09)
T_{max} (hr)*	5 (2.5, 6.5)	5 (2, 5.92)	-
AUC_{0-4} (hr*ng/mL)	30.5±11.6	30.3±11.6	1.01 (0.90, 1.11)
AUC_{4-8} (hr*ng/mL)	42.7±10.2	38.8±10.4	1.11 (1.06, 1.15)
AUC_{8-12} (hr*ng/mL)	27.3±7.4	20.8±6.9	1.34 (1.25, 1.42)
AUC_{inf} (hr*ng/mL)	143.9±41.2	118.1±36.1	1.21 (1.17, 1.26)
$T_{1/2}$ (hr)	5.2 ± 0.8	5.1 ± 0.8	-

Treatment A: 40 mg MPH ERCT- Fasting
Treatment B: 40 mg MPH ERCT – Fed
**Median (range)*

SIGNATURES

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3. INDIVIDUAL STUDY REVIEW

3.1 Relative Bioavailability (1) and Food Effect Study

Report # B7491004 **Study Period:** 6/27/2012-7/12/2012
Title: A Three-Way Crossover Relative Bioavailability Study Comparing Methylphenidate HCl Extended-Release Chewable Tablets and METHYLIN Chewable Tablets under Fasting Conditions and Determining the Effect of Food on 40 mg Methylphenidate ER Chewable Tablets.

- **Objective:** To evaluate the relative bioavailability in healthy subjects between: 1) methylphenidate HCl extended release 40 mg chewable tablets (MPH ERCT) from Tris Pharma, Inc., USA and Methylin™ 10 mg immediate release chewable tablets (Methylin IRCT) from Mallinckrodt administered under fasting conditions, and 2) MPH ERCT 40 mg from Tris Pharma administered under fasting and fed conditions.
- **Study Design:** This was an open-label, single- and multi-dose, randomized, 3-period, 3-sequence, 3-treatment, crossover study, designed to evaluate the relative bioavailability of MPH ERCT, administered to healthy male and female subjects under fasting conditions as compared to Methylin IRCT. This study also assessed the impact of food on the bioavailability of MPH ERCT. The following treatments were administered to subject in accordance to a randomization scheme:
  • Treatment A: MPH ERCT 1x40 mg/tablet administered under fasting conditions
  • Treatment B: MPH ERCT 1x40 mg administered under fed conditions
  • Treatment C: Methylin IRCT (2 x 10 mg/tablet), 6 hours apart (total dose 40 mg), first dose administered under fasting conditions.
- **Blood Sampling Times (PK):** Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, 16 and 24 hours post dose.
- **Analytical Method:**

Analyte	**Total/Racemic Methylphenidate**
Method	LC-MS/MS
Matrix	plasma
Range (ng/mL)	0.40 to 40.0
Performance	acceptable

- **Results:**

Formulations

Table 1. Products used in B7491004

	Manufacturer	**Formulation**	**Lot #**	**Expiration Date**
Methylphenidate HCl 40 mg	Tris Pharma, Inc.	Extended Release chewable tablets	TB-103A	04/2014
Methylin™ 10 mg	Mallinckrodt Inc.	Immediate-Release chewable tablets	0762T80399	05/2013

Study Population

	All subjects
Treated/Completed/Withdrawn Due To AE/Other Reasons	33/31/1/1
Age (mean±SD)	32±10
Male/Female	15/16
BMI (mean±SD)	25±2.6
Race (Caucasian/Black/Asian/Hispanic)	9/11/1/10

Pharmacokinetics

Table 1: Mean (SD) Methylphenidate Pharmacokinetic Parameters

Based on Measured Plasma Methylphenidate Concentrations

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
C_{max} (ng/mL)	A	31	12.513 (29)	12.081	B vs A	104.05	99.38 - 108.94	11
	B	31	12.998 (29)	12.571	A vs C	80.00	76.30 - 83.87	11
	C	29	15.572 (27)	15.102				
AUC_t (ng.h/mL)	A	31	111.782 (31)	107.493	B vs A	120.61	117.02 - 124.31	7
	B	31	133.437 (27)	129.651	A vs C	87.64	84.96 - 90.41	7
	C	29	127.646 (31)	122.653				
AUC_{inf} (ng.h/mL)	A	31	118.122 (30)	113.642	B vs A	121.40	118.04 - 124.86	7
	B	31	142.590 (29)	137.963	A vs C	89.11	86.57 - 91.73	7
	C	29	132.388 (30)	127.525				
T_{max} (h)	A	31	4.16 (28)					
	B	31	4.27 (27)					
	C	29	6.43 (40)					
k_{el} (1/h)	A	31	0.1366 (18)					
	B	31	0.1349 (13)					
	C	29	0.2141 (21)					
T_{half} (h)	A	31	5.21 (15)					
	B	31	5.24 (15)					
	C	29	3.38 (21)					
			Median	Range				
T_{max} (h)	A	31	5.00	2.00- 5.92				
	B	31	5.00	2.50- 6.50				
	C	29	7.50	0.75- 8.57				

Treatment A: Methylphenidate HCl Extended Release 40 mg chewable tablets - Fasting
Treatment B: Methylphenidate HCl Extended Release 40 mg chewable tablets - Fed
Treatment C: Methylin™ 10 mg chewable tablets (immediate release)- Fasting
-Source: -Table 11.4.7-1 of CSR

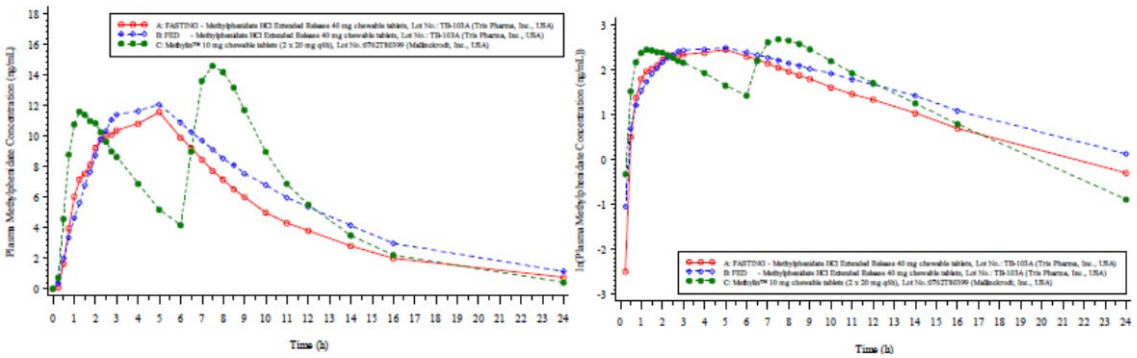
Table 2: Methylphenidate Partial AUC Analysis

Based on Measured Plasma Methylphenidate Concentrations

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
$AUC_{0-0.5}$ (ng.h/mL)	A	31	0.227 (104)	0.163	B vs A	150.28	110.60 - 204.21	76
	B	31	0.337 (100)	0.245	A vs C	30.70	22.53 - 41.83	76
	C	29	0.753 (96)	0.532				
AUC_{0-2} (ng.h/mL)	A	31	9.786 (51)	8.797	B vs A	88.81	77.81 - 101.38	32
	B	31	8.692 (49)	7.813	A vs C	57.93	50.55 - 66.38	32
	C	29	16.054 (36)	15.186				
AUC_{0-3} (ng.h/mL)	A	31	19.741 (43)	18.339	B vs A	96.22	87.36 - 105.99	23
	B	31	19.013 (43)	17.646	A vs C	74.66	67.58 - 82.47	23
	C	29	25.712 (32)	24.565				
AUC_{0-4} (ng.h/mL)	A	31	30.307 (38)	28.566	B vs A	100.86	93.13 - 109.24	19
	B	31	30.521 (38)	28.812	A vs C	89.00	81.98 - 96.61	19
	C	29	33.465 (30)	32.098				

Treatment A: Methylphenidate HCl Extended Release 40 mg chewable tablets - Fasting
Treatment B: Methylphenidate HCl Extended Release 40 mg chewable tablets - Fed
Treatment C: Methylin™ 10 mg chewable tablets (immediate release)- Fasting
-Source: Table 11.4.7-2 of CSR

Figure 1: Mean Plasma Methylphenidate Concentration vs. Time Profiles: normal concentration (left panel); ln(concentration) (right panel)



-Source: Figure 11.4.7-1 and Figure 11.4.7-2 of CSR

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusions:**
  1) MPH ERCT and Methylin IRCT had different shapes of the concentration-time curves. Compared with Methylin IRCT given twice (6hr apart), C_{max} of MPH ERCT of equivalent dose was 20% lower and did not meet the BE criteria; AUC_{inf} was about 10% lower, but met the BE criteria.
  2) Food has no clinically meaningful effect on the PK of MPH ERCT. MPH ERCT can be administered regardless of food.
- **Reviewer's Comments:** MPH ERCT and Methylin IRCT had different shapes of the concentration-time curves. Owing to the strong relationship of concentration levels and PD effect for MPH products, conventional BE metrics are not appropriate to assess the bioequivalence between formulations. Partial AUC analysis is needed to detect PK difference between formulations and/or treatments. Compared to equivalent dose (i.e., 40mg) of Methylyin IRCT (20mg given 6hrs apart), MPH AUC0-3, AUC3-7, and AUC7-12 was 25% lower, 52% higher, and 46% lower, respectively, after MPH ERCT was administered (Table 3). MPH concentration-time curves are significantly different between the two formulations, and they are not bioequivalent. However, the approval decision will be based on the results of the efficacy and safety trial for MPH ERCT.

Table 3: PK parameters (mean±SD) of MPH after administration of 40 mg MPH ERCT or Methylin IR chewable tablet (20mg*2, 6hr apart)

Parameters	Treatment A (n=31)	Treatment C (n=29)	Geomean ratio (trtA/trtC, 90% CI)
AUC0-3 (hr*ng/mL)	19.7±8.5	25.7±8.1	0.75 (0.70, 0.80)
AUC3-7 (hr*ng/mL)	41.6±11.0	27.5±8.3	1.52 (1.46, 1.58)
AUC7-12 (hr*ng/mL)	28.5±9.2	51.7±13.7	0.54 (0.51, 0.57)
AUCinf (hr*ng/mL)	118.1±36.1	132.3±39.8	0.89 (0.87, 0.91)

Treatment A: MPH ERCT - Fasting
Treatment C: Methylin™ IRCT - Fasting

Figure 2: Distribution of MPH PK Parameter Ratios Between Treatments

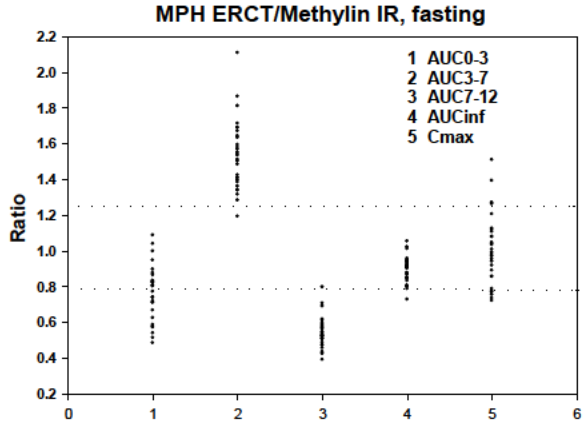
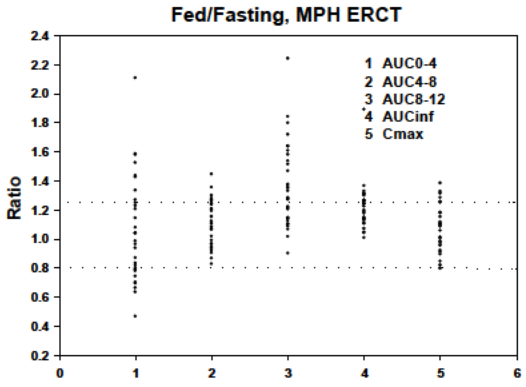


Table 4: PK parameters (mean±SD) of MPH

Parameters	Treatment B (n=31)	Treatment A (n=31)	Geomean ratio (90% CI)
Cmax (ng/mL)	13.0±3.7	12.5 ±3.7	1.04 (0.99, 1.09)
AUC0-4 (hr*ng/mL)	30.5±11.6	30.3±11.6	1.01 (0.90, 1.11)
AUC4-8 (hr*ng/mL)	42.7±10.2	38.8±10.4	1.11 (1.06, 1.15)
AUC8-12 (hr*ng/mL)	27.3±7.4	20.8±6.9	1.34 (1.25, 1.42)
AUCinf (hr*ng/mL)	143.9±41.2	118.1±36.1	1.21 (1.17, 1.26)

Treatment A: 40 mg MPH ERCT- Fasting
Treatment B: 40 mg MPH ERCT - Fed

Figure 3: Distribution of MPH PK Parameter Ratios Between Treatments



Overall Comments:

1) An adequate link between MPH ERCT and Methylin ® has been established through the relative bioavailability study.
2) The mean PK profile of MPH ERCT is consistent with the expectations for an extended-release formulation and is sufficient to support a once-daily dosing.

3) MPH is an established therapeutic agent for the treatment of ADHD, and it has been shown to be effective in the dose range of 18 mg to 72 mg from other formulations. So the selected doses in the registration trial (ie., 20 mg to 60 mg) are reasonable.
4) Food has no clinical meaningful effect on the exposure of MPH after MPH ERCT administration. MPH ERCT can be taken without regards to food.

3.2 Relative Bioavailability (2)-Chewed vs Swallowed Whole

Report # B7491002 **Study Period:** 2/12/2011-3/8/2011
Title: A Three-Way Crossover Pilot Relative Bioavailability Study Comparing Methylphenidate 40 mg ER Chewable Tablets (Chewed And Swallowed Whole) Versus 25mg/5mL ER Suspension Under Fasted Conditions

- **Objective:** To assess the relative bioavailability of 40 mg ER chewable methylphenidate tablets administered chewed or swallowed whole compared to that of 40 mg MPH ER powder for oral suspension in healthy adult subjects when administered under fasted conditions.
- **Study Design:** This was an open-label, single-dose, randomized, three-period, three-treatment crossover study conducted under fasted conditions. A 7-day washout period was observed between the doses:
  • Treatment A: 1 x 40 mg ERCT (chewed for 20 seconds) under fasting conditions
  • Treatment B: 1 x 40 mg ERCT (swallowed whole) under fasting conditions
  • Treatment C: 1 x 40 mg ER suspension followed by 240 mL water under fasting conditions
- **Blood Sampling Times (PK):** Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours after drug administration.
- **Analytical Method:**

Analyte	Racemic/total methylphenidate
Method	LC-MS/MS
Matrix	plasma
Range (ng/mL)	0.1 to 40
Performance	acceptable

- **Results:**
  Formulations Products used in B7491002

Tested Product	**Manufacturer**	**Formulation**	**Batch #**
Methylphenidate HCl 40 mg	Tris Pharma	Prototype I Extended Release chewable tablets	RD0323-037C
Methylphenidate HCl 25mg/5mL ER oral suspension	Tris Pharma	Extended Release oral suspension	RD0323-178S

Study Population

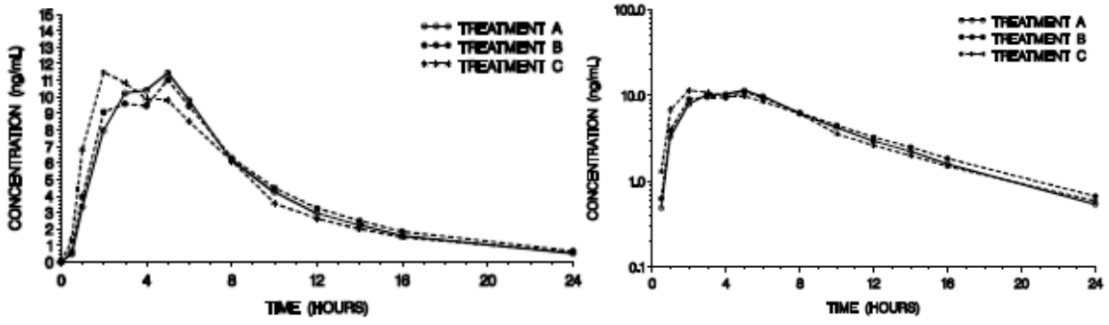
	All subjects
Treated/Completed/Withdrawn Due To AE/Other Reasons	12/9/0/3
Age (mean±SD)	43±11
Male/Female	5/7
BMI (mean±SD)	26.4±2.6
Race (Caucasian/Black/Asian/Hispanic)	11/1/0/0

Pharmacokinetics

Table 1: Mean (SD) Methylphenidate Pharmacokinetic Parameters: Treatment A (Tablet Chewed) vs Treatment B (Tablet Swallowed Whole), Untransformed Data

Parameter	Least Square Means		Ratio of Means A/B (%)	90% Confidence Interval Lower – Upper (%)	Intra-subject Variability (%)*
	Treatment A	Treatment B			
AUC_{0-t} (ng·h/mL)	98.7087	98.8393	99.87	89.57 – 110.16	13.9
AUC_{0-4} (ng·h/mL)	26.1167	26.1180	99.99	90.97 – 109.02	11.3
AUC_{0-inf} (ng·h/mL)	102.6258	104.1147	98.57	89.08 – 108.06	12.8
C_{max} (ng/mL)	12.4146	11.6964	106.14	95.06 – 117.22	14.4
T_{max} (h)	4.00	4.25	94.07	71.55 – 116.59	32.9
Kel (h^{-1})	0.1431	0.1381	103.64	89.49 – 117.79	20.0
$T_{1/2}$ (h)	4.94	5.31	93.16	79.68 – 106.64	18.3

Figure 1: Mean methylphenidate plasma concentrations for Treatment A (tablet chewed), Treatment B (tablet swallowed whole) and Treatment C (suspension).



-*source: Figure 14-1 of Study Report*

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusion:** There was no significant difference in MPH PK when MPH ERCT was chewed or swallowed as a whole. Methylphenidate ERCT can be taken either way.
- **Reviewers Comments:**

  1) There was also a third treatment group (treatment C) in this study, in which

methylphenidate ER suspension was administered to the enrolled subjects. Since no labeling was claimed toward comparison between methylphenidate ER and Quillivant ER suspension, this part of the study results was not reviewed.

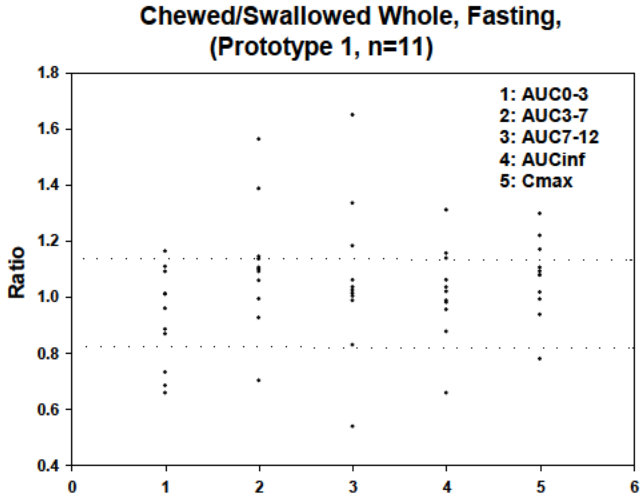
2) Partial AUC analysis was performed to detect PK difference between the two treatments. Our analysis also supported the conclusion that chewing the tablet does not affect the exposure of MPH. MPH ERCT can be administered either way.

Table 2: Partial AUC comparison between treatments

Parameters	TrtA (chewed for 20 seconds, n=12)	TrtB (swallowed whole, n=11)	Geomean ratio (%, trtA/trtB, 90% CI)
Cmax (ng/mL)	12.4±3.4	11.9±2.1	1.06 (0.99, 1.13)
AUCinf (hr*ng/mL)	102.6±29.9	107.1±27.4	1.00 (0.92, 1.08)
AUC0-3 (hr*ng/mL)	15.8±7.3	17.2±6.7	0.91 (0.92, 1.08)
AUC3-7 (hr*ng/mL)	40.7±12.2	38.7±8.6	1.09 (0.98, 1.20)
AUC7-12 (hr*ng/mL)	24.6±7.9	25.6±7.6	1.02 (0.89, 1.16)

Trt A: 40 mg MPH ERCT (chewed for 20 seconds) under fasting conditions
Trt B: 40 mg MPH ERCT (swallowed whole) under fasting conditions

Figure 2: Distribution of MPH PK Parameter Ratios Between Treatments



3) The formulation used in this study was prototype 1. The difference between prototype and commercial formulation was listed in the Table below.

Composition	Prototype 1	Commercial Formulation
	(b) (4)	

Our partial AUC analysis indicated exposure to MPH is bioequivalent when tablet was chewed or swallowed as whole. However, since the formulation used in the study was prototype 1, a bridging in dissolution needs to be established between the two formulations to extrapolate the conclusion obtained from prototype 1 to the commercial formulation. For details in dissolution please refer to ONDQA review. Final conclusion will be based on the totality of the information (See QBR 2.1.5).

3.3 Relative Bioavailability (3)-MPH ERCT vs Quillivant XR suspension

Report # B7491003 **Study Period:** 7/17/2011-8/2/2011
Title: A Relative Bioavailability Study of Two Formulations of Methylphenidate 40 mg ER Chewable Tablets Versus Methylphenidate 25 mg/5 mL ER Oral Suspension Under Fasted Conditions

- **Objective:** To assess the relative bioavailability of two 40 mg formulations of Methylphenidate HCl ER Chewable Tablet (ERCT) compared to 40 mg of Methylphenidate HCl ER Oral Suspension (25 mg/5 mL) following a single oral dose in healthy adult subjects when administered under fasted conditions.
- **Study Design:** This was an open-label, single-dose, randomized, three-period, three-treatment crossover study conducted under fasted conditions. A 7-day washout period was observed between the doses:
  • Treatment A: 1 x 40 mg ERCT (prototype 1; chewed for 20 seconds) followed by 240 mL under fasting conditions
  • Treatment B: 1 x 40 mg ERCT (prototype 2; chewed for 20 seconds) followed by 240 mL under fasting conditions
  • Treatment C: 8 mL x 25 mg/5 mL of Quillivant XR Suspension (40 mg) followed by 240 mL water under fasting conditions
- **Blood Sampling Times (PK):** Predose, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours after drug administration.

- **Analytical Method:**

Analyte	Racemic/total methylphenidate
Method	LC-MS/MS
Matrix	plasma
Range (ng/mL)	0.1 to 40.0
Performance	acceptable

- **Results:**

Products used in Study

Tested Product	**Manufacturer**	**Formulation**	**Lot #**
Methylphenidate HCl 40 mg	Tris Pharma	Prototype I Extended Release chewable tablets	RD0323-186
Methylphenidate HCl 40 mg	Tris Pharma	Prototype II Extended Release chewable tablets	RD0323-190
Methylphenidate HCl 25mg/5mL ER oral suspension	Tris Pharma	Extended Release oral suspension	RD0323-178S

Study Population

	All subjects
Treated/Completed/Withdrawn Due To AE/Other Reasons	15/12/1/2
Age (mean±SD)	37.5±12.2
Male/Female	7/8
BMI (mean±SD)	26.6±3.8
Race (Caucasian/Black/American Indian or Alaskan Native)	6/8/1

Pharmacokinetics

Table 1: Methylphenidate pharmacokinetic parameters following single oral doses

	Summary Statistics of PK Parameters[a] by Treatment (Geometric mean, CV%)		
Parameter, unit	**Treatment A**	**Treatment B**	**Treatment C**
N[b]	12	12	12
C_{max} (ng/mL)	15.56 (17.4)	16.87 (21.1)	15.67 (21.3)
AUC_{0-t} (ng.h/mL)	130.44 (22.5)	135.19 (26.4)	126.10 (25.2)
AUC_{0-inf} (ng.h/mL)	136.40 (23.3)	142.51 (26.6)	132.13 (25.7)
AUC_{0-4} (ng.h/mL)	30.79 (29.5)	34.37 (26.7)	37.95 (24.1)
AUC_{0-Tmax} (ng.h/mL)	29.17 (44.6)	36.05 (37.7)	32.49 (49.6)
$AUC_{Tmax-Last}$ (ng.h/mL)	99.38 (20.8)	97.12 (29.4)	90.50 (27.7)
T_{max} (h)[a]	4.00 (2.5- 6.0)	4.00 (2.0- 6.0)	4.25 (2.0- 6.0)
$t_{½}$ (h)[a]	4.66 (13.5)	5.25 (26.3)	5.17 (19.4)

Treatment A Prototype 1 Methylphenidate HCl ERCT (chewed);
Treatment B Prototype 2 Methylphenidate HCl ERCT (chewed);
Treatment C Reference Product Methylphenidate HCl ER powder for oral suspension
Source CSR s11-0154-abbr-sap

Table 2: Statistical Summary of Treatment Comparisons of Treatment A vs Treatment C and Treatment B vs Treatment C

	Test	Reference	Ratio (test/reference) of Geometric mean	90% CI for Ratio
Treatment A (test) vs Treatment C (reference)				
C_{max} (ng/mL)	15.56	15.67	99.28	91.94-107.21
AUC_{0-t} (ng.h/mL)	130.44	126.10	103.44	98.38-108.77
AUC_{0-inf} (ng.h/mL)	136.41	132.14	103.23	98.38-108.33
AUC_{0-4} (ng.h/mL)	30.79	37.95	81.15	68.68-95.89
AUC_{0-Tmax} (ng.h/mL)	29.17	32.49	89.77	72.36-111.38
$AUC_{Tmax-Last}$ (ng.h/mL)	99.38	90.51	109.81	99.21-121.53
Treatment B (test) vs Treatment C (reference)				
C_{max} (ng/mL)	16.87	15.67	107.63	98.15-118.03
AUC_{0-t} (ng.h/mL)	135.19	126.10	107.21	99.49-115.53
AUC_{0-inf} (ng.h/mL)	142.51	132.14	107.85	99.58-116.82
AUC_{0-4} (ng.h/mL)	34.37	37.95	90.58	78.50-104.51
AUC_{0-Tmax} (ng.h/mL)	36.05	32.49	110.97	85.68-143.74
$AUC_{Tmax-Last}$ (ng.h/mL)	97.12	90.51	107.30	90.71-126.93

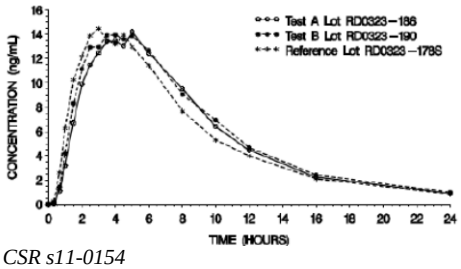
Treatment A Prototype 1 Methylphenidate HCl ERCT (chewed);
Treatment B Prototype 2 Methylphenidate HCl ERCT (chewed);
Treatment C Reference Product Methylphenidate HCl ER powder for oral suspension
- *Source CSR s11-0154-abbr-sap appendix 16.1.9.6.3*

Table 3: Statistical Summary of Treatment Comparisons of Treatment A vs Treatment B

	Test (Treatment A)	Reference (Treatment B – reference for statistical comparison)	Ratio (test/reference) of Geometric mean	90% CI for Ratio
C_{max} (ng/mL)	15.56	16.87	92.24	85.50-99.16
AUC_{0-t} (ng.h/mL)	130.44	135.19	96.49	88.65-105.02
AUC_{0-inf} (ng.h/mL)	136.41	142.51	95.71	87.30-104.94
AUC_{0-4} (ng.h/mL)	30.79	34.37	89.59	76.73-104.61
AUC_{0-Tmax} (ng.h/mL)	29.17	36.05	80.90	67.41-97.08
$AUC_{Tmax-Last}$ (ng.h/mL)	99.38	97.12	102.34	89.84-116.57

Treatment A Prototype 1 Methylphenidate HCl ERCT (chewed);
Treatment B Prototype 2 Methylphenidate HCl ERCT (chewed);
- *Source CSR s11-0154-abbr-sap appendix 16.1.9.6.3*

Figure 1: Mean methylphenidate plasma concentrations for Treatment A (prototype 1 chewed), Treatment B (prototype 2 chewed) and Treatment C (suspension).



-source CSR s11-0154

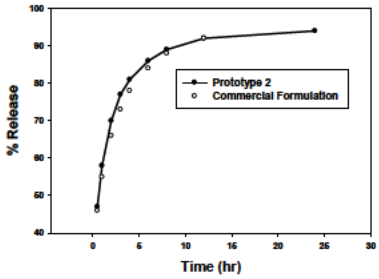
- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Conclusions:** Both prototype 1 and prototype 2 formulations met the traditional BE criteria compared to Quillivant ER suspension for C_{max} and AUC_{inf}. However, partial AUC analysis indicated prototype 1 had about 19% lower exposure in the early phase (AUC_{0-4}) with 90% CI of 68.7-95.9. For prototype 2, AUC_{0-4} was about 10% lower compared to reference, with 90% CI of 78.5-104.5.
- **Reviewers Comments:**

The formulation used in this study was prototype 2. The difference between prototype and

commercial formulation was listed in the Table below.

Composition	Prototype 2	Commercial Formulation
	(b) (4)	

In vitro dissolution profiles indicated that the drug release profiles are very similar for the two formulations (Figure below).



Based on the similarity of the in vitro dissolution profiles between the formulations, it is reasonable to speculate that exposure to MPH could be similar between commercial formulation and Quillivant ER suspension after same dose administration.

4. NDA FILING FORM

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	207960	**SDN**	000	Relative IND	111020
Applicant	Pfizer		**Submission Date**		2/4/2015
Generic Name	Methylphenidate HCl		**Brand Name**		Quillivant Chewable XR
Drug Class	Central Nervous System (CNS) stimulant				
Indication	Attention Deficit Hyperactivity Disorder (ADHD)				
Dosage Regimen	Once daily				
Dosage Form	Extended-Release Chewable Tablets (ERCT)		**Route of Administration**		PO
OCP Division	DCP1		**OND Division**		OND1
OCP Review Team	**Primary Reviewer(s)**			**Secondary Reviewer/ Team Leader**	
Division	Huixia Zhang			Hao Zhu	
Pharmacometrics					
Genomics					
Review Classification	☑ Standard ☐ Priority ☐ Expedited				
Filing Date	4/4/2015		**74-Day Letter Date**		4/19/2015
Review Due Date	11/4/2015		**PDUFA Goal Date**		12/4/2015

Application Background

Pfizer is seeking approval of methylphenidate (MPH) HCl Extended-Release Chewable Tablets (ERCT) for the treatment of ADHD in patients aged 6 years and older, via 505b(2) approach. The reference listed drug for this application is the orally administered METHYLIN® (methylphenidate HCl) 10 mg Chewable Tablets (NDA 21475).

In this submission, one pivotal relative BA /food effect study (Study B7491004) in healthy adult volunteers, and a Phase 3 laboratory classroom study (Study B7491005) to evaluate efficacy/safety in pediatric ADHD patients (6 to 12 years old) were conducted to support the development and registration of MPH ERCT. In addition, two pilot studies were also conducted. Study B7491002 evaluated the relative BA comparing MPH ERCT tablet formulation (Prototype 1, administered chewed and swallowed whole) versus Quillivant XR oral suspension. Study B7491003 evaluated the relative BA between two formulations of MPH ERCT.

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
If yes list comment(s)

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

☐ Yes
☑ No
If yes explain

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			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		2	Pilot studies
☑ Bioequivalence		1	
☑ Food Effect		1	Bioequivalence and food effect was conducted in one study.
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ 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**	3
Total Number of Studies to be Reviewed				3

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	☑Yes ☐No ☐N/A	

reference product for a 505(b)(2) application?		
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	Individual concentration data are included in the study report. Will request sponsor to send data in in .xpt format.
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	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested	☑Yes ☐No	

during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐N/A	
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		
This is optional, discuss with your TL content and format		

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

/s/

HUIXIA ZHANG
10/27/2015

HAO ZHU
10/27/2015

RAMANA S UPPOOR
10/27/2015