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APPLICATION NUMBER:

22-306

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

Original NDA: 22-306

Submission Dates: 7/25, 8/19, and 9/5/2008

Brand Name: So-Aqueous™

Generic Name: Sotalol Hydrochloride

Dosage Form & Strength: Injection, 15 mg/mL

Indication: Substitution for Oral Sotalol Therapy,
Maintenance of Normal Sinus Rhythm,
Documented Life-Threatening Ventricular
Arrhythmia

Applicant: The Academic Pharmaceuticals.

Submission: Original NDA, Orphan Designation

Clinical Division: Cardiovascular-Renal Products, HFD-110

OCP Divisions: Clinical Pharmacology 1 and Pharmacometrics

Primary Reviewer: Elena V. Mishina, Ph.D.

Team Leader (Acting): Angelica Dorantes, Ph.D.

Pharmacometrics Reviewer: Christoffer Tornoe, Ph.D.

Pharmacometrics Team Leader: Pravin Jadhav, Ph.D.

Amendment to the Original Review Dated 4/20/09

Background

The Recommendation from the original Clinical Pharmacology review dated April 20, 2009, for NDA 22-306 for So-Aqueous included the following comment;

“The sponsor should evaluate in vitro the possible binding of sotalol to the _____ tubing.”

b(4)

However, please note that the same information was previously requested by Dr. Thomas M. Wong (reviewer chemist). On January 15, 2009, the sponsor provided the requested information addressing this issue. Dr. Wong’s reviewed this information and his review dated February 27, 2009, p. 23 states that there is no sotalol loss due to _____ binding.

b(4)

Recommendation

Based on the information provided by Dr. Wong in his chemistry review, OCP’s concern regarding the possible binding of sotalol to the _____ tubing has been already addressed by the sponsor. Therefore, there is not longer need to convey the above comment to the sponsor.

b(4)

Elena Mishina, Ph. D.
Senior Clinical Pharmacologist

Date _____

Angelica Dorantes, Ph. D.
Cardio-Renal Acting Team Leader

cc list: NDA 22-306, HFD 110 (FortneyR, KarkowskyA), HFD-860 (MehulM, DorantesA, UppoorR).

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this page is the manifestation of the electronic signature.**

/s/

Elena Mishina
5/14/2009 02:23:20 PM
BIOPHARMACEUTICS
Angelica, I added the page in the review which
describes the binding. Otherwise, it is fine.

Angelica Dorantes
5/14/2009 06:12:21 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

Original NDA: 22-306

Submission Dates: 7/25, 8/19, and 9/5/2008

Brand Name: So-Aqueous™

Generic Name: Sotalol Hydrochloride

Dosage Form & Strength: Injection, 15 mg/mL

Indication: Substitution for Oral Sotalol Therapy,
Maintenance of Normal Sinus Rhythm,
Documented Life-Threatening Ventricular Arrhythmia

Applicant: The Academic Pharmaceuticals.

Submission: Original NDA, Orphan Designation

Clinical Division: Cardiovascular-Renal Products, HFD-110

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Primary Reviewer: Elena V. Mishina, Ph.D.

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Pharmacometrics Reviewer: Christoffer Tornoe, Ph.D.

Pharmacometrics Team Leader: Pravin Jadhav, Ph.D.

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1 EXECUTIVE SUMMARY

The Academic Pharmaceuticals is seeking the approval of Original NDA 22-306 for So-AqueousTM (sotalol hydrochloride, solution for intravenous infusion) for those patients who are unable to take oral sotalol therapy due to surgery, intubation, acute illness, etc. Sotalol hydrochloride is currently approved under NDA 22-151 in oral formulations (Betapace AF) for the treatment of life threatening ventricular arrhythmias and for the maintenance of sinus rhythm in patients with a history of symptomatic atrial fibrillation.

So-AqueousTM is intended to be marketed as a solution for IV infusion and it is proposed to be administered as an infusion of 75 mg of sotalol over — hours. **b(4)**

The clinical pharmacology program for NDA 22-306 includes one pharmacokinetic study (Study No. 12103) which evaluates the bioequivalence between the orally and intravenously administered sotalol, and also includes the simulations performed by the sponsor.

The sotalol IV dose of 75 mg infused over 2.5 hr was not bioequivalent to the 80 mg oral dose. The exposure for the IV dose was lower when it was compared to the oral dose. The sponsor claims that the lack of bioequivalence was due to a protocol violation because the IV tubing was not flushed and the volume of the drug administered was less than intended. However, there is no information available to verify the exact dose of sotalol that was administered during the infusion. Also, the possible *in vitro* binding of sotalol to the — tubing was not evaluated. **b(4)**

The reviewer's population PK analysis confirmed that less than the intended 75 mg IV dose was administered in study 12103. However, it was not possible to estimate the exact IV dose that was administered in the BE study.

1.1 RECOMMENDATION:

The Office of Clinical Pharmacology has reviewed the information submitted under NDA 22-306 for So-AqueousTM and finds the results from bioequivalence study No. 12103 not acceptable.

However, taking into account that the study was not properly powered to demonstrate bioequivalence and also that a critical protocol's violation occurred during the infusion of the drug, OCP considers that the sponsor should be given the opportunity to provide additional data to support the approval of their product.

According to CFR 320.24, there are different types of evidence that can be submitted to establish bioavailability or bioequivalence. The selection of the method depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. In general, the following two approaches (*in vivo* or *in vitro*) are acceptable for determining the bioavailability or bioequivalence of a drug product:

(i) An *in vivo* study in humans in which the concentration of the active ingredient in an appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or

(ii) An *in vitro* test that has been correlated with and is predictive of human *in vivo* bioavailability data.

Although, an acceptable *in vivo* BE study can be considered the “Gold Standard” choice to support the approval of this product, in this particular case there is an alternative *in vitro* approach that also can be used to support the approval of this product. The *in vitro* approach is supported by the reviewer’s PK population-simulated data predicting the concentration-time profiles for sotalol.

The following comments should be properly addressed by the sponsor.

COMMENTS:

1. The sponsor should perform an *in vitro* pump study with sotalol solution for IV infusion where 1) the procedures used in study 12103 are applied, and 2) the IV tubing is adequately flushed after administration of sotalol. In both cases, the amount delivered should be measured to verify that the intended amount of sotalol was delivered. The sponsor should evaluate *in vitro* a possible binding of sotalol to the _____ tubing. If the *in vitro* studies confirm the administered amount of the IV dose, this information may be used for the approval consideration. If the *in vitro* pump study cannot resolve the discrepancies found in the data, the sponsor may have to repeat the *in vivo* study using IV and oral formulations.
2. The agency should conduct site inspection to verify the validity of the records.

b(4)

1.2 PHASE IV COMMITMENTS:

Not Applicable

Elena Mishina, Ph. D.
Senior Clinical Pharmacologist

Date _____

Christoffer Tornoe, Ph.D.
Pharmacometrics Reviewer

Pravin Jadhav, Ph.D.
Pharmacometrics Team Leader

Angelica Dorantes, Ph. D.
Cardio-Renal Acting Team Leader

CPB Briefing was held on April 7, 2009.

Attendees: A.Dorantes, M.Mehta, T.Ong, P. Jadhav, NA. Rahman, C.Noory, K. Dimova, C. Tornoe, E. Mishina, L. Zhang, R. Uppoor, K. Kong, R. Fortney, J. Cho, B. Yu, Y. Harigaya, A. Noory, S. Agaswal, R. Kumi, R. Madabushi, I. Zagorewski, K. Reynolds, S. Brar, D. Menon-Andersen, I. Yonis, S. Lu, R. Owen, S. Au, R. Jain, N. Stockbridge, M. Pacanowski, I. Zineh, J. Earp, A. Karkawsky, P. Hinderling.

cc list: NDA 22-306, HFD 110 (FortneyR, KarkowskyA), HFD-860 (MehulM, DorantesA, UppoorR).

1.3 Summary of OCP Findings

1.3.1 Background

The Academic Pharmaceuticals is seeking the approval of NDA 22-306 for So-Aqueous™ (sotalol hydrochloride, solution for intravenous infusion) for those patients who are unable to take oral sotalol therapy (surgery, intubation, acute illness, etc).

1.3.2 Current Submission

The investigation of So-Aqueous™ was performed under the IND 66,955. The clinical pharmacology program for the NDA 22-307 includes one bioequivalence study between orally and intravenously administered sotalol and PK simulated data.

The original submission date for NDA 22-306 was on October 22, 2007. However, the review's clock has started on 7/25/08 when the orphan status was granted to this NDA. The BE study and the PK-simulated data submitted under the NDA 22-306 were reviewed.

1.3.3. Biopharmaceutics

Bioequivalence between 80 mg PO dose and 75 mg IV infusion over 2.5 hours of sotalol was not established in the study 12103 with respect to both C_{max} and AUC.

In addition, the study 12103 was underpowered. The 25% CV was used for the estimation of the sample size for this study. The sotalol parameter variability for the IV administration was well above 25% (C_{max} 55%, AUC 39%).

The sponsor admitted the violation of the protocol and proposed (based on the simulations) that the IV dose administered in this study was 62 instead of 75 mg (no data provided). The reviewer's population PK analysis confirmed that less than the intended 75 mg IV dose was administered in study 12103. The estimated IV bioavailability relative to PO was 73.4% and by assuming a PO bioavailability of 100%, the estimated IV dose relative to PO is 55 mg (i.e. $0.734 * 75 \text{ mg} = 55 \text{ mg}$). Because bioavailability after PO administration cannot be estimated from the current data, the exact IV dose cannot be determined. If the PO bioavailability in this study was 90 to 95% (typical for sotalol), then the IV dose would be 57 to 61 mg. The infusion time of 2.5 hours used in study 12103 is too short to match C_{max} following 80 mg PO. The sponsor proposed to increase the infusion time to — Reviewer's analysis confirmed that an appropriate infusion time is 4-5 hours.

b(4)

2 QUESTION BASED REVIEW

2.1 General Attributes

History of Regulatory Development

Sotalol hydrochloride is currently approved in oral formulations (Betapace AF) for the treatment of life threatening ventricular arrhythmias and for the maintenance of sinus rhythmus in patients with a history of symptomatic atrial fibrillation. Sotalol is an antiarrhythmic drug with Vaughan Williams Class II (beta-adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties.

So-AqueousTM (sotalol hydrochloride, solution for intravenous infusion) is being developed by Academic Pharmaceuticals under NDA 22-306.

In the present submission, the sponsor is seeking the approval of So-AqueousTM for those patients who are unable to take oral sotalol therapy (surgery, intubation, acute illness, etc) based on one bioequivalence study between orally and intravenously administered sotalol.

The original submission of NDA 22-306 was on October 22, 2007. However, the review clock has started on 7/25/08 when the orphan status was granted to this NDA.

The detailed information regarding the Clinical Pharmacology of sotalol hydrochloride was provided and reviewed under NDA 19-865 and NDA 21-151.

This review will use the abbreviated QBR with the questions pertaining only to this submission.

What are the proposed dosages and route of administration?

The sponsor recommends that the 75 mg dose sotalol for IV infusion will be administered as a — hours infusion.

b(4)

2.2 General Clinical Pharmacology

Pharmacokinetics

Sotalol hydrochloride is currently approved in oral formulations (Betapace AF) for the treatment of life threatening ventricular arrhythmias and for the maintenance of sinus rhythmus in patients with a history of symptomatic atrial fibrillation.

The detailed information regarding the Clinical Pharmacology of sotalol hydrochloride was provided and reviewed under NDA 19-865 and NDA 21-151. It is summarized in the section below.

Absorption, Distribution, Metabolism, Excretion

In healthy subjects, the oral bioavailability of sotalol is 90-100%. After oral administration, peak plasma concentrations are reached in 2.5 to 4 hours, and steady-state plasma concentrations are attained within 2-3 days (i.e., after 5-6 doses when administered twice daily). Over the dosage range 160-640 mg/day sotalol displays dose proportionality with respect to plasma concentrations. Distribution occurs to a central (plasma) and to a peripheral compartment, with a mean elimination half-life of 12 hours. Dosing every 12 hours, results in trough plasma concentrations which are approximately one-half of those at peak. Sotalol does not bind to plasma proteins and is not metabolized. Oral sotalol has low inter-subject variability in plasma

levels. The pharmacokinetics of the d- and l- enantiomers of sotalol are essentially identical. Sotalol crosses the blood brain barrier poorly. Excretion is predominantly via the kidney in the unchanged form, and therefore lower doses are necessary in conditions of renal impairment.

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The investigation of sotalol for IV infusion was performed under IND 66,955. The clinical pharmacology program for NDA 22-306 includes one bioequivalence study.

At the IND stage, the FDA advised the sponsor

1. To provide the assurance of the complete dose administration during the infusion with the automated pump;
2. To guarantee the required statistical power of the study (the intended size of the study was 15 subjects which was calculated by the sponsor based on the assumed 25% variability of the sotalol PK parameters);
3. To simulate the possible IV infusion profiles in order to plan the BE study.

The BE study and sponsor's simulations submitted under NDA 22-306 were reviewed.

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes. The sponsor measured the concentrations of racemic sotalol in plasma. Since the absolute bioavailability of sotalol is close to a 100%, and the pharmacokinetics of 2 stereoisomers are very similar, the assay method used LC/MS/MS with _____ is acceptable. The assay method was properly validated, chromatograms were shown.

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What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

Sotalol has a moderately variable pharmacokinetics. In study 12103, C_{max} had CV of 41% (PO) and 55% (IV), and AUC had CV of 26% (PO) and 39% (IV). It is unusual that the variability associated with IV infusion is higher than after the PO dose and possibly may be explained by the erratic IV dose administration in this study.

2.3 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure?

The effects of intrinsic factors were not studied in this NDA.

However, the modeling and simulation performed by the reviewer identified body weight as a covariate for sotalol clearance and central volume of distribution (see Figure 1) with a consistent relationship for the IV/PO (study 12103) and PO (study 11620) studies.

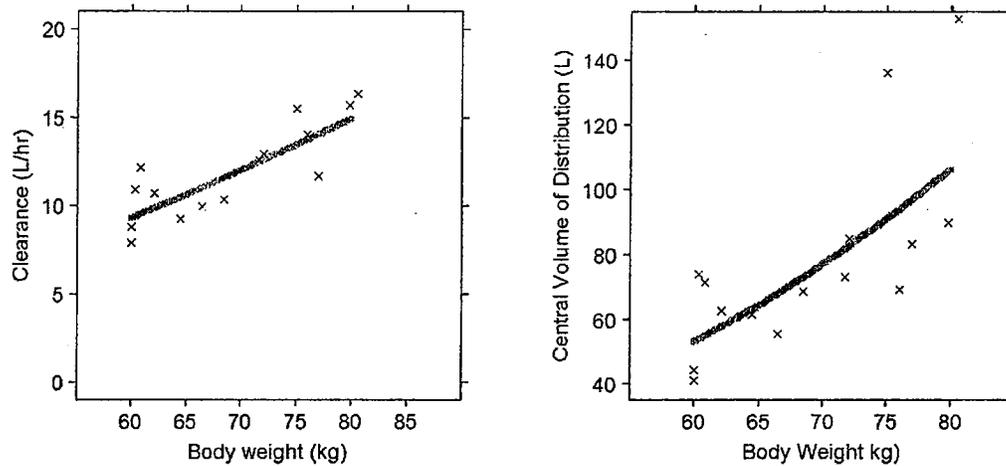


Figure 1: Identified sotalol PK parameter-covariate relationships. (Left) Clearance and (Right) Central volume of distribution vs. body weight. The red line is the estimated population relationship and the black symbols represent the empirical Bayes individual estimates.

Nevertheless, the dosage of sotalol should not require adjustment for body weight (please see Appendix II)

Is there any the pharmacogenomic data submitted with this NDA?

No, this submission does not include pharmacogenomic information.

2.4 Extrinsic Factors

Were any drug-drug interactions studied in this NDA?

This submission did not evaluate any DDI.

2.5 General Biopharmaceutics

What are the significant, unresolved issues related to in vivo BA and BE?

The acceptability of the BE study (No. 12103) is an issue.

To address this issue the following pharmacometric analyses were conducted by Dr. Christoffer Tornøe from the Division of Pharmacometrics at OCP.

FDA's PHARMACOMETRIC DATA ANALYSES

Is the observed PK data in study 12103 consistent with prior sotalol PK information?

Yes, the sotalol PK data following 80 mg PO ($t_{max} = 3$ hr, $t_{1/2} = 10$ hr) are consistent with the PK information from the sotalol label (reported $t_{max} = 2.5-4$ hr, $t_{1/2} = 12$ hr). However, the PK data following 75 mg sotalol IV infusion administered over 2.5 hr were consistently lower than 80 mg PO and literature PK information (Am J Cardiol. 1993 Aug 12;72(4):19A-26A) suggesting that the subjects may have received less than the total 75 mg IV dose.

What IV sotalol dose was administered in study 12103?

According to the sponsor, a significant portion of the sotalol infusion remained in the IV tubing due to a safety device in the infusion system to prevent air being given to the patient. The volume of infusion remaining in the tubing was found to be 13 mL (out of 75 mL of 1 mg/mL solution) in a pump study resulting in 62 mg of the IV dose being administered. The reviewer's estimate is consistent with the sponsor's measure of 62 mg. The reviewer's population PK analysis using the IV/PO PK data from study 12103 confirmed that less than the intended 75 mg IV dose was administered in study 12103. The estimated IV bioavailability relative to PO was 75%. The approved sotalol label states that the oral bioavailability of sotalol is 90-100% and by assuming a PO bioavailability of either 90% or 100%, the estimated IV dose relative to PO is 62 mg or 56 mg (i.e. $0.75 * 75$ mg / 0.9 = 62 mg or $0.75 * 75$ mg = 56 mg).

Is 75 mg IV 2.5 hr infusion bioequivalent with 80 mg PO?

No, the infusion time of 2.5 hr is too short to match C_{max} following 80 mg PO. The sponsor proposed to increase the infusion time to — Reviewer's analysis confirmed that 4-5 hours is an appropriate infusion time (see Figure 2 and Table 1).

b(4)

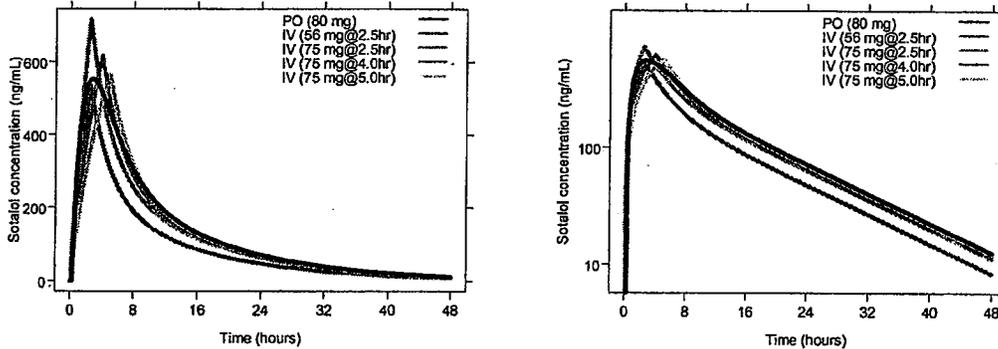


Figure 2: Simulated sotalol concentration-time profiles on (Left) normal and (Right) log scale.

Table 1: Population predicted C_{max} following different PO and IV doses.

Dose	C_{max} (ng/mL)
80 mg PO	553
56 mg IV @ 2.5 hr	535
75 mg IV @ 2.5 hr	717
75 mg IV @ 4 hr	617
75 mg IV @ 5 hr	565

2.6 Analytical section

How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma samples collected in clinical studies were analyzed for sotalol racemic mixture.

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

An LC-MS/MS method with \square technique was used to assay racemic sotalol. The lower limit of quantitation was 1 ng/mL; the upper limit of quantitation was 750 ng/mL. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range.

b(4)

The sponsor properly validated the assay method, reported, intra/inter-assay precision, and intra/inter-assay accuracy, storage conditions and freeze/thaw stability data. The following table lists the assay parameters.

LC-MS/MS Assay Characteristics of Sotalol in Plasma

Parameter	
Linearity	1.00ng/mL to 750 ng/mL
Precision (CV %)	6.7 to 10.7
Accuracy, %	0.3 to 2.5
LLOQ	1.00 ng/mL

Were the validation characteristics of the assay acceptable?

Yes, the provided data support the validation of the LC-MS/MS assay.

What is the overall conclusion regarding NDA 22-306?

Overall, the provided data do not support the approval of the bioequivalence study No. 12103. Therefore, from the clinical pharmacology viewpoint, NDA 22-306 for So-Aqueous is not acceptable.

3 DETAILED LABELING RECOMMENDATIONS

GENERAL

The proposed labeling is included in Appendix I.

CLINICAL PHARMACOLOGY COMMENTS

Labeling Comments:

- OCP is not reviewing the proposed labeling for So-Aqueous Injection at this time.
- The labeling for this product will be reviewed at a later time when all the BE-pending issues are resolved.

4 APPENDIX I

4.1 Individual Study Reviews

A RANDOMIZED, TWO-DOSE, TWO-PERIOD, CROSSOVER STUDY ON THE BIOEQUIVALENCE OF ORAL AND INTRAVENOUS SOTALOL

Study number: 12103

Principal Investigator: Dr. S Freestone, Inveresk Clinical Research

Sponsor: Academic Pharmaceuticals, Inc.

PI: Richard A. Preston, M.D.

Study Center: University of Miami, Clinical Pharmacology 1500 NW 12th Avenue, Suite 15W
Miami, FL 33136-1028

Study Dates: 9/24/2004 - 10/22/2004

Phase of Development: I

Objective	Primary: to evaluate bioequivalence between intravenous and oral administration of sotalol. Secondary: to assess the pharmacokinetics of a single dose of sotalol when administered as a 2.5 hr IV infusion in healthy subjects.
Study Design	A randomized, two-treatment, two-period, crossover bioequivalence study between 80 mg oral sotalol and 75 mg intravenous sotalol administered over 2.5 hr.
Study Population	Sotalol naïve healthy subjects (women of non childbearing potential or men) from 18 to 45 years of age
Investigational Drug	So-Aqueous TM (10 ml vials containing 150 mg sotalol HCl, concentration 15 mg/mL). An IV infusion of 75 mg sotalol administered over 2.5 hr with a constant infusion rate. Batch number: API 021017
Reference Product	Betapace AF tablet, 80 mg oral dose, Batch number: W20190
Assay	LC-MS/MS method with Γ techniques
Statistics	Noncompartmental analysis WinNonlin Professional software package Γ Cp were determined directly from the observed data. The AUC _{0-48 hr} and AUC _{0-∞} were estimated. For bioequivalence testing, log-transformed (ln) AUC _{0-∞} , AUC _{0-t} , and C _{max} determinations were used. The oral formulation was used as the reference (R) and the intravenous formulation as the test (T) formulation. The statistics employs linear mixed-effect model procedures with the following sources of variation: sequence, subjects nested in sequences, period, and formulation. The ratio of the geometric least square means (T/R) and the 90% confidential interval of the ratio were computed. Bioequivalence between T and R can be concluded, if the 90 percent confidence interval for the ratio of geometric least square means is within the equivalence limits of 80-125 percent.

b(4)

b(4)

Results**Protocol Deviations and Violations**

In response to the comments from the FDA regarding the unusual initial results suggested that IV administration delivered less sotalol than oral administration, the sponsor reevaluated the study results. The sponsor reported a systematic protocol violation revealed after the completion of the dosing phase of the study. The sponsor speculated that the administered IV dose was 62 mg instead of planned 75 mg. This dose was estimated by the sponsor based on the assumption of the volume of the remaining (not flashed) tubing. However, the individual measurements of the administered volume of infusion were not reported.

Assay

Sotalol (racemic mixture) in blood was determined with LC/MS/MS method using _____ technique. The performance characteristics of the assay are acceptable. The representative mass-chromatograms are shown.

b(4)

Table 2: Assay Characteristics of Sotalol in Plasma

Parameter	
Linearity	1.00ng/mL to 750 ng/mL
Precision (CV %)	6.7 to 10.7
Accuracy, %	0.3 to 2.5
LLOQ	1.00 ng/mL

Demographics:

Eighteen subjects entered the study and 16 of them completed the study (2 dropouts). One subject was considered to be an outlier due to very low sotalol plasma concentrations.

Please see the table below.

Demographic and Baseline Characteristics Of All Subjects

Healthy Volunteer		15
Age (years);	Mean ± SD	32±8
	Min/Max	19/45
	Median	33
Gender: Male		6
	Female	9
Race/Ethnic:	White (Caucasian)	6
	Hispanic	9
Height, cm	Mean ± SD	166.1±8.2
	Min/Max	152.0/178.0
	Median	166.5
Weight, kg	Mean ± SD	69.6±7.7
	Min/Max	60.0/80.5
	Median	70.1

Pharmacokinetics

Table 3: The individual pharmacokinetic parameters of sotalol

Subject	Initials	C max		T max		AUC _{0-48 hrs}		AUC _{0-∞}	
		IV	Oral	IV	Oral	IV	Oral	IV	Oral
1		459	1538	2.50	2.00	3535	7343	3602	7425
2		622	410	2.00	3.50	4614	4460	4742	4703
3		593	326	2.50	2.50	4197	3225	4304	3317
4		356	635	2.50	3.00	3177	6893	3249	7241
5		607	795	3.00	3.00	3630	7816	3685	8165
6		532	812	2.50	2.50	3690	8802	3811	9335
8		617	748	3.00	3.50	4979	6991	5075	7730
9		523	591	2.00	2.50	4198	6311	4242	6656
10		591	845	2.50	2.00	5146	8933	5291	9150
11		1848	626	2.50	1.50	9944	5979	10134	6246
12		465	508	2.50	2.00	3650	4935	3727	5226
14		962	649	2.50	3.50	8640	8815	8948	9862
16		764	683	2.00	1.50	7342	8403	7444	9763
17		675	548	2.50	2.00	5622	6635	5749	6910
18		1467	1126	2.00	1.00	7018	7821	7146	8114
	Mean	739	723	2.43	2.40	5292	6891	5410	7323
	SD	405	296	0.32	0.78	2048	1694	2097	1897
	Median	600	642	2.50	2.50	4406	6942	4523	7333
	Min	356	326	2	1	3177	3225	3249	3317
	Max	1848	1538	3	4	9944	8933	10134	9862
	CV	0.55	0.41	0.13	0.33	0.39	0.25	0.39	0.26

b(6)

The mean plasma concentrations of sotalol after one administration of 80 mg oral sotalol and a 2.5-hr infusion of intravenous sotalol is shown below.

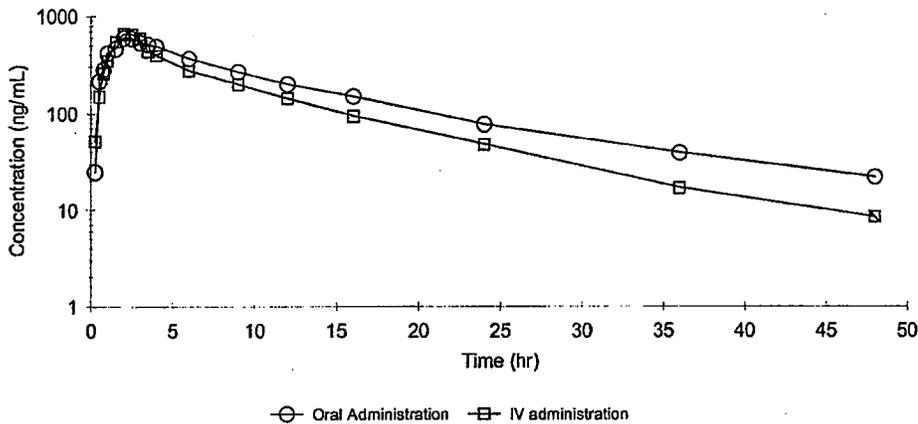


Figure 3. Sponsor's plot of the mean plasma concentrations of sotalol after the administration of 80 mg Oral Sotalol and a 2.5-hr infusion of "75" mg IV Sotalol.

The sponsor claimed that IV dose of sotalol was 62 mg (no data to support this claim). Based on that assumption, the sponsor performed a bioequivalence analysis. Its results are shown below.

Table 4: Summary Results - Bioequivalence Test

Treatment	C _{max} (ng/ml)	AUC ₀₋₄₈ hr(hr*ng/ml)	AUC _{0-∞} (hr*ng/ml)
80 mg Oral Sotalol (mean±SD)	723±296	6891±1694	7323±1897
62 mg IV Sotalol (mean±SD)	739±405	5292±2048	5410±2097
Ratio of Geometric LS means	97.7%	73.7%	71.1%
90% Confidence Interval	76.4%-124.9%	62.7%-86.4%	60.5%-83.5 %

Based on the BE criteria, two treatments of sotalol (oral 80 mg dose and adjusted by the sponsor IV 62 mg dose) were not bioequivalent with respect to both C_{max} and AUC.

Reviewer Comments

1. The sotalol parameter variability for the IV administration was well above 25% (C_{max} 55%, AUC 39%). The 25% CV was used for the estimation of the sample size for this study. Therefore, the study was underpowered. In the previous communications with the sponsor (June 24, 2004), FDA reviewer requested reconsider the size of the population recruited for this study.
2. The individual data on the volumes of the IV solution administered in this study were not available for review.

5 APPENDIX II: Pharmacometrics Review

5.1 Key Review Questions

The purpose of this review is to address the following key questions.

5.1.1 Are the observed PK data in study 12103 consistent with prior sotalol PK information?

Yes, the sotalol PK data following 80 mg PO ($t_{max} = 3$ hr, $t_{1/2} = 10$ hr) are consistent with the PK information from the sotalol label (reported $t_{max} = 2.5$ -4 hr, $t_{1/2} = 12$ hr). However, the PK data following 75 mg sotalol IV infusion administered over 2.5 hr were consistently lower than 80 mg PO and literature PK information (Am J Cardiol. 1993 Aug 12;72(4):19A-26A) suggesting that the subjects may have received less than the total 75 mg IV dose.

5.1.2 What IV sotalol dose was administered in study 12103?

According to the sponsor, a significant portion of the sotalol infusion remained in the IV tubing due to a safety device in the infusion system to prevent air being given to the patient. The volume of infusion remaining in the tubing was found to be 13 mL (out of 75 mL of 1 mg/mL solution) in a pump study resulting in 62 mg of the IV dose being administered.

The reviewer's estimate is consistent with the sponsor's measure of 62 mg. The reviewer's population PK analysis using the IV/PO PK data from study 12103 confirmed that less than the intended 75 mg IV dose was administered in study 12103. The estimated IV bioavailability relative to PO was 75%. The approved sotalol label states that the oral bioavailability of sotalol is 90-100% and by assuming a PO bioavailability of either 90% or 100%, the estimated IV dose relative to PO is 62 mg or 56 mg (i.e. $0.75 * 75$ mg / $0.9 = 62$ mg or $0.75 * 75$ mg = 56 mg).

5.1.3 Is the 75 mg IV sotalol infusion over 2.5 hr bioequivalent to the 80 mg PO?

No, the infusion time of 2.5 hr is too short to match C_{max} following 80 mg PO. The sponsor proposed to increase the infusion time to — Reviewer's analysis confirmed that 4-5 hours is an appropriate infusion time interval (see Figure 2 and Table 1).

b(4)

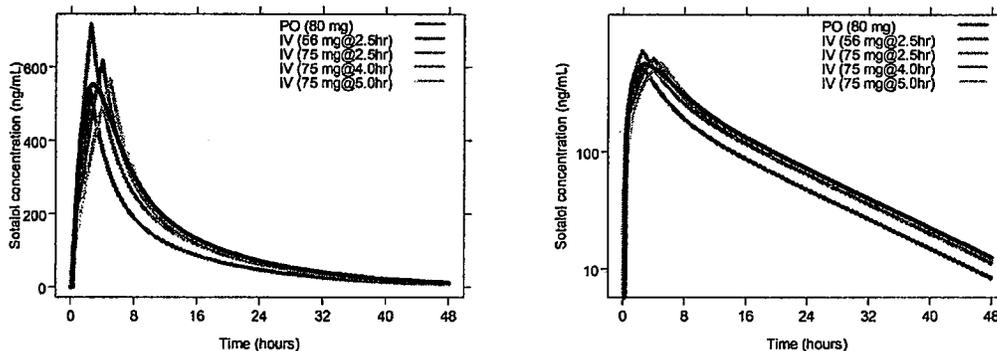


Figure 4: Simulated sotalol concentration-time profiles on (Left) normal and (Right) log scale.

Table 5: Population predicted C_{max} following different PO and IV doses.

Dose	C_{max} (ng/mL)
80 mg PO	553
56 mg IV @ 2.5 hr	535
75 mg IV @ 2.5 hr	717
75 mg IV @ 4 hr	617
75 mg IV @ 5 hr	565

5.2 Results of Sponsor's Analysis

A two-compartment disposition model with first-order elimination was used for modeling and obtaining PK parameter estimates for IV sotalol administration using WinNonlin PK Model 9: 2 compartment IV-Infusion, micro-constants, no lag time, 1st order elimination. For the modeling, the sponsor substituted the intended dose of 75 mg by the estimated dose of 62 mg. Using the individual PK parameters individual simulations with increasing lengths of infusions were performed. The results are shown in Table 6.

Subject	Length of Infusion		
	IV 3 hr	3.5 hr	4 hr
	C _{max} ng/ml	C _{max} ng/ml	C _{max} ng/ml
1	592	557	528
2	675	625	586
3	680	641	608
4	477	455	434
5	594	558	527
6	563	526	495
8	749	700	659
9	648	606	571
10	748	708	674
11	1952	1822	1706
12	504	471	444
14	1225	1157	1097
16	974	932	895
17	767	723	684
18	1203	1094	1006
Mean	823	772	728
SD	386	359	335
% of oral C_{max}	113.9%	106.7%	100.6%

Source: Table 11.3.F in sponsor's CSR 4 S7 on page 49.

The result of bioequivalence testing for individually simulated C_{max} values are shown in Table 7.

Table 7: Pharmacokinetic Results and Bioequivalence Testing of C_{max} for 80 mg IV Sotalol with Increasing Length of Infusions and 80 mg Oral Sotalol.

	2.5 hr	3 hr	3.5 hr	4 hr
Geometric LS Means				
Oral Sotalol (ng/mL)	672	672	672	672
IV Sotalol (ng/mL)	806	750	704	664
Ratio of Geometric LS Means	120%	112%	105%	99%
90% Confidence Interval	96%-149%	89.7%-138.8%	84.2%-130.1%	79.6%-122.8%

Source: Table 11.3.G in sponsor's CSR 4 S7 on page 50

The result shows that a 3.5 hr IV infusion would result in a 5% greater geometric least square mean (GeoLSM) than observed following oral administration. The 4 hr IV infusion would result in almost identical GeoLSM to the oral administration (99%) with a 90% confidence interval that is 0.4% less than the lower limit of the bioequivalence criteria.

Reviewer's comment on the sponsor's PK data analysis:

The sponsor should had preferably used both the PO and IV data and estimated the PK parameters using non-linear mixed-effects modeling instead of a standard two-stage method as implemented in WinNonlin. This approach could have provided further evidence to the sponsor's claim that the subjects received 62 mg instead of the intended 75 mg IV dose by estimating the IV bioavailability relative to PO.

5.3 Reviewer's Data Analysis

5.3.1 Introduction

The above mentioned limitations of sponsor's analysis were addressed in reviewer's analysis below.

5.3.2 Objectives

The objectives for reviewer's analysis are described below:

1. To estimate the proportion of the IV dose that remained in the IV tubing using population PK modeling of the PK data following IV and PO doses.
2. To identify the infusion time of a 75 mg IV dose that will match C_{max} following 80 mg PO.

5.3.3 Methods

5.3.3.1 Data Sets

Data sets used are summarized in Table 8.

Table 8. Analysis Data Sets

Study Number	Name	Link to EDR
12103	15 Intravenous.xls	NA
12103	Individual Oral Concentrations.xls	NA
12103	Patient demographic 15 volunteers.xls	NA

5.3.3.2 Software

NONMEM and S-PLUS were used for reviewer's analysis.

5.3.3.3 Models

A two-compartment disposition model with first-order absorption (with lag time) and elimination was used to describe the totalol concentration-time profile following IV and PO administration.

5.3.4 Results

The sotalol concentration-time profiles following 80 mg PO were found to be consistent with prior PK information from the sotalol label. However, the concentration-time profiles following 75 mg sotalol IV infusion administered over 2.5 hr were consistently lower than 80 mg PO and literature PK information (*Am J Cardiol.* 1993 Aug 12;72(4):19A-26A) suggesting that the subjects received less than the total 75 mg IV dose.

The PK data from IV and PO administration from study 12103 were combined for reviewer's PK modeling and the bioavailability of IV relative to PO was estimated to get an estimate of the percentage of the IV dose administered.

The PK parameter estimates for the reviewer's final sotalol PK model are shown in Table 9 and the population predicted concentration-time profiles are shown in Figure 5. The estimated bioavailability of IV relative to PO was 75%. Assuming a PO bioavailability of either 90% or 100%, the estimated IV dose relative to PO is 62 mg or 56 mg (i.e. $0.75 \times 75 \text{ mg} / 0.9 = 62 \text{ mg}$ or $0.75 \times 75 \text{ mg} = 56 \text{ mg}$).

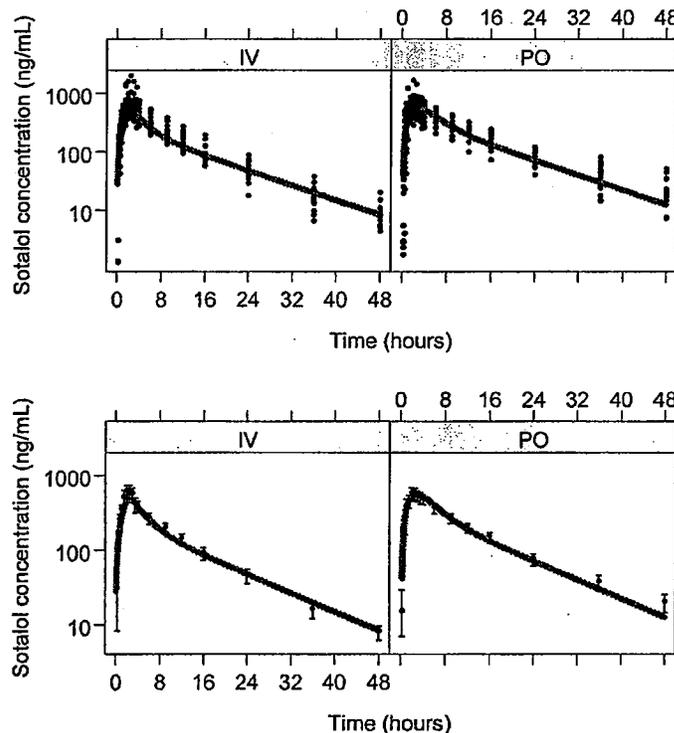


Figure 5: Concentration-time profiles following (Left) IV and (Right) PO administration of sotalol. The solid red line is the population predicted and the (Top) dots represent the individual observed sotalol concentrations and (bottom) the mean (95% CI) sotalol concentrations are shown at each time point.

Body weight was identified as a covariate for sotalol clearance and central volume of distribution (see Figure 6).

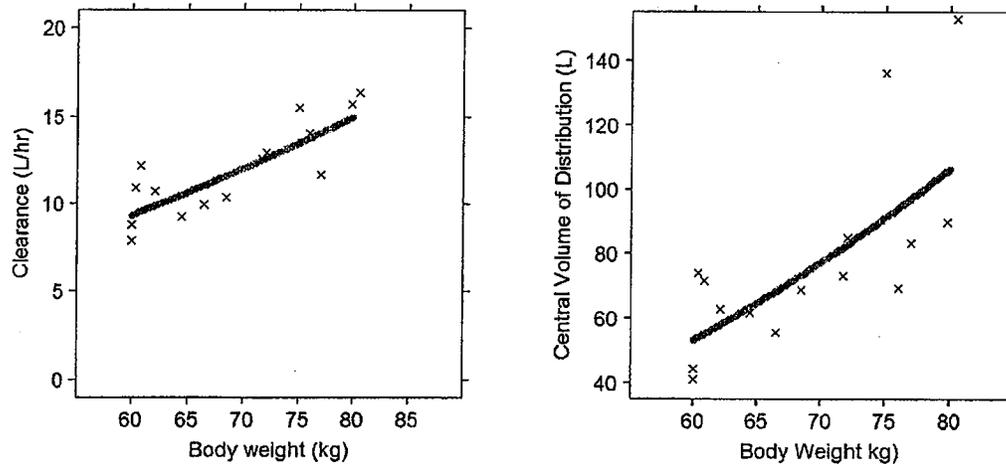


Figure 6: Identified sotalol PK parameter-covariate relationships. (Left) Clearance and (Right) Central volume of distribution vs. body weight. The red line is the estimated population relationship and the black symbols represent the empirical Bayes individual estimates.

Simulations were performed to identify an infusion time of a 75 mg IV dose that will match C_{max} following 80 mg PO. The tested infusion time of 2.5 hr was found to be too short to match C_{max} following 80 mg PO. The sponsor proposes to increase the infusion time to — but reviewer's analysis shows that 5 hours is more appropriate (see Figure 2 and Table 1).

b(4)

5.4 Appendix A: Reviewer's Population PK Analysis

Table 9 Reviewer's Final Sotalol PK Model Parameter Estimates.

Parameter	Unit	Population parameters		Inter-individual variability	
		Estimate	%RSE	Estimate (CV%)	%RSE
<u>Fixed-Effects Parameters</u>					
Clearance (CL) for 70 kg subject	[L/hr]	12.0	5.78	14.1	19.6
Inter-compartmental clearance (Q)	[L/hr]	9.22	24.6	-	-
Central volume of distribution (Vc) for 70 kg subject	[L]	77.1	8.82	26.7	16.1
Peripheral volume of distribution (Vp)	[L]	52.3	7.42	-	-
Absorption rate constant (Ka)	[1/hr]	0.605	33.7	68.5	22.4
Absorption lag time	[hr]	0.231	2.37	-	-
IV bioavailability relative to PO (F _{IV})	[-]	0.746	6.90	-	-
<u>Covariate-relationships</u>					
CL-WT exponent	[-]	1.64	60.2	-	-
Vc-WT exponent	[-]	2.41	64.3	-	-
<u>Intra-Individual Variability</u>					
Proportional error	[CV%]	47.8	11.2	-	-

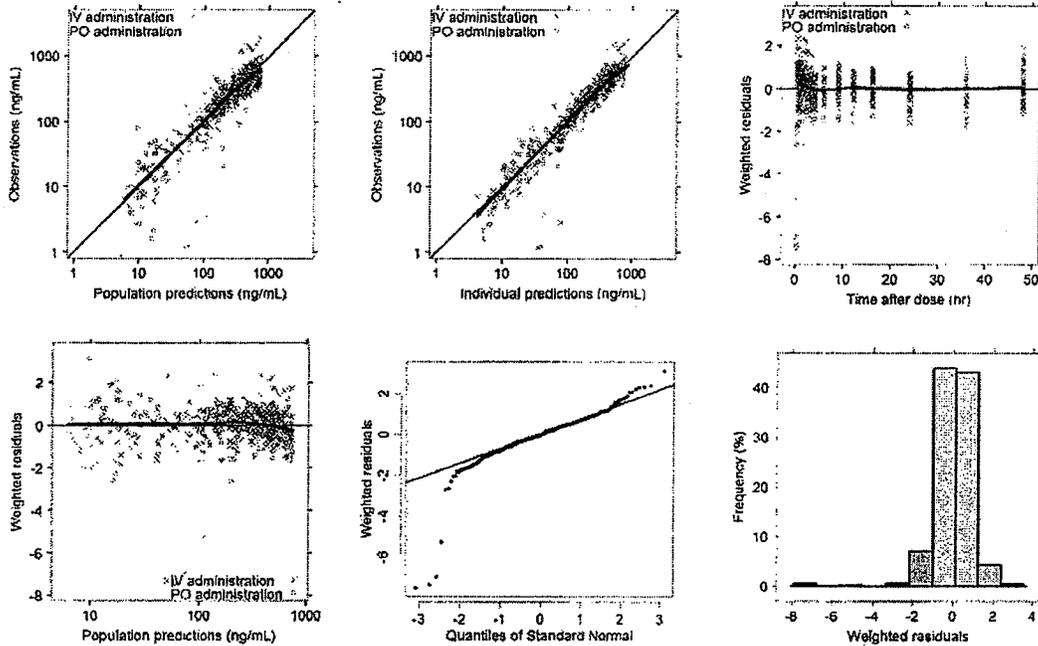


Figure 7: Goodness-of-fit graphs for reviewer’s final sotalol PK model following IV (black crosses) and PO (red circles) administration of sotalol. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the red line is a local smoothing regression line.

6 APPENDIX III: OCP Filing Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information			Information
NDA Number	22-306	Brand Name		So-Aqueous
OCP Division (I, II, III)	DIV-1	Generic Name		Sotalol
Medical Division	Cardiovascular-Renal	Drug Class		Antiarrhythmic
OCP Reviewer	ELENA MISHINA	Indication(s)		For patients who are unable to take oral sotalol therapy
OCP Team Leader (Acting)	Elena Mishina	Dosage Form		Solution for infusion
Date of Submission	7/25 & 8/19, 2008	Dosing Regimen		75 mg
Estimated Due Date of OCP Review	4/2/2009	Route of Administration		IV infusion
PDUFA Due Date	5/26/2009	Sponsor		The Academic Pharmaceuticals
Division Due Date	3/26/2009	Priority Classification		S
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	1		
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Electrophysiology Study				
PK Simulated Data	X	1	1	
Total Number of Studies Reviewed		2	2	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	DCP1: Elena V. Mishina, Ph.D.		Date:	
	DPM: Christoffer Tornoe, Ph.D.		Date:	
Secondary reviewer Signature and Date	DCP1 Team Leader (actg): Angelica Dorantes, Ph.D.		Date:	
	DPM Team Leader: Pravin Jadhav, Ph.D.		Date:	

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BIOPHARMACEUTICS

Pravin Jadhav
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