

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214044Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	214044
Link to EDR	\\Cdsub1\EVSPROD\NDA214044\0001
Submission Date	11/1/19; PDUFA date: 9/1/2020
Submission Type	Standard Review; 505(b)(2) referencing Ultram (N20281)
Proposed Brand Name	QDOLO™
Generic Name	Tramadol Hydrochloride Oral Solution
Dosage Form and Strength	Solution, 25 mg/5 mL
Route of Administration	Oral
Proposed Indication	Management of pain severe enough to require an opioid analgesic for which alternative treatments are inadequate
Dosage Regimen	• Start at 25 mg (5 mL)/day and titrate in 25 mg (5 mL) increments as separate doses every 3 days to reach 100 mg (20 mL)/day (25 mg (5mL) four times a day). Thereafter the total daily dose may be increased by 50 mg (10 mL) as tolerated every 3 days to reach 200 mg (40 mL)/day (50 mg (10 mL) four times a day). After titration, Tramadol Hydrochloride Oral Solution 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg (80 mL)/day (2.2, 2.3). • For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, Tramadol Hydrochloride Oral Solution 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain relief every four to six hours, not to exceed 400 mg (80 mL)/day. • Severe Hepatic impairment: Recommended dose is 50 mg (10 mL) every 12 hours. • Severe Renal Impairment: Increase the Tramadol Hydrochloride Oral Solution dosing interval to 12 hours, and limit maximum daily dose to 200 mg (40 mL) (2.2). • Geriatric Patients: Do not exceed a total dose of 300 mg (60 mL)/day in patients over 75 years old.
Applicant	Athena Bioscience, LLC
Associated IND	I 127021 (by Sponsor (b) (4) prior to filing of this application, the intellectual property was acquired by Athena Bioscience, LLC)
OCP Reviewer	David Lee, Ph.D.
OCP Team leader	Yun Xu, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric pharmacology (OCP/DNP) has reviewed the information submitted in the current application, NDA 214044, for tramadol hydrochloride oral solution (“QDOLO™”), submitted on 11/1/19. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable. No additional comments or communications need to be conveyed to the Applicant at this time.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	This 505(b)(2) submission is based on two in vivo relative bioavailability pharmacokinetic (PK) studies, Study 197/18 (fasted bioequivalence study), which is considered as the pivotal study, and Study 198/18 (food effect). Ultram (50 mg oral tablet; N20281; Janssen Pharmaceuticals, Inc.) was used as the listed product in the comparison. No clinical Phase 3 safety and efficacy trials were conducted. The results from Study 197/18* indicated that bioequivalence (BE) was established for tramadol between the Applicant’s product and Ultram 50 mg tablet under fasted conditions. The results from Study 198/18# indicated that there is no food effect observed for tramadol for the Applicant’s product. The similar exposure for tramadol was observed between the Applicant’s product and Ultram 50 mg tablet under fed conditions. It was noted that tramadol Cmax was slightly lower [not bioequivalent with point estimate of 78.12% (90% CI: 73.25-83.31)] post tramadol HCl oral solution administration compared to Ultram tablet. The slight difference in tramadol Cmax between the two products under fed conditions are not deemed to be clinically significant since the two products (tramadol HCl oral solution 5 mg/mL and Ultram 50 mg tablet) are bioequivalent under fasted conditions and there is no food effect observed for the Applicant’s product. Therefore, tramadol HCl oral solution can be taken regardless of food. Additionally, it is noted that BE information was submitted for metabolite, O-desmethytramadol, , which is considered as supportive information. The results from Study 197/18*

indicated that BE was established for metabolite, O-desmethyl tramadol, between the Applicant's product and Ultram 50 mg tablet under fasted conditions. The results from Study 198/18[#] indicated that there is no food effect observed for metabolite, O-desmethyl tramadol, for the Applicant's product. The similar extent of food effect for metabolite, O-desmethyl tramadol, was observed between the Applicant's product and Ultram 50 mg tablet under fed conditions.

Based on the Study 197/18 (a fasted relative bioavailability study), a request was submitted to Office of Study Integrity and Surveillance (OSIS) inspect the clinical and analytical study sites located at (b) (4)

Center for Drug Evaluation and Research (CDER), Office of Study Integrity and Surveillance (OSIS) consult form, Request for Biopharmaceutical Inspections, has been filled out, submitted, and, received by OSIS on 12/18/2019 (DARRTS date). It was determined that inspections are not warranted at this time for both clinical and analytical sites [No Action Indicated (NAI)]. There are no comments to be conveyed to the Applicant regarding the inspection based on OSIS recommendation.

In all, from a clinical pharmacology perspective, the results from the fasted BE (Study 197/8) and food effect studies (Study 198/8) support approval of tramadol HCl oral solution.

*Study 197/18 title: An open label, balanced, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study of Tramadol HCl oral solution (50 mg / 10mL) manufactured for (b) (4) and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects under fasting condition.

#Study 198/18 title: An open label, balanced, randomized, single dose, three treatment, three period, three sequence, crossover, oral food effect and fed Bioequivalence study of Tramadol HCl oral solution (50 mg/10 mL) manufactured for (b) (4), and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects.

General dosing instructions	The Applicant proposes the following dosing regimens, which are identical to Ultram Tablet 50 mg Package Insert: • Do not use Tramadol Hydrochloride Oral Solution concomitantly with other tramadol-containing products. • Do not administer Tramadol Hydrochloride Oral Solution at a dose exceeding 400 mg (80 mL)/day. • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5.1)]. • Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.1)]. • Monitor patients closely for respiratory depression, especially within the first 24–72 hours of initiating therapy and following dosage increases with Tramadol Hydrochloride Oral Solution and adjust the dosage accordingly [see Warnings and Precautions (5.3)]. • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1). • Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse (2.1). • Monitor patients closely for respiratory depression, especially within the first 24–72 hours of initiating therapy and following dosage increases with Tramadol Hydrochloride Oral Solution and adjust the dosage accordingly (2.1). • Start at 25 mg (5 mL)/day and titrate in 25 mg (5 mL) increments as separate doses every 3 days to reach 100 mg (20 mL)/day (25 mg (5mL) four times a day). Thereafter the total daily dose may be increased by 50 mg (10 mL) as tolerated every 3 days to reach 200 mg (40 mL)/day (50 mg (10 mL) four times a day). After titration, Tramadol Hydrochloride Oral Solution 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg (80 mL)/day (2.2, 2.3). • For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, Tramadol Hydrochloride Oral Solution 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain
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	relief every four to six hours, not to exceed 400 mg (80 mL)/day. • Conversion from Tramadol Hydrochloride Oral Solution to Extended-Release Tramadol: The relative bioavailability of Tramadol Hydrochloride Oral Solution compared to extended-release tramadol is unknown, so conversion to extended-release formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression. • Severe Hepatic impairment: Recommended dose is 50 mg (10 mL) every 12 hours. • Severe Renal Impairment: Increase the Tramadol Hydrochloride Oral Solution dosing interval to 12 hours, and limit maximum daily dose to 200 mg (40 mL) (2.2). • Geriatric Patients: Do not exceed a total dose of 300 mg (60 mL)/day in patients over 75 years old. • Do not abruptly discontinue Tramadol Hydrochloride Oral Solution in a physically-dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide (2.2).
Dosing in patient subgroups (intrinsic and extrinsic factors)	No formal assessment was conducted with the Applicant's product. The Applicant is referring to the information in listed drug product label.
Labeling	The proposed package insert is identical to the text of the Ultram Tablet 50 mg Package Insert with the following exceptions, which reflect the change from Ultram Tablet to the proposed tramadol oral solution: 1. ULTRAM is replaced with TRAMADOL HYDROCHLORIDE ORAL SOLUTION. 2. The volume of TRAMADOL HYDROCHLORIDE ORAL SOLUTION in milliliters is added after the dose of tramadol in milligrams, e.g., "25 mg (5 mL)" replaces "25 mg." 3. "Tablet" and "Tablets" are replaced with "Oral Solution." 4. "ULTRAM" is replaced with "Tramadol HCl Tablets," "tramadol hydrochloride," or "tramadol." There are no issues with the proposed Labeling since tramadol BE was established between the Applicant's product and Ultram Tablet 50 mg under fasted conditions. Additional information may be included in Section 12.3 of the proposed label to describe the comparative bioavailability data between Applicant's product and the reference product Ultram Tablet. When this review is submitted into DARRTS,

	discussion is still ongoing on this topic. See Section 2.4 of the review for detailed information.
Bridge between the to-be-marketed and clinical trial formulations	The final to-be-marketed formulation was used in PK studies, Study 197/18 (fasted) and Study 198/18 (food effect).
Other (specify)	Not applicable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The Applicant has submitted tramadol hydrochloride oral solution as a 505(b)(2) submission, which is based on the previous findings of safety and efficacy of Ultram Tablet (50 mg oral tablet; N20281; Janssen Pharmaceuticals, Inc.). With respect to clinical studies/trials for the Applicant's product development program, this submission is based on pharmacokinetic (PK) bridging, i.e., demonstration of bioequivalence (BE), between the Applicant's tramadol hydrochloride oral solution and Ultram Tablet. Therefore, no Phase 3 safety and efficacy trials were conducted. However, the Applicant does state they have conducted a literature search (2014-2019 window) to update or bridge any information, e.g., efficacy and safety of tramadol, which may not have specifically addressed in Ultram Prescribing Information. The reader is referred to clinical review for further discussion related to literature efficacy and safety updates.

The proposed indication is for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults. The proposed dosage form is an oral solution with tramadol 25 mg/5 mL. The proposed package insert is identical to Ultram Tablet 50 mg Package Insert with the exception that which reflect the change from Ultram Tablet to the proposed tramadol HCl oral solution.

The Applicant has submitted two relative bioavailability PK studies, Study 197/18 (fasted BE study) and Study 198/18 (food effect), by providing tramadol bioequivalence (BE) data as a necessary comparison information for the approval. Additionally, it is noted that BE information was also submitted for metabolite M1, O-desmethyl tramadol, between tramadol hydrochloride oral solution and Ultram tablet, which is considered as supportive information. The fasted BE study is considered as a pivotal study. The final to-be-marketed formulation was used in the bioequivalence study.

Office of Study Integrity and Surveillance (OSIS) inspection request

A request was submitted to Office of Study Integrity and Surveillance (OSIS) inspect the clinical and analytical study sites for Study 197/18, a fasted relative bioavailability study. (b) (4)

Center for Drug Evaluation and Research (CDER), Office of Study Integrity and Surveillance (OSIS) consult form, Request for Biopharmaceutical Inspections, has been filled out, submitted, and, received by OSIS on 12/18/2019 (DARRTS date).

OSIS recommendation

It was determined that inspections are not warranted at this time for both Clinical and analytical sites.

The rationale for this is based on the fact that an inspection was conducted under a different **Non-Responsive** submissions, **Non-Responsive**, and, that the final classification for the inspection was No Action Indicated (NAI).

Rationale		
The Office of Regulatory Affairs (ORA) inspected the clinical site in February 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions Non-Responsive		
Non-Responsive		
OSIS inspected the analytical site in Non-Responsive which falls within the surveillance interval. The inspection was conducted under the following submissions: Non-Responsive		
Non-Responsive		
The final classification for the inspections was No Action Indicated (NAI).		
Therefore, based on the rationale described above, an inspection is not warranted at this time.		
Inspection Sites		
Facility Type	Facility Name	Facility Address
Clinical	Actimus Biosciences Pvt., Ltd.	3 rd and 4 th Floor, Varun Towers, Kasturiba Marg, Siripuram, Visakhapatnam, Andhra Pradesh, India
Analytical	(b) (4)	(b) (4)

(Decline to conduct an on-site inspection memo; DARRTS date 02/11/2020, JAMES J LUMALCURI)

Reviewer's comment: No issues are identified at this juncture and there are no comments to be conveyed to the Applicant regarding the inspection.

2.1 Pharmacology and Clinical Pharmacokinetics

2.1.1. What is the proposed indication?

Tramadol hydrochloride oral solution is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Warnings and Precautions (5.1)], reserve TRAMADOL HYDROCHLORIDE ORAL

SOLUTION for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The following general dosing administration is proposed according to the Label:

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Do not use TRAMADOL HYDROCHLORIDE ORAL SOLUTION concomitantly with other tramadol-containing products.
- Do not administer TRAMADOL HYDROCHLORIDE ORAL SOLUTION at a dose exceeding 400 mg (80 mL)/day.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5.1)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24–72 hours of initiating therapy and following dosage increases with TRAMADOL HYDROCHLORIDE ORAL SOLUTION and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

2.2 Initial Dosage

Initiating Treatment with TRAMADOL HYDROCHLORIDE ORAL SOLUTION

For patients not requiring rapid onset of analgesic effect, the tolerability of TRAMADOL HYDROCHLORIDE ORAL SOLUTION can be improved by initiating therapy with the following titration regimen: Start TRAMADOL HYDROCHLORIDE ORAL SOLUTION at 25 mg (5 mL)/day and titrated in 25 mg (5 mL) increments as separate doses every 3 days to reach 100 mg (20 mL)/day (25 mg (5 mL) four times a day). Thereafter the total daily dose may be increased by 50 mg (10 mL) as tolerated every 3 days to reach 200 mg (40 mL)/day (50 mg (10 mL) four times a day). After titration, TRAMADOL HYDROCHLORIDE ORAL SOLUTION 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg (80 mL)/day.

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, TRAMADOL HYDROCHLORIDE ORAL SOLUTION 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain relief every four to six hours, not to exceed 400 mg (80 mL)/day.

Conversion from TRAMADOL HYDROCHLORIDE ORAL SOLUTION to Extended-Release Tramadol

The relative bioavailability of TRAMADOL HYDROCHLORIDE ORAL SOLUTION compared to extended-release tramadol is unknown, so conversion to extended-release formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression.

Dosage Modification in Patients with Hepatic Impairment

The recommended dose for adult patients with severe hepatic impairment is 50 mg (10 mL) every 12 hours.

Dosage Modification in Patients with Renal Impairment

In all patients with creatinine clearance less than 30 mL/min, it is recommended that the dosing interval of TRAMADOL HYDROCHLORIDE ORAL SOLUTION be increased to 12 hours, with a maximum daily dose of 200 mg (40 mL). Since only 7% of an administered dose is removed by hemodialysis, dialysis patients can receive their regular dose on the day of dialysis.

Dosage Modification in Geriatric Patients

Do not exceed a total dose of 300 mg (60 mL)/day in patients over 75 years old.

2.3 Titration and Maintenance of Therapy

Individually titrate TRAMADOL HYDROCHLORIDE ORAL SOLUTION to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving TRAMADOL HYDROCHLORIDE ORAL SOLUTION to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as to monitor for the development of addiction, abuse, or misuse [see *Warnings and Precautions (5.1)*]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the TRAMADOL HYDROCHLORIDE ORAL SOLUTION dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.2.2 Therapeutic individualization

2.2.2.1 Pediatric development iPSP

The Applicant refers to the Agreed iPSP (DARRTS date 9/3/19), and, is seeking: 1) a deferral for the planned pharmacokinetic, efficacy and safety studies in patients 12 – <17 years of age until after the drug product is approved; and, 2) a partial waiver for pediatric patients less than 12 years of age because there is evidence strongly suggesting that the drug would be unsafe. Tramadol is contraindicated in: 1) all children younger than 12 years of age, and, 2) postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

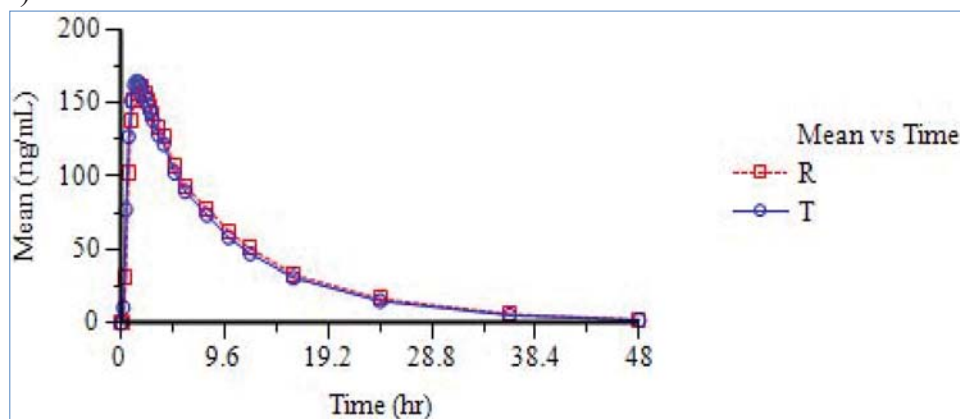
2.2.2.2 Clinical pharmacokinetic findings

Study 197/18

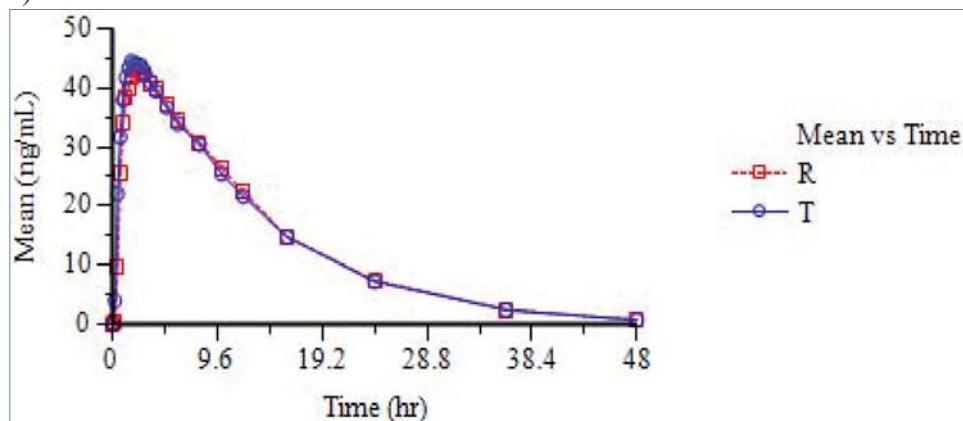
Study 197/18 was a Phase 1, open label, randomized, single dose, two treatment, two period, two sequence, crossover fasted oral relative bioavailability study in healthy male adult subjects. The subjects were administered tramadol HCl oral solution 50 mg and Ultram Tablet 50 mg. The mean plasma concentrations profiles of tramadol and O-desmethyl tramadol are presented in Figure 1.

Figure 1 Mean tramadol (a) and M1, O-desmethyl tramadol (b) plasma concentration versus time under fasted conditions (Study 197/18)

a)



b)



Test Formulation: Tramadol hydrochloride oral solution 5 mg/mL fasted

Reference Formulation: Ultram tablet 50 mg fasted

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\16-2-6-individuals-efficacy-response-data-fasting-1.pdf; p.10/79

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Study 198/18

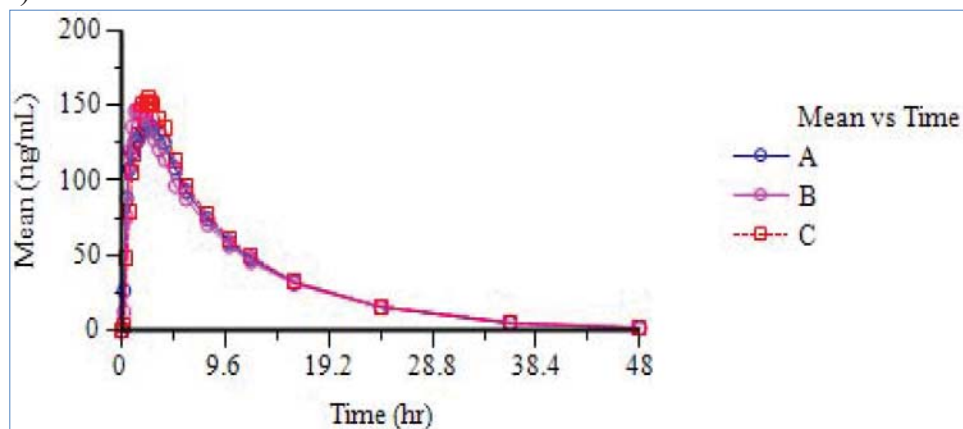
Study 198/18 was a Phase 1, open label, randomized, single dose, three treatment, three period, three sequence, crossover food effect study in healthy male subjects. The subjects were

administered tramadol hydrochloride oral solution 50 mg under fed and fasted conditions and Ultram tablet 50 mg under fed conditions.

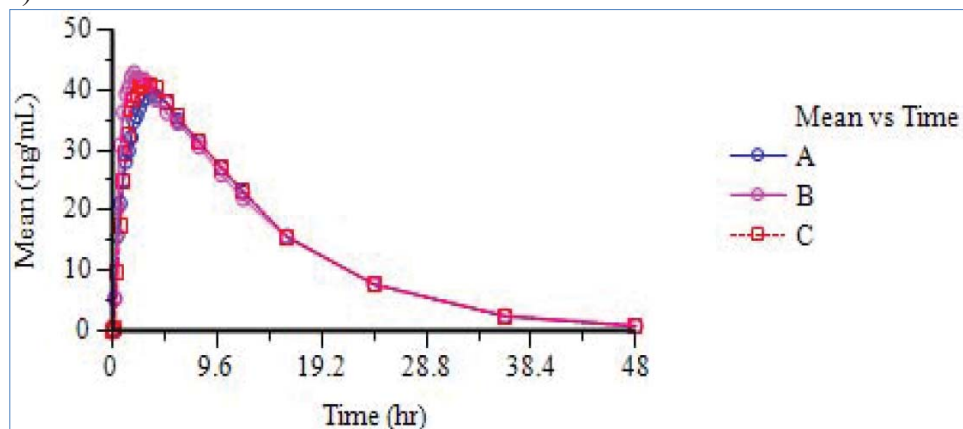
The mean plasma concentrations profiles of tramadol and O-desmethyl tramadol are presented in Figure 2.

Figure 2 Mean tramadol (a) and M1, O-desmethyl tramadol (b) plasma concentration versus time under fed and fasted conditions (Study 198/18)

a)



b)



A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed

B: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fasted

C: 'Reference Formulation' - Ultram 50 mg tablet Fed

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\16-2-6-individuals-efficacy-response-data-fast-fed-1.pdf; p. 11/50

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\16-2-6-individuals-efficacy-response-data-fast-fed-1.pdf; p. 13/50

Tables 1 and 2 display plasma pharmacokinetic parameters (mean±SD) of tramadol and metabolite M1, O-desmethyl tramadol, from Studies 197/18 and 198/18, respectively.

Table 1 Summary of Pharmacokinetic Results for Tramadol from Studies 197/18 and 198/18

Study	Parameters	Test (T) Tramadol HCl oral solution 5 mg/mL Fasted	Reference (R) Ultram tablet 50 mg Fasted	Test (A) Tramadol HCl oral solution 5 mg/mL Fed	Reference (C) Ultram tablet 50 mg Fed
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
197/18	T _{max} [#] (hr)	1.5 (0.50 – 2.50)	1.5 (0.75 – 3.0)	-	-
	C _{max} (ng/mL)	180.20 ± 33.81	173.51 ± 29.59	-	-
	AUC _{0-t} (hr*ng/mL)	1623.93 ± 502.43	1681.64 ± 578.06	-	-
	AUC _{0-inf} (hr*ng/mL)	1658.31 ± 525.97	1721.47 ± 624.72	-	-
	t _{1/2} (hr)	7.65 ± 1.63	7.61 ± 1.82	-	-
198/18	T _{max} [#] (hr)	1.88 (0.75 – 3.00)	-	2.00 (0.50 – 3.50)	1.875 (0.75 – 4.00)
	C _{max} (ng/mL)	160.15 ± 34.10	-	146.22 ± 28.50	186.63 ± 32.87
	AUC _{0-t} (hr*ng/mL)	1577.24 ± 585.27	-	1606.04 ± 574.38	1650.63 ± 514.55
	AUC _{0-inf} (hr*ng/mL)	1610.43 ± 616.17	-	1635.90 ± 594.44	1681.64 ± 536.06
	t _{1/2} (hr)	7.68 ± 1.51	-	7.33 ± 1.194	7.42 ± 1.42

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Table 2 Summary of Pharmacokinetic Results for metabolite M1, O-desmethyl tramadol, from Studies 197/18 and 198/18

Study	Parameters	Test (T) Tramadol HCl oral solution 5 mg/mL Fasted	Reference (R) Ultram tablet 50 mg Fasted	Test (A) Tramadol HCl oral solution 5 mg/mL Fed	Reference (C) Ultram tablet 50 mg Fed
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
197/18	T _{max} [#] (hr)	2.0 (0.50 – 5.00)	2.25 (1.25 – 10.00)	-	-
	C _{max} (ng/mL)	47.77 ± 19.06	46.14 ± 18.28	-	-
	AUC _{0-t} (hr*ng/mL)	624.12 ± 205.58	624.10 ± 199.82	-	-
	AUC _{0-inf} (hr*ng/mL)	638.95 ± 207.13	639.26 ± 198.04	-	-
	t _{1/2} (hr)	7.94 ± 1.65	8.06 ± 2.11	-	-
198/18	T _{max} [#] (hr)	2.00 (0.75 – 3.50)	-	3.50 (1.75 – 5.00)	2.125 (1.00 – 5.00)
	C _{max} (ng/mL)	45.66 ± 13.95	-	41.35 ± 11.53	44.79 ± 14.05
	AUC _{0-t} (hr*ng/mL)	635.30 ± 181.16	-	623.14 ± 167.54	626.76 ± 143.85
	AUC _{0-inf} (hr*ng/mL)	648.10 ± 181.52	-	635.05 ± 169.97	639.90 ± 145.57
	t _{1/2} (hr)	8.01 ± 1.47	-	7.56 ± 1.10	7.70 ± 1.176

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\report-body-fasting.pdf; p.74/112

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 80/128

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Bioequivalence analysis

Study 197/8

Base on tramadol exposure information, under fasted conditions, the bioequivalence analysis results indicated that tramadol HCl oral solution 5 mg/mL and Ultram 50 mg tablet were bioequivalent; the 90% CIs for the geometric least squares mean ratios of AUC_{0-t}, AUC_{0-inf}, and C_{max} for all analytes were within the 80% to 125% range.

The metabolite M1, O-desmethyl tramadol, exposure information also indicated that it was bioequivalent between tramadol HCl oral solution 5 mg/mL and Ultram 50 mg tablet.

Refer to Tables 7 and 8 in this review for detailed numbers of the bioequivalence analysis in Study 197/8.

Study 198/8

Food effect statistical analysis of tramadol HCl oral solution

Base on tramadol exposure information, no food effect was observed for tramadol HCl oral solution, based on the bioequivalence analysis results (the 90% CIs for the geometric least squares mean ratios of AUC_{0-t}, AUC_{0-inf}, and C_{max} for all analytes were within the 80% to 125% range).

The metabolite M1, O-desmethyl tramadol, exposure information also exhibited the same conclusion.

Under fed condition comparison between tramadol HCl oral solution and Ultram tablet

Under fed conditions, the extent of tramadol and its metabolite, O-desmethyl tramadol, exposures met BE criteria between tramadol HCl oral solution 5 mg/mL and Ultram 50 mg tablet, with an exception of tramadol C_{max} being slightly lower [not bioequivalent with point estimate of 78.12% (90% CI: 73.25-83.31)] post tramadol HCl oral solution administration compared to Ultram tablet. The slight difference in tramadol C_{max} between the two products under fed conditions are not deemed to be clinically significant since the two products (tramadol HCl oral solution 5 mg/mL and Ultram 50 mg tablet) are bioequivalent under fasted conditions and there is no food effect observed for the Applicant's product.

Therefore, tramadol HCl oral solution can be taken regardless of food.

Refer to Tables 13, 14, 15 and 16 in this review for detailed numbers of the bioequivalence analysis in Study 198/8.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

The proposed package insert is identical to the text of the Ultram Tablet 50 mg Package Insert with the following exceptions, which reflect the change from Ultram Tablet to the proposed tramadol oral solution:

1. ULTRAM is replaced with TRAMADOL HYDROCHLORIDE ORAL SOLUTION.
2. The volume of TRAMADOL HYDROCHLORIDE ORAL SOLUTION in milliliters is added after the dose of tramadol in milligrams, e.g., “25 mg (5 mL)” replaces “25 mg.”
3. “Tablet” and “Tablets” are replaced with “Oral Solution.”
4. “ULTRAM” is replaced with “Tramadol HCl Tablets,” “tramadol hydrochloride,” or “tramadol.”

There are no issues with the proposed Labeling since tramadol BE was established between the Applicant’s product and Ultram 50 mg tablet under fasted conditions.

Additional information may be included in Section 12.3 of the proposed label to describe the comparative bioavailability data between Applicant’s product and the reference product Ultram Tablet. The draft language is proposed below. When this review is submitted into DARRTS, the discussion is still ongoing on this topic.

“Following a single dose of tramadol oral solution 50 mg and Ultram 50 mg tablet under fasted conditions in healthy adult subjects, the following table displays mean plasma concentrations of tramadol and M1 pharmacokinetic parameters (Table X).

Table X Summary of single dose tramadol and M1 pharmacokinetic parameters under fasted condition in healthy adult subjects

Parameters	Tramadol hydrochloride oral solution 50 mg Fasted	Ultram tablet 50 mg Fasted	Tramadol hydrochloride oral solution 50 mg Fasted	Ultram tablet 50 mg Fasted
	Tramadol		M1	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
T _{max} [#] (hr)	1.5 (0.50 – 2.50)	1.5 (0.75 – 3.0)	2.0 (0.50 – 5.00)	2.25 (1.25 – 10.00)
C _{max} (ng/mL)	180.20 ± 33.81	173.51 ± 29.59	47.77 ± 19.06	46.14 ± 18.28
AUC _{0-t} (hr*ng/mL)	1623.93 ± 502.43	1681.64 ± 578.06	624.12 ± 205.58	624.10 ± 199.82
AUC _{0-inf} (hr*ng/mL)	1658.31 ± 525.97	1721.47 ± 624.72	638.95 ± 207.13	639.26 ± 198.04
t _{1/2} (hr)	7.65 ± 1.63	7.61 ± 1.82	7.94 ± 1.65	8.06 ± 2.11

median (min – max)”

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

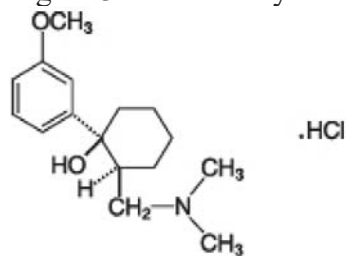
3.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substances in tramadol hydrochloride oral solution?

Tramadol hydrochloride oral solution contains tramadol as an active ingredient. According to Ultram Tablet's Package Insert, the following information is provided:

The chemical name for tramadol hydrochloride is ($\pm$)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The molecular weight of tramadol hydrochloride is 299.8. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7.

Tramadol hydrochloride structural formula is shown in Figure 3.

Figure 3 Tramadol hydrochloride structural formula



(Source: Ultram Package Insert)

3.1.2 Tramadol hydrochloride oral solution formulation

The quantitative compositions of the proposed drug products (per unit basis), with the functions of the inactive ingredients, are presented in Table 3.

Table 3 Composition of Tramadol Hydrochloride Oral Solution, 25 mg/5 mL

Tramadol Hydrochloride Oral Solution, 25 mg/5 mL			
Ingredient	Weight (mg per 5 mL)	% (w/w)	Function
Tramadol Hydrochloride USP	25.000	(b) (4)	Active ingredient
Propylene Glycol USP	(b) (4)	(b) (4)	(b) (4)
Glycerin USP	(b) (4)	(b) (4)	(b) (4)
Sodium Benzoate NF	(b) (4)	(b) (4)	(b) (4)
Sodium Citrate Dihydrate USP	(b) (4)	(b) (4)	(b) (4)
Citric Acid USP (b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucralose (b) (4) NF	(b) (4)	(b) (4)	(b) (4)
Grape Flavor (b) (4)	(b) (4)	(b) (4)	(b) (4)
Purified Water	(b) (4)	(b) (4)	(b) (4)
Total Per 5 mL		100%	

Source: m3\32 -body-data\32p-drug-prod\tramadol-hcl-oral-solution-(b) (4)\32p1-desc-comp.pdf; p.1/3

Tramadol hydrochloride oral solution formulation used in the PK studies is listed below in Table 4, which the ingredients and the quantitative compositions are the same as Table 3.

Table 4 Formulation used for pharmacokinetic studies

Ingredient	Amount (mg) / mL	Amount (% w/w)
	5 mg/mL	5 mg/mL
Tramadol Hydrochloride USP	(b) (4)	(b) (4)
Propylene Glycol USP	(b) (4)	(b) (4)
Glycerin USP	(b) (4)	(b) (4)
Sodium Benzoate NF	(b) (4)	(b) (4)
Sodium Citrate Dihydrate USP	(b) (4)	(b) (4)
Citric Acid USP (b) (4)	(b) (4)	(b) (4)
Sucralose (b) (4)	(b) (4)	(b) (4)
Grape Flavor (b) (4)	(b) (4)	(b) (4)
Purified Water	(b) (4)	(b) (4)
Total		100.0

Source: m2\27-clin-sum\ summary-biopharm-1.pdf; Table 6; p.11/28

3.1.4 What is proposed route of administration for tramadol hydrochloride oral solution?

Tramadol hydrochloride oral solution is proposed to be administered via an oral route.

3.2 General Pharmacology and Pharmacokinetic Characteristics

3.2.1 What are the proposed mechanism(s) of actions for tramadol?

The following information has been obtained from Ultram Tablet with respect tramadol. Ofirmev's active ingredient is acetaminophen. [Source: Ultram® Tablet; 12.1 Mechanism of Action; N 20281].

12.1 Mechanism of Action

ULTRAM contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin reuptake. Although the mode of action is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. Tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound [see Clinical Pharmacology (12.2)].

Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information from fasted Study 197/18 provide pivotal or supportive evidence?

Summary: Following a single dose of tramadol oral 5 mg/mL solution or Ultram 50 mg tablet under fasted conditions, mean plasma concentrations of tramadol (noted that as well for the metabolite, O-desmethyl tramadol) were similar between treatments. Under fasted conditions, tramadol oral 5 mg/mL solution is bioequivalent to Ultram 50 tablet as assessed by AUC_{0-t}, AUC_{0-inf}, and C_{max} for tramadol plasma concentrations (the 90% CIs for the geometric least squares means ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} for all analytes were within the predefined bioequivalence acceptance limits of 80% to 125%). It is noted that the metabolite, O-desmethyl tramadol, was also bioequivalent between treatments.

Reviewer comment: The results from Study 197/18 are acceptable.

As indicated previously the basis for submission is reliance on the previous findings of safety and efficacy of Ultram (Tramadol Hydrochloride 50 mg Tablets; N 20281; by Janssen Pharmaceuticals, Inc.) by providing tramadol BE information only (additionally, metabolite, O-desmethyl tramadol information was submitted). No clinical trials were conducted.

Study 197/18 was a Phase 1, open label, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study in healthy male adult subjects (between 18-45 years of age with BMI between 18.50 - 24.90 kg/m²; BW at least 50 kg) after overnight fasting of at least 10 hr. The following treatments were administered:

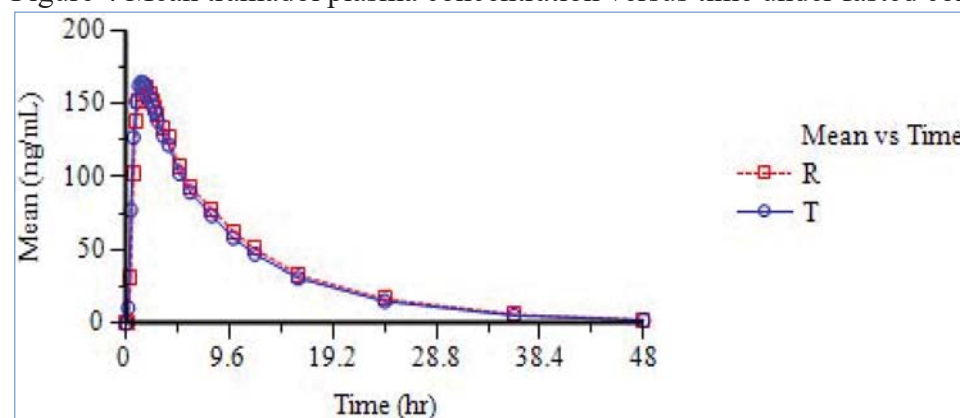
Treatment	Product	Fasted	Lot number
Test	Tramadol hydrochloride oral solution 5 mg/mL	Fasted	50 mg/10 mL; Lot Number: CL PB525
Reference	Ultram tablet 50 mg	Fasted	50 mg; Lot Number: CL 17GG660; Janssen Pharmaceuticals, Inc.

Each treatment period was separated by a washout interval of at least 7 days. The study was conducted in Andhra Pradesh, India.

Thirty-six subjects (Asian) participated, which 31 subjects completed the study. Thirty-three subjects were analyzed (two subjects discontinued: (b) (6) (vomiting) and (b) (6) (epigastric pain); noted that subjects (b) (6) & (b) (6) were included in the analysis due to only missing two samples). Blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hr post dose. Analysis of tramadol (its metabolite O-desmethyl tramadol) in plasma concentration was performed by a validated LC-MS/MS analytical method.

The mean plasma concentrations profiles of tramadol and metabolite are presented in Figures 4 and 5, respectively.

Figure 4 Mean tramadol plasma concentration versus time under fasted conditions (Study 197/18)

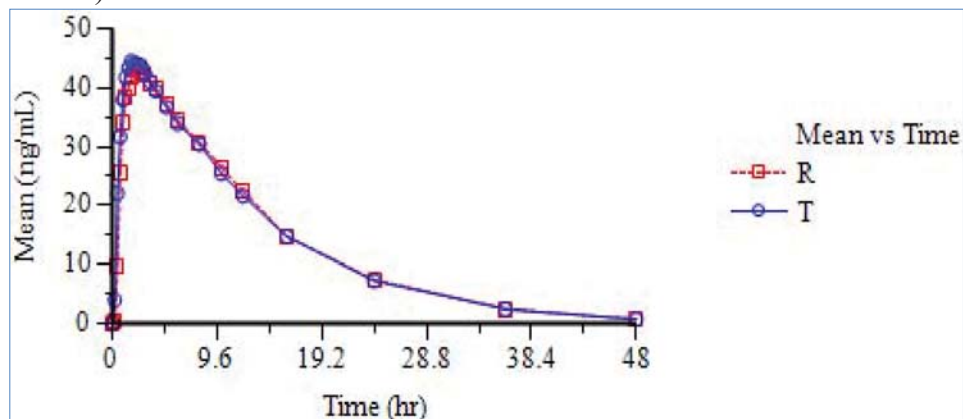


Test Formulation: Tramadol hydrochloride oral solution 5 mg/mL fasted

Reference Formulation: Ultram tablet 50 mg fasted

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\16-2-6-individuals-efficacy-response-data-fasting-1.pdf; p.10/79

Figure 5 Mean O-desmethyl tramadol plasma concentration versus time under fasted conditions 197/18)



Test Formulation: Tramadol hydrochloride oral solution 5 mg/mL fasted

Reference Formulation: Ultram tablet 50 mg fasted

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\16-2-6-individuals-efficacy-response-data-fasting-1.pdf; p.12/79

Plasma pharmacokinetic parameters (mean±SD) of tramadol and metabolite, O-desmethyl tramadol, are presented in Tables 5 and 6, respectively.

Table 5 Summary of Pharmacokinetic Results for Tramadol (Study 197/18)

Parameters	Test (T) Tramadol hydrochloride oral solution 5 mg/mL Fasted	Reference (R) Ultram tablet 50 mg Fasted
	Mean ± SD	Mean ± SD
T _{max} [#] (hr)	1.5 (0.50 – 2.50)	1.5 (0.75 – 3.0)
C _{max} (ng/mL)	180.20 ± 33.81	173.51 ± 29.59
AUC _{0-t} (hr*ng/mL)	1623.93 ± 502.43	1681.64 ± 578.06
AUC _{0-inf}	1658.31 ± 525.97	1721.47 ± 624.72
t _{1/2} (hr)	7.65 ± 1.63	7.61 ± 1.82

For T_{max} median (min – max)

Test Formulation: Tramadol hydrochloride oral solution 5 mg/mL fasted

Reference Formulation: Ultram tablet 50 mg fasted

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\report-body-fasting.pdf; p.73/112

Table 6 Summary of Pharmacokinetic Results for O-Desmethyl Tramadol (Study 197/18)

Parameters	Test (T) Tramadol hydrochloride oral solution 5 mg/mL Fasted	Reference (R) Ultram tablet 50 mg Fasted
	Mean $\pm$ SD	Mean $\pm$ SD
T _{max} [#] (hr)	2.0 (0.50 – 5.00)	2.25 (1.25 – 10.00)
C _{max} (ng/mL)	47.77 $\pm$ 19.06	46.14 $\pm$ 18.28
AUC _{0-t} (hr*ng/mL)	624.12 $\pm$ 205.58	624.10 $\pm$ 199.82
AUC _{0-inf}	638.95 $\pm$ 207.13	639.26 $\pm$ 198.04
t _{1/2} (hr)	7.94 $\pm$ 1.65	8.06 $\pm$ 2.11

For T_{max} median (min – max)

Test Formulation: Tramadol hydrochloride oral solution 5 mg/mL fasted

Reference Formulation: Ultram tablet 50 mg fasted

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\report-body-fasting.pdf; p.74/112

The mean tramadol and its metabolite, O-desmethyl tramadol, exposures (C_{max}, AUC_{0-t} and AUC_{0-inf}) were similar for both treatments under fasting conditions.

Statistical analyses of the log-transformed plasma PK parameters of tramadol and metabolite, O-desmethyl tramadol, under fasting conditions are presented in Tables 7 and 8, respectively.

Table 7 Statistical Analysis of Plasma Pharmacokinetic Parameters of tramadol (Study 197/18)

Parameters	Geometric Mean		% Ratio Test/Ref	90% CI	
	Test (Tramadol hydrochloride oral solution 5 mg/mL) Fasted	Reference (ULTRAM) Fasted		Lower	Upper
C _{max} (ng/mL)	177.46	171.35	103.56	98.68	108.70
AUC _{0-t} (hr×ng/mL)	1553.77	1609.16	96.56	93.62	99.59
AUC _{0-∞} (hr×ng/mL)	1584.24	1641.66	96.50	93.51	99.59

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\report-body-fasting.pdf; p.91/112

Table 8 Statistical Analysis of Plasma Pharmacokinetic Parameters of metabolite, O-desmethyl tramadol (Study 197/18)

Parameters	Geometric Mean		% Ratio Test/Ref	90% CI	
	Test (Tramadol hydrochloride oral solution 5 mg/mL) Fasted	Reference (ULTRAM) Fasted		Lower	Upper
C _{max} (ng/mL)	42.75	40.99	104.29	99.70	109.08
AUC _{0-t} (hr×ng/mL)	578.40	580.08	99.71	96.84	102.66
AUC _{0-∞} (hr×ng/mL)	594.09	597.87	99.37	96.41	102.42

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\report-body-fasting.pdf; p.92/112

Base on tramadol exposure information, under fasted conditions, the bioequivalence analysis results indicated that tramadol hydrochloride oral solution 5 mg/mL and Ultram 50 mg tablet were bioequivalent; the 90% CIs for the geometric least squares mean ratios of AUC_{0-t}, AUC_{0-inf}, and C_{max} for all analytes were within the 80% to 125% range.

Metabolite, O-desmethyl tramadol, exposure information also indicated that it was bioequivalent under fasted conditions between tramadol hydrochloride oral solution 5 mg/mL and Ultram 50 mg tablet.

3.3.2 To what extent does the available clinical pharmacology information from food effect Study 198/18 provide pivotal or supportive evidence?

Summary: Following a single dose of tramadol oral 5 mg/mL solution under fed conditions, no food effect was observed based on tramadol exposure information (bioequivalence analysis results indicated that the 90% CIs for the geometric least squares mean ratios of AUC_{0-t}, AUC_{0-inf}, and C_{max} were within the 80% to 125% range). Metabolite, O-desmethyl tramadol, exposure information also exhibited the same conclusion.

Under fed conditions, the extent of tramadol and its metabolite, O-desmethyl tramadol, exposures were similar between tramadol hydrochloride oral solution 5 mg/mL and Ultram 50 mg tablet, with an exception of tramadol C_{max} being slightly lower (not bioequivalent with point estimate of 78.12% (90% CI: 73.25-83.31) post tramadol hydrochloride oral solution administration compared to Ultram tablet. The slight difference in tramadol C_{max} between the two products under fed conditions are not deemed to be critical since the two products (tramadol hydrochloride oral solution 5 mg/mL and Ultram 50 mg tablet) are bioequivalent under fasted conditions and there is no food effect observed for the Applicant's product.

Reviewer comment: The results from Study 198/18 are acceptable.

Study 198/18 was a Phase 1, open label, randomized, single dose, three treatment, three period, three sequence, crossover food effect study in healthy male subjects (between 18-45 years of age with BMI between 18.50 - 24.90 kg/m²; BW at least 50 kg) after overnight fasting of at least 10 hr, and, 30 minutes after start of the high-fat breakfast. The following treatments were administered:

Treatment	Product	Fed/fasted	Lot number
A	Tramadol hydrochloride oral solution 5 mg/mL	Fed	'Test'; 50 mg/10 mL; Lot Number: CL PB525
B	Tramadol hydrochloride oral solution 5 mg/mL	Fasted	'Test'; 50 mg/10 mL; Lot Number: CL PB525
C	Ultram tablet 50 mg	Fed	'Reference' 50 mg; Lot Number: CL 17GG660; Janssen Pharmaceuticals, Inc.

Each treatment period was separated by a washout interval of at least 7 days. The study was conducted in Andhra Pradesh, India.

It is noted that the Agency recommended to incorporate Ultram 50 mg tablet fed treatment in the study design, in order to compare directly between tramadol hydrochloride oral solution 5 mg/mL and Ultram 50 mg tablet; this was to make sure that QDOLO's extent of food effect is similar to Ultram.

Eighteen subjects (Asian) participated. Blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hr post dose. Analysis of tramadol (its metabolite O-desmethyl tramadol) in plasma concentration was performed by a validated LC-MS/MS analytical method.

Discussion on the test meal:

Originally, the Applicant has had submitted food effect protocol to the Agency on 2/27/18. The following comment was conveyed (safety IND review in DARRTS 3/20/18 and Advice Letter in DARRTS 4/17/18) to the Applicant regarding the test meal contents:

1. With respect to Protocol 015-16, entitled *An open-label, balanced, randomized, single dose, two-treatment (fed vs fasting), two-period, two-sequence, crossover, oral food effect study of Tramadol HCl oral solution (50 mg/10 mL) of (b) (4) in healthy adult human subjects*, the test meal contents are not a typical test meal as recommended in the Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf>. However, we acknowledge that the approximate ratios of protein, carbohydrate, and fat are similar. Since it appears that you will not conduct any additional trials, e.g., Phase 3, we recommend that you follow the guidance document, and utilize the recommended high fat meal in this study.

The Applicant provide the rationale regarding the test meal (via email on 5/30/18) stating that:

Response: The test meal contents are not a typical test meal detailed as an example in the Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies due to the difference in the food habits of the study subjects in this geographic region. However, we ensured that the calorie content from protein, carbohydrate and fats are as recommended in the guideline for the proposed meal.

The menu of high fat high calories breakfast and the contribution of protein, carbohydrate and fats from these menu items along with their associated calorie contents are described in the below table.

High Fat high calorie Breakfast

Name of Cooked Food		Wt. In (g)	Proteins (calories)	Carbohydrates (calories)	Fats (calories)	Total Calories
Example meal ¹	Proposed Meal					
Toast (2_slices]	Bread	40	15.2	103.2	8.1	126.5
Butter	Butter	20	0	0	144.0	144.0
Two Eggs (fried in butter)	Omelet	50	24.0	2.0	103.5	129.5
Two strips of bacon	Chicken Tikka	75	64.0	6.0	88.2	158.2
Hash brown potatoes (4 oz.)	French Fries	25	7.0	60.0	72.0	139.0
Milk (Whole)	Milk (Whole) with 10g Sugar	240 mL	41.28	88.0	140.4	269.6
	Total Calories		151.48	259.12	556.2	966.8
	Total %		15.66%	26.80%	57.52%	100%
	Total = 966.8					

¹Example test meal from FDA guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies.

As per FDA recommendations, a high-fat high-calorie test meal with approximately 800 to 1000 calories needs to be provided for fed BE studies. In the above table, the total calorie content is 966.8 which is in between 800 to 1000 calories. As per guideline, approximately 50 percent of total caloric content of the meal should be from fat. In the above table, the contribution from fat is 556.2 calories which is 57.52% of the total calories content. As per guideline, the test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. In the above table, the test meal derives approximately 151.48, 259.12, and 556.2 calories from protein, carbohydrate, and fat, respectively.

Therefore, the proposed test meal of study 015-16 complies with the regulatory requirement and, unless it is deemed unacceptable, it is our intent to proceed with our proposed test meal. If the proposed test meal is not acceptable, please provide us a detailed rationale. The alternative is to ship pre-packaged meals to the test site in India. This presents several logistics issues that may be of more concern.

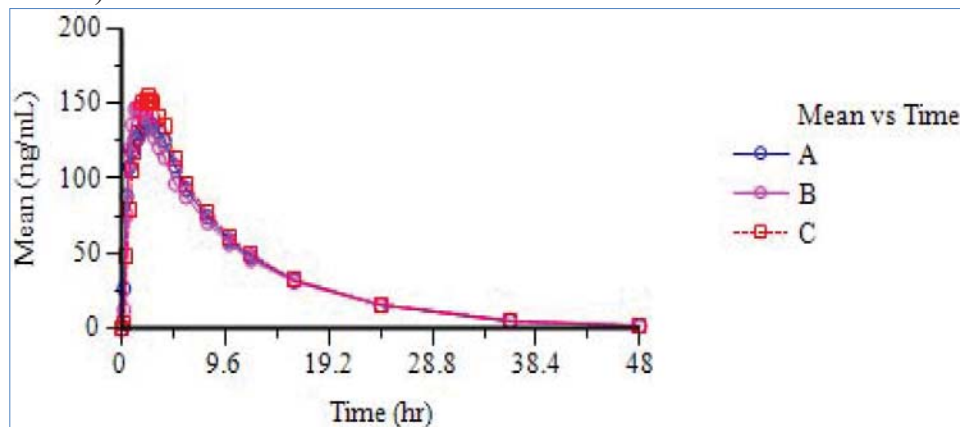
The Applicant's rationale was discussed internally and concluded that the Applicant's proposal was reasonable. The following comment was conveyed to the Applicant (via email dated 5/30/18):

Your proposal appears reasonable. In the protocol, we recommend that you include the rationale stated in your email with the comparative table of food content to justify use of an alternative meal.

Reviewer's comment: No issues regarding the test meal utilized in the food effect study

The mean plasma concentrations profiles of tramadol and metabolite, O-desmethyl tramadol are presented in Figures 6 and 7, respectively.

Figure 6 Mean tramadol plasma concentration versus time under fed and fasted conditions (Study 198/18)



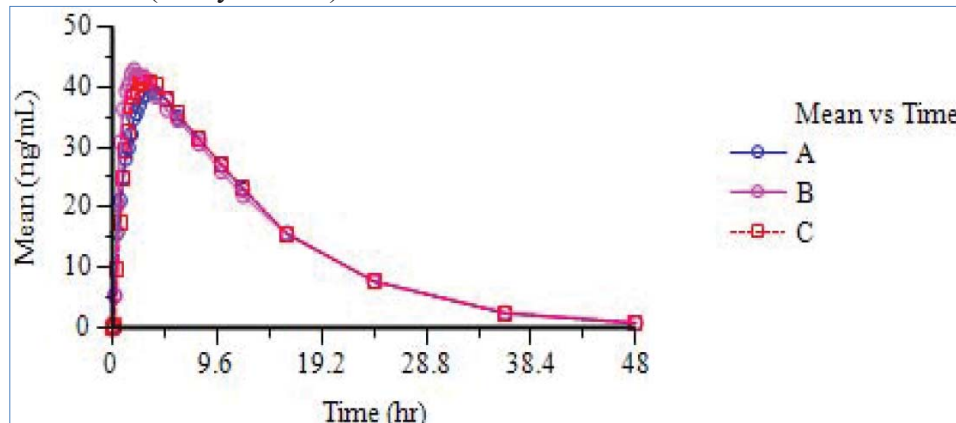
A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed

B: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fasted

C: 'Reference Formulation' - Ultram 50 mg tablet Fed

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\16-2-6-individuals-efficacy-response-data-fast-fed-1.pdf; p. 11/50

Figure 7 Mean O-desmethyl tramadol plasma concentration versus time under fed and fasted conditions (Study 198/18)



A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed

B: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fasted

C: 'Reference Formulation' - Ultram 50 mg tablet Fed

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\16-2-6-individuals-efficacy-response-data-fast-fed-1.pdf; p. 13/50

Food effect PK parameters of tramadol hydrochloride oral solution

Plasma pharmacokinetic parameters (mean±SD) of tramadol and metabolite, O-desmethyl tramadol, are presented in Tables 9 and 10, respectively, following Treatments A and B, tramadol hydrochloride oral solution 5 mg/mL under fed and fasted conditions.

Table 9 Summary of food effect Pharmacokinetic Results for Tramadol following Treatments A and B, tramadol hydrochloride oral solution 5 mg/mL under fed and fasted conditions (Study 198/18)

	Test (A) Tramadol hydrochloride oral solution 5 mg/mL Fed	Test (B) Tramadol hydrochloride oral solution 5 mg/mL Fasted
	Mean ± SD	Mean ± SD
T _{max} [#] (hr)	2.00 (0.50 – 3.50)	1.88 (0.75 – 3.00)
C _{max} (ng/mL)	146.22 ± 28.50	160.15 ± 34.10
AUC _{0-t} (hr*ng/mL)	1606.04 ± 574.38	1577.24 ± 585.27
AUC _{0-inf} (hr*ng/mL)	1635.90 ± 594.44	1610.43 ± 616.17
t _{1/2} (hr)	7.33 ± 1.194	7.68 ± 1.51

For T_{max} median (min – max)

A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed

B: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fasted

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 80/128

Table 10 Summary of food effect Pharmacokinetic Results for O-Desmethyl Tramadol following Treatments A and B, tramadol hydrochloride oral solution 5 mg/mL under fed and fasted conditions (Study 198/18)

	Test (A) Tramadol hydrochloride oral solution 5 mg/mL Fed	Test (B) Tramadol hydrochloride oral solution 5 mg/mL Fasted
	Mean ± SD	Mean ± SD
# T _{max} (hr)	3.50 (1.75 – 5.00)	2.00 (0.75 – 3.50)
C _{max} (ng/mL)	41.35 ± 11.53	45.66 ± 13.95
AUC _{0-t} (hr*ng/mL)	623.14 ± 167.54	635.30 ± 181.16
AUC _{0-inf} (hr*ng/mL)	635.05 ± 169.97	648.10 ± 181.52
t _{1/2} (hr)	7.56 ± 1.10	8.01 ± 1.47

For T_{max} median (min – max)

A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed

B: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fasted

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 80/128

The mean tramadol and its metabolite, O-desmethyl tramadol, exposures (C_{max}, AUC_{0-t} and AUC_{0-inf}) were similar for both treatments under fasted and fed conditions.

Under fed condition PK parameters of tramadol hydrochloride oral solution and Ultram tablet

Plasma pharmacokinetic parameters (mean±SD) of tramadol and metabolite, O-desmethyl tramadol, are presented in Tables 11 and 12, respectively, following Treatments A and C, tramadol hydrochloride oral solution 5 mg/mL and Ultram 50 mg tablet under fed conditions.

Table 11 Summary of under fed conditions Pharmacokinetic Results for Tramadol following Treatments A and C, tramadol hydrochloride oral solution 5 mg/mL and Ultram tablet 50 mg (Study 198/18)

Parameters	Test (A) Tramadol hydrochloride oral solution 5 mg/mL Fed	Reference (C) Ultram tablet 50 mg Fed
	Mean ± SD	Mean ± SD
T _{max} # (hr)	2.00 (0.50 – 3.50)	1.875 (0.75 – 4.00)
C _{max} (ng/mL)	146.22 ± 28.50	186.63 ± 32.87
AUC _{0-t} (hr*ng/mL)	1606.04 ± 574.38	1650.63 ± 514.55
AUC _{0-inf} (hr*ng/mL)	1635.90 ± 594.44	1681.64 ± 536.06
t _{1/2} (hr)	7.33 ± 1.19	7.42 ± 1.42

For T_{max} median (min – max)

A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed

C: 'Reference Formulation' - Ultram 50 mg tablet Fed

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 79/128

Table 12 Summary of under fed conditions Pharmacokinetic Results for O-Desmethyl Tramadol following Treatments A and C, tramadol hydrochloride oral solution 5 mg/mL and Ultram tablet 50 mg (Study 198/18)

	Test (A) Tramadol hydrochloride oral solution 5 mg/mL Fed	Reference (C) Ultram tablet 50 mg Fed
	Mean ± SD	Mean ± SD
T _{max} [#] (hr)	3.50 (1.75 – 5.00)	2.125 (1.00 – 5.00)
C _{max} (ng/mL)	41.35 ± 11.53	44.79 ± 14.05
AUC _{0-t} (hr*ng/mL)	623.14 ± 167.54	626.76 ± 143.85
AUC _{0-inf} (hr*ng/mL)	635.05 ± 169.97	639.90 ± 145.57
t _{1/2} (hr)	7.56 ± 1.10	7.70 ± 1.176

For T_{max} median (min – max)

A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed

C: 'Reference Formulation' - Ultram 50 mg tablet Fed

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 79/128

The mean tramadol and its metabolite, O-desmethyl tramadol, exposures (C_{max}, AUC_{0-t} and AUC_{0-inf}) were similar for both treatments under fed conditions.

Food effect statistical analysis of tramadol hydrochloride oral solution

Statistical analyses of the log-transformed plasma PK parameters of tramadol and metabolite, O-desmethyl tramadol, are presented in Tables 13 and 14, respectively.

Table 13 Food effect statistical analysis of Plasma Pharmacokinetic Parameters of tramadol following Treatments A and B, tramadol hydrochloride oral solution 5 mg/mL under fed and fasted conditions (Study 198/18)

Parameter	Geometric Mean		% Ratio Test/Ref	90% CI	
	A: Test Tramadol hydrochloride oral solution 5 mg/mL Fed	B: Reference Tramadol hydrochloride oral solution 5 mg/mL Fasted		Lower	Upper
C_{max} (ng/mL)	143.62	156.76	91.62	85.91	97.71
AUC_{0-t} (hr×ng/mL)	1515.80	1484.14	102.13	98.49	105.91
$AUC_{0-\infty}$ (hr×ng/mL)	1541.65	1510.52	102.06	98.36	105.91

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 101/128

Table 14 Food effect statistical analysis of Plasma Pharmacokinetic Parameters of metabolite, O-desmethyl tramadol following Treatments A and B, tramadol hydrochloride oral solution 5 mg/mL under fed and fasted conditions (Study 198/18)

Parameter	Geometric Mean		% Ratio Test/Ref	90% CI	
	A: Test Tramadol hydrochloride oral solution 5 mg/mL Fed	B: Reference Tramadol hydrochloride oral solution 5 mg/mL Fasted		Lower	Upper
C_{max} (ng/mL)	39.54	43.06	91.83	86.62	97.35
AUC_{0-t} (hr×ng/mL)	601.08	607.18	99.00	94.86	103.31
$AUC_{0-\infty}$ (hr×ng/mL)	612.89	620.71	98.74	94.72	102.94

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 102/128

Base on tramadol exposure information, no food effect was observed for tramadol hydrochloride oral solution, based on the bioequivalence analysis results (the 90% CIs for the geometric least squares mean ratios of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} for all analytes were within the 80% to 125% range). Metabolite, O-desmethyl tramadol, exposure information also exhibited the same conclusion.

Under fed condition statistical analysis between tramadol hydrochloride oral solution and Ultram tablet

Statistical analyses of the log-transformed plasma PK parameters of tramadol and metabolite, O-desmethyl tramadol, between tramadol hydrochloride oral solution and Ultram tablet are presented in Tables 15 and 16, respectively.

Table 15 Statistical comparison of tramadol PK parameters following Treatments A and C, tramadol hydrochloride oral solution 5 mg/mL and Ultram tablet 50 mg under fed conditions (Study 198/18)

Parameter	Geometric Mean		% Ratio Test/Ref	90% CI	
	A: Test Tramadol hydrochloride oral solution 5 mg/mL Fed	C: Reference Ultram tablet 50 mg Fed		Lower	Upper
C_{max} (ng/mL)	143.62	183.86	78.12	73.25	83.31
AUC_{0-t} (hr×ng/mL)	1515.80	1580.46	95.91	92.49	99.45
$AUC_{0-\infty}$ (hr×ng/mL)	1541.65	1607.66	95.89	92.41	99.51

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 99/128

Table 16 Statistical comparison of metabolite, O-desmethyl tramadol, PK parameters following Treatments A and C, tramadol hydrochloride oral solution 5 mg/mL and Ultram tablet 50 mg under fed conditions (Study 198/18)

Parameter	Geometric Mean		% Ratio Test/Ref	90% CI	
	A: Test Tramadol hydrochloride oral solution 5 mg/mL Fed	C: Reference Ultram tablet 50 mg Fed		Lower	Upper
C_{max} (ng/mL)	39.54	42.76	92.47	87.22	98.03
AUC_{0-t} (hr×ng/mL)	601.08	609.96	98.54	94.43	102.84
$AUC_{0-\infty}$ (hr×ng/mL)	612.89	623.17	98.35	94.34	102.53

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p. 100/128

Under fed conditions, the extent of tramadol and its metabolite, O-desmethyl tramadol, exposures met BE criteria between tramadol HCl oral solution 5 mg/mL and Ultram 50 mg tablet, with an exception of tramadol C_{max} being slightly lower [not bioequivalent with point estimate of 78.12% (90% CI: 73.25-83.31)] post tramadol HCl oral solution administration compared to Ultram tablet. The slight difference in tramadol C_{max} between the two products under fed conditions are not deemed to be clinically significant since the two products (tramadol HCl oral solution 5 mg/mL and Ultram 50 mg tablet) are bioequivalent under fasted conditions and there is no food effect observed for the Applicant's product.

Therefore, tramadol HCl oral solution can be taken regardless of food.

3.3.3 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and safety.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Pharmacokinetic samples were analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay (LC-MS/MS). Plasma samples were analyzed at (b) (4)

Fasted study 197/18

Sample analysis for this study followed analytical test procedure in Report No: BAR/366-00 entitled, "Simultaneous Quantification of Tramadol and O-Desmethyl Tramadol in K2EDTA human Plasma by using LC-MS/MS for the Study No: 197/18." The following tables, Tables 17 - 20, summarize the analytical method Report No: BAR/366-00.

Table 17 Evaluation of Calibration Curve Standards for Tramadol (ng/mL)

	STD 1	STD 2	STD 3	STD 4	STD 5	STD 6	STD 7	STD 8	STD 9	STD 10
N	20	20	20	20	20	20	20	20	20	20
Average	1.0058	1.9830	5.0154	25.7085	51.3207	100.2033	200.8358	299.7275	392.4577	487.8441
Standard Deviation	0.01407	0.06091	0.10152	0.36004	0.57165	1.03259	2.06330	2.07525	4.31385	8.39748
CV (Precision %)	1.4	3.1	2.0	1.4	1.1	1.0	1.0	0.7	1.1	1.7
Nominal Conc. (ng/mL)	1.002	2.004	5.010	25.049	50.099	100.197	200.395	300.577	400.236	500.295
Accuracy (%)	100.4	99.0	100.1	102.6	102.4	100.0	100.2	99.7	98.1	97.5

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fasting-197-18; p.27/88

Table 18 Evaluation of Calibration Curve Standards for O-Desmethyl Tramadol (ng/mL)

	STD 1	STD 2	STD 3	STD 4	STD 5	STD 6	STD 7	STD 8	STD 9	STD 10
N	19	19	19	19	19	19	19	19	19	19
Average	0.4938	1.0132	2.5576	12.7442	25.4996	50.8689	99.3392	147.4777	195.4446	244.3445
Standard Deviation	0.01067	0.03972	0.05207	0.16892	0.33436	2.41120	0.88198	1.80653	2.45346	2.91597
CV (Precision %)	2.2	3.9	2.0	1.3	1.3	4.7	0.9	1.2	1.3	1.2
Nominal Conc. (ng/mL)	0.500	1.000	2.500	12.499	25.003	50.006	100.012	150.032	200.043	250.054
Accuracy (%)	98.8	101.3	102.3	102.0	102.0	101.7	99.3	98.3	97.7	97.7

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fasting-197-18; p.30/88

Table 10 Evaluation of Quality Control Samples for Tramadol (ng/mL)

	HQC	MQC	AQC	LQC
N	86	86	86	86
Average	351.3961	238.9330	6.9637	2.4323
Standard Deviation	7.95981	4.48575	0.15584	0.08744
CV (Precision %)	2.3	1.9	2.2	3.6
Nominal Conc. (ng/mL)	375.936	250.373	7.511	2.554
Accuracy (%)	93.5	95.4	92.7	95.2

HQC: High Quality Control; MQC: Middle Quality Control; AQC: Additional Quality Control; LQC: Low Quality Control
Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fasting-197-18; p.46/88

Table 20 Evaluation of Quality Control Samples for O-Desmethyl Tramadol (ng/mL)

	HQC	MQC	AQC	LQC
N	84	84	84	84
Average	181.6936	122.2451	4.6612	1.2442
Standard Deviation	4.21619	1.92836	0.11369	0.05660
CV (Precision %)	2.3	1.6	2.4	4.5
Nominal Conc. (ng/mL)	188.415	125.485	5.019	1.275
Accuracy (%)	96.4	97.4	92.9	97.6

HQC: High Quality Control; MQC: Middle Quality Control; AQC: Additional Quality Control; LQC: Low Quality Control
Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fasting-197-18; p.50/88

Food effect study 198/18

Sample analysis for this study followed analytical test procedure in Report No: BAR/373-00 entitled, "Simultaneous Quantification of Tramadol and O-Desmethyl Tramadol in K2EDTA human Plasma by using LC-MS/MS for the Study No: 198/18." The following tables, Tables 21 - 24, summarize the analytical method Report No: BAR/373-00.

Table 21 Evaluation of Calibration Curve Standards for Tramadol (ng/mL)

	STD 1	STD 2	STD 3	STD 4	STD 5	STD 6	STD 7	STD 8	STD 9	STD 10
N	20	20	20	20	20	20	20	20	20	20
Average	1.0076	1.9776	4.9898	25.8485	51.3068	100.4013	200.6512	299.2111	393.2472	487.3721
Standard Deviation	0.01289	0.05390	0.09969	0.23269	0.57907	1.14030	1.75605	5.13732	6.84743	5.43992
CV (Precision %)	1.3	2.7	2.0	0.9	1.1	1.1	0.9	1.7	1.7	1.1
Nominal Conc. (ng/mL)	1.002	2.004	5.01	25.049	50.099	100.197	200.395	300.577	400.236	500.295
Accuracy (%)	100.6	98.7	99.6	103.2	102.4	100.2	100.1	99.5	98.3	97.4

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fast-fed-198-18; p.20/77

Table 22 Evaluation of Calibration Curve Standards for O-Desmethyl Tramadol (ng/mL)

	STD 1	STD 2	STD 3	STD 4	STD 5	STD 6	STD 7	STD 8	STD 9	STD 10
N	20	20	20	20	20	20	20	20	20	20
Average	0.4900	1.0617	2.5357	12.6628	25.3425	50.2700	99.0037	149.3319	195.5252	244.6084
Standard Deviation	0.01306	0.09738	0.06637	0.21154	0.34295	0.58836	1.24668	2.52456	2.60563	3.00023
CV (Precision %)	2.7	9.2	2.6	1.7	1.4	1.2	1.3	1.7	1.3	1.2
Nominal Conc. (ng/mL)	0.500	1.000	2.500	12.499	25.003	50.006	100.012	150.032	200.043	250.054
Accuracy (%)	98.0	106.2	101.4	101.3	101.4	100.5	99.0	99.5	97.7	97.8

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fast-fed-198-18; p.22/77

Table 23 Evaluation of Quality Control Samples for Tramadol (ng/mL)

	HQC	MQC	AQC	LQC
N	80	80	80	80
Average	350.4387	240.4007	7.2135	2.4014
Standard Deviation	6.16920	4.76132	0.21818	0.09263
CV (Precision %)	1.8	2.0	3.0	3.9
Nominal Conc. (ng/mL)	375.936	250.373	7.511	2.554
Accuracy (%)	93.2	96.0	96.0	94.0

HQC: High Quality Control; MQC: Middle Quality Control; AQC: Additional Quality Control; LQC: Low Quality Control
Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fast-fed-198-18; p.32/77

Table 24 Evaluation of Quality Control Samples for O-Desmethyl Tramadol (ng/mL)

	HQC	MQC	AQC	LQC
N	80	80	80	80
Average	180.2986	121.1992	4.7866	1.2179
Standard Deviation	3.29805	2.40071	0.13514	0.07559
CV (Precision %)	1.8	2.0	2.8	6.2
Nominal Conc. (ng/mL)	188.415	125.485	5.019	1.275
Accuracy (%)	95.7	96.6	95.4	95.5

HQC: High Quality Control; MQC: Middle Quality Control; AQC: Additional Quality Control; LQC: Low Quality Control
Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\bioanalyt-analyt-tramadol-fast-fed-198-18; p.36/77

Bioanalytical Method Validation Report No. BMVR174-00

The reports, No: BAR/366-00 and BAR/373-00, were previously validated over the range of 1.002 ng/mL to 500.456 ng/mL and 0.500 ng/mL to 250.168 ng/mL for tramadol and O-desmethyl tramadol, respectively, as reported in bioanalytical project number, Bioanalytical Method Validation Report No. BMVR174-00 (see Table x for validation method summary table. The method is linear over the range of 1.002 ng/mL to 500.456 ng/mL, and, 0.500 ng/mL to 250.168 ng/mL for tramadol and O-desmethyl tramadol, respectively. Tables 25 and 26 summarized the bioanalytical method validation findings for tramadol and O-desmethyl tramadol, respectively.

Table 25 Bioanalytical Method Validation - Tramadol (Fasting Study-197/18 and Fasting/Fed Study- 198/18)

Information Requested	Data				
Analyte	Tramadol				
Internal standard (IS)	Tramadol -D6				
Method description	The Analytes Tramadol and O-Desmethyl Tramadol & the Internal standards Tramadol– D6 and O-Desmethyl Tramadol – D6 were extracted from a 100µL of aliquot of human K ₂ EDTA plasma using Liquid Liquid Extraction method according to procedure mentioned in STP174-01. The samples are injected into a LC equipped with MS/MS. The mobile phase was a mixture of 2mM Ammonium Acetate with 0.0165% Formic Acid in water: Acetonitrile (20:80). The detection method used was tandem mass spectrometry. The validated calibration range of this assay is from 1.002 ng/mL to 500.456 ng/mL for Tramadol and 0.500 ng/mL to 250.168 ng/mL for O-Desmethyl Tramadol.				
Limit of quantification	1.002 ng/mL				
Average recovery of drug (%)	80.8				
Average recovery of IS (%)	80.0				
Standard curve concentrations (ng/mL)	1.002, 2.004, 5.010, 25.050, 50.100, 100.200, 200.399, 300.674, 400.365, 500.456.				
QC concentrations (ng/mL)	HQC	DQC	MQC	LQC	LLOQ QC
	375.803	1491.201	250.285	2.553	1.053
QC Intraday precision range (%)	Intraday batch (PA02&PA03) precision ranged from 0.5% to 4.1%.				
QC Intraday accuracy range (%)	Intraday batch (PA02&PA03) accuracy ranged from 97.2% to 106.8%.				
QC Interday precision range (%)	Interday batch (PA01&PA02) precision ranged from 0.5% to 4.1%.				
QC Interday accuracy range (%)	Interday batch (PA01&PA02) accuracy ranged from 92.6% to 102.7%.				
Bench-top stability (hrs)	22 hours 50 minutes @ Bench top temperature.				

Stock stability (days)	09 days 19 hours. @ refrigerator (2°C-8°C)
Processed stability (hrs)	Auto Injector Stability for 58 hours 31 minutes @ 04°C
Freeze-thaw stability (cycles)	05 cycles
Long-term storage stability (days)	216 days @ -70°C ± 15°C & -25°C±5°C
Dilution integrity	Concentration diluted to 4-folds
Selectivity	Interference observed at the retention time of analyte and internal standard in the blank plasma was within the acceptance criteria.

Sources: m2\27-clin-sum\summary-biopharm-1; p.8/28; and, m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\17-7-bioanalytical-method-validation-data-fast.pdf; 70-75/236.

Table 26 Bioanalytical Method Validation - O-desmethyl tramadol (Fasting Study-197/18 and Fasting/Fed Study- 198/18)

Information Requested	Data				
Analyte	O-Desmethyl Tramadol				
Internal standard (IS)	O-Desmethyl Tramadol – D6				
Method description	The Analytes Tramadol and O-Desmethyl Tramadol & the Internal standards Tramadol– D6 and O-Desmethyl Tramadol – D6 were extracted from a 100µL of aliquot of human K ₂ EDTA plasma using Liquid Liquid Extraction method according to procedure mentioned in STP174-01. The samples are injected into a LC equipped with MS/MS. The mobile phase was a mixture of 2mM Ammonium Acetate with 0.0165% Formic Acid in water: Acetonitrile (20:80). The detection method used was tandem mass spectrometry. The validated calibration range of this assay is from 1.002 ng/mL to 500.456 ng/mL for Tramadol and 0.500 ng/mL to 250.168 ng/mL for O-Desmethyl Tramadol.				
Limit of quantification	0.500 ng/mL				
Average recovery of drug (%)	82.5				
Average recovery of IS (%)	81.8				
Standard curve concentrations (ng/mL)	0.500, 1.000, 2.501, 12.505, 25.014, 50.029, 100.057, 150.101, 200.134, 250.168				
QC concentrations (ng/mL)	HQC	DQC	MQC	LQC	LLOQ QC
	188.115	740.453	125.285	1.278	0.525
QC Intraday precision range (%)	Intraday batch (PA02&PA03) precision ranged from 0.4% to 6.2%.				
QC Intraday accuracy range (%)	Intraday batch (PA02&PA03) accuracy ranged from 98.5% to 101.8%.				
QC Interday precision range (%)	Interday batch (PA01&PA02) precision ranged from 0.6% to 7.4%.				
QC Interday accuracy range (%)	Interday batch (PA01&PA02) accuracy ranged from 91.0% to 101.9%.				
Bench-top stability (hrs)	22 hours 50 minutes @ Bench top temperature.				
Stock stability (days)	09 days 19 hours. @ refrigerator (2°C-8°C)				
Processed stability (hrs)	Auto Injector Stability for 58 hours 31 minutes @ 04°C				
Freeze-thaw stability (cycles)	05 cycles				
Long-term storage stability (days)	216 days @ -70°C ± 15°C & -25°C±5°C				
Dilution integrity	Concentration diluted to 4-folds				
Selectivity	Interference observed at the retention time of analyte and internal standard in the blank plasma was within the acceptance criteria.				

Sources: m2\27-clin-sum\summary-biopharm-1; p.9/28; and, m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\study-report-5314-fasted\17-7-bioanalytical-method-validation-data-fast.pdf; 76-81/236.

4.2 Clinical PK and/or PD Assessments

4.2.1 Fasted bioequivalence Study 197/18

Title: An open label, balanced, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study of Tramadol HCl oral solution (50 mg / 10mL) manufactured for (b) (4) and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects under fasting condition.

Report Date: 7/25/19

The following synopsis report was provided by the Applicant:

2.0 SYNOPSIS

Name of Sponsor/Company: (b) (4)	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of the Finished Product: Tramadol HCl oral solution (50 mg / 10mL)	Volume:	
Name of the Active Ingredients: Tramadol Hydrochloride	Page:	
Title of Study: An open label, balanced, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study of Tramadol HCl oral solution (50 mg / 10mL) manufactured for (b) (4) and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects under fasting condition.		
Study Number : 197/18		
Investigators:		
Principal Investigator	Dr. A. Venkata Subba Reddy	
Bioanalytical Investigator	(b) (4)	
Pharmacokinetic & Statistical Investigator		
Study Centre (s): Clinical Facility: Actimus Biosciences Private Limited, 4 th Floor, Varun Towers, Kasturiba Marg, Siripuram, Visakhapatnam-530 003, Andhra Pradesh, India Tel: +91-891-6672-000, 100-200 Fax: +91-891-6672111		
(b) (4)		
Publication (reference): Not Applicable		

Study Period: Clinical phase: Study Start Date: 27 May 2019 (Period-I Check in) Study Completion Date: 07 Jun 2019 (Last Sample collection date) Bioanalytical phase: (b) (4) (b) (4)		Phase of Development: Bioequivalence Phase Intended for NDA
Objectives: 1. To compare the rate and extent of absorption of Tramadol HCl oral solution (50 mg/10 mL) manufactured for (b) (4) and Ultram [®] (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects under fasting condition. 2. To assess the safety and tolerability following oral administration of investigational product.		
Methodology: An open label, balanced, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study. Subjects underwent screening evaluation to determine eligibility within 28 days prior to the check in of 1 st period. Subjects were confined within the facility from at least 11.00 hours before drug administration to 48.00 hours after drug administration. Subjects were randomized to either 10 mL of Test (T) or one tablet of Reference (R). Blood samples were drawn from pre-dose (0.00 hr) collected within 01 hour prior to drug administration and up to 48.00 hours post dose. Analysis of Tramadol in plasma concentration was performed by a validated LC-MS/MS analytical method.		
Number of Subjects (Planned and Analysed)		
Planned and Randomized	:	36 healthy, adult, human subjects were randomized and checked-in to the study.
Withdrawal/ Drop out	:	05 (Five Subjects)
Details of withdrawal/drop out	:	- Subject numbers (b) (4) & (b) (6) were voluntarily withdrawn from the study due to personal reasons after 28.00 hr post dose lunch in period-II. - Subject number (b) (6) was withdrawn from the study due to AE (Vomiting) after 4.00 hr post dose sample in period-I. - Subject number (b) (6) was voluntarily withdrawn from the study due to personal reason during period-II check-in. - Subject number (b) (6) was withdrawn from the study due to AE (Epigastric Pain) after 1.00 hr post dose sample in period-I.
Completed and Analysed	:	31 subjects were completed the study and 33 subjects were analysed. Note: A total of 33 subject samples were utilized for pharmacokinetic and statistical analysis as subject (b) (6) & (b) (6) were only two missing samples.
Diagnosis and Main Criteria for Inclusion: Subjects participated in the study were healthy, adult, males between 18-45 years of age; body mass index of 18.50 and 24.90 Kg/(height in m) ² , with body weight at least 50 kgs. Study participants were of normal health as determined by medical history, demographic data (including sex, ethnicity, race, age, body weight (kg), height (cm) and BMI (kg/m ²), vital signs measurements, 12 lead - ECG, chest X-ray, physical examination and laboratory tests performed within 28 days prior to the check-in of 1 st period. Medical examination, Vitals, Breath Alcohol Analysis (BAA), Urine Drug Screening (UDS) were performed on admission day of each period.		
	Test Product (T)	Reference Product (R)
Name	Tramadol Oral solution 5mg/mL (50 mg / 10mL)	Tramadol HCl (Ultram [®]) 50 mg/Tab
Strength	50 mg / 10 mL	50 mg/ Tab

Manufactured by/ Manufactured for	Manufacturer: (b) (4) Sponsor: (b) (4) (b) (4) (b) (4) (b) (4)	Manufacturer: Janssen Pharmaceuticals, Inc., Sponsor: (b) (4) Southfield (b) (4)
Lot No.	CL PB525	CL 17GG660
Mfg Date	NA	NA
Expiry Date	09/2019	03/2020
Mode of Administration	Oral	Oral
Duration of Treatment: 27 May 2019 to 07 Jun 2019 (from date of period-I check-in to Last study sample collection) Period-I : 27 May 2019 to 30 May 2019 Period-II : 04 Jun 2019 to 07 Jun 2019 Wash out period: At least 07 days, between each Drug administration. Blood Sampling Points: In each period, a total of 24 blood samples (1 x 05ml each) were collected as per the following schedule: Pre-dose (0.00 hour) sample within 01 hour prior to drug administration and the others at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00hrs post dose into 5 mL K ₂ EDTA vacutainers.		
Bioanalytical Method:		
Analytes	Tramadol	O-Desmethyl Tramadol
Analytical Method	LC – MS / MS	LC – MS / MS
Lower Limit of Quantification	1.002 ng/mL	0.500 ng/mL
Calibration Range during Study Sample Analysis	1.002 ng/mL to 500.295 ng/mL	0.500 ng/mL to 250.054 ng/mL
Criteria for Evaluation: Pharmacokinetics: Based on the plasma concentrations of Tramadol and O-Desmethyl Tramadol, the pharmacokinetic parameters: C _{max} , AUC _{0-t} , AUC _{0-inf} , T _{max} , t _{1/2} and K _{e1} were calculated by using "Non-compartmental model" for Treatments Test (I) and Reference (R). Pharmacokinetic analysis was done by using Phoenix® WinNonlin® Software, Version 6.3. Safety: Vitals (Blood Pressure, Pulse Rate and Oral Temperature) were examined on the day of admission at fitness assessment, prior to administration of the study drug (0.00 hr) and at 1.00, 3.00, 6.00, 10.00, 24.00, 36.00 hours post dose (Within ± 45 minutes variation) and at the time of check out (48.00 hours post dose). Blood Pressure was measured in Sitting Position.		
Statistical Methods: Analysis of Variance: Analysis of Variance (ANOVA) was estimated at alpha (α) 0.05 on the ln-transformed PK Parameters C _{max} , AUC _{0-t} and AUC _{0-inf} using PROC GLM procedure of SAS. The analysis of variance model included sequence, subjects nested within sequence, period and treatment as factors. The significance of the sequence effect at alpha (α) 0.10 was tested using the subjects nested within the sequence as the error term. 90% Confidence Intervals: Consistent with the two one-sided tests for Bioequivalence, 90% confidence intervals for the difference between treatments least-square means were calculated for ln-transformed C _{max} , AUC _{0-t} and AUC _{0-inf} . The confidence intervals were expressed as percentages relative to the LSM of the reference treatments. Ratio Analysis: Ratios of means of each test and reference formulations were estimated using the LSM for ln-transformed C _{max} , AUC _{0-t} and AUC _{0-inf} . The geometric means were reported for the ln-transformed C _{max} , AUC _{0-t} and AUC _{0-inf} .		

Descriptive Statistics:

The descriptive statistics (such as Mean, Standard Deviation, Minimum, Median, Maximum, Coefficient of Variation) for the relevant Pharmacokinetic parameters were estimated for both test and reference formulations. The Geometric Mean and Coefficient of Variation were estimated C_{max} , AUC_{0-4} and AUC_{0-inf} . Arithmetic mean and standard deviation were estimated for C_{max} , AUC_{0-4} , AUC_{0-inf} , T_{max} , $t_{1/2}$ and K_{el} .

Bioequivalence Criteria:

Based on the Analysis, Bioequivalence is declared if the Test and Reference ratios of the geometric least squares means for ln-transformed pharmacokinetic parameters C_{max} , AUC_{0-4} and AUC_{0-inf} and their 90% confidence intervals are within 80.00%-125.00% for Tramadol.

Note: The data of metabolite, 'O-Desmethyl Tramadol' was submitted as supportive evidence.

SUMMARY – CONCLUSIONS**SAFETY RESULTS:**

- All the Subjects vital signs were within normal range in both the periods.
- Well-being questionnaire was performed at the time of vital signs monitoring. All the subjects were within normal health status at the time of well-being questionnaire, other than the subjects that experienced adverse events during in-house part of the study.
- Medical examination was performed at check-in and check-out for each study period and all the subjects were found to be in normal health.
- The test and reference products were well tolerated by the subjects.
- Two adverse events were reported during in-house part of the study and both determined to be possibly associated with study drug and expected.
- Refer Table 27 for Adverse event details.
- Subject no (b) (6) had AE (Vomiting) in Period-I post dose, the subject was withdrawn from the study and the AE was resolved upon follow-up of the subject. Refer Subject no (b) (6) Adverse Event Follow Up Recording Form for follow-up details.
- Subject no. (b) (6) had AE (Epigastric Pain) in Period-I post dose, the subject was withdrawn from the study and the AE was resolved upon follow-up of the subject. Refer Subject no (b) (6) Adverse Event Follow Up Recording Form for follow-up details.
- Subject numbers (b) (6) & (b) (6) were voluntarily withdrawn from the study due to personal

reasons after 28.00 hr post dose lunch in period-II.

- Subject number (b) (6) was voluntarily withdrawn due to personal reason during period-II check-in.
- All the post study safety assessments performed at the end of the study were evaluated and found to be normal or with no clinical significance.
- **Serious/Significant adverse events:** No serious adverse events reported during the entire duration of the study.

Deaths: No deaths reported during the entire duration of the study.

PHARMACOKINETIC AND STATISTICAL RESULTS:

The data included subjects who successfully completed the clinical phase. Summarized in Table No's 1A, 2A, 1B and 2B are the pharmacokinetic and statistical results for Tramadol and O-Desmethyl Tramadol inclusive of data from completed subjects.

Tramadol:**Table 1A: Summary of Pharmacokinetic Data for Tramadol**

	Arithmetic Mean $\pm$ SD (N = 33)	
	Test product (T)	Reference product (R)
T_{max} (hr)	1.500 (0.500 – 2.500)	1.500 (0.750 – 3.000)
C_{max} (ng/mL)	180.2017 $\pm$ 33.80524	173.5143 $\pm$ 29.58931
AUC_{0-4} (hr*ng/mL)	1623.9252 $\pm$ 502.42885	1681.6377 $\pm$ 578.06464
AUC_{0-inf} (hr*ng/mL)	1658.3115 $\pm$ 525.96905	1721.4670 $\pm$ 624.71658
$t_{1/2}$ (hr)	7.6460 $\pm$ 1.63351	7.6095 $\pm$ 1.81820
K_{el} (1/hr)	0.0951 $\pm$ 0.02256	0.0959 $\pm$ 0.02193

Note: # For T_{max} median (min – max)

Tramadol:**Table 2A: Geometric Means and Confidence Intervals for Tramadol (N=33)**

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test	Reference		Lower	Upper		
C_{max} (ng/mL)	177.4574	171.3489	103.56	98.68	108.70	1.0000	11.6
AUC_{0-4} (hr*ng/mL)	1553.7687	1609.1581	96.56	93.62	99.59	1.0000	7.4
AUC_{0-inf} (hr*ng/mL)	1584.2425	1641.6618	96.50	93.51	99.59	1.0000	7.6

O-Desmethyl Tramadol:

Table 1B: Summary of Pharmacokinetic Data for O-Desmethyl Tramadol

	Arithmetic Mean $\pm$ SD (N = 33)	
	Test product (T)	Reference product (R)
# T _{max} (hr)	2.000 (0.500 – 5.000)	2.250 (1.250 – 10.000)
C _{max} (ng/mL)	47.7739 $\pm$ 19.06335	46.1375 $\pm$ 18.27749
AUC _{0-t} (hr*ng/mL)	624.1160 $\pm$ 205.57693	624.0954 $\pm$ 199.82172
AUC _{0-inf} (hr*ng/mL)	638.9461 $\pm$ 207.12774	639.2625 $\pm$ 198.04379
t _{1/2} (hr)	7.9352 $\pm$ 1.64827	8.0580 $\pm$ 2.11006
K _{el} (1/hr)	0.0911 $\pm$ 0.01917	0.0904 $\pm$ 0.01862

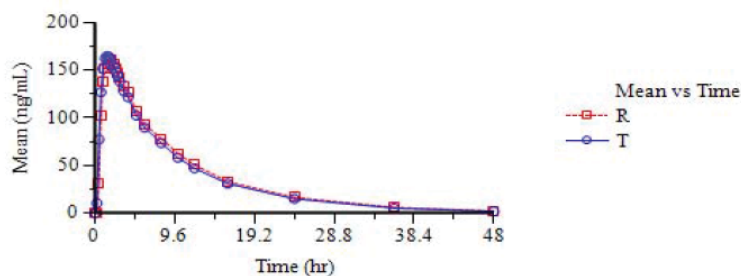
Note: # For T_{max} median (min – max)

O-Desmethyl Tramadol:

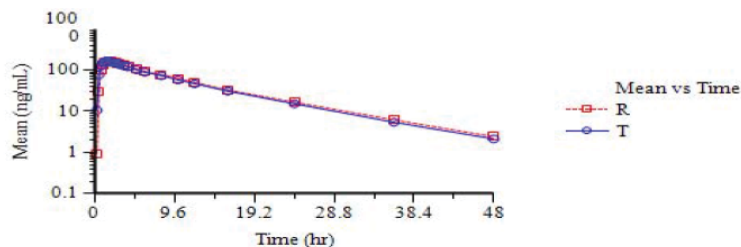
Table 2B: Geometric Means and Confidence Intervals for O-Desmethyl Tramadol (N=33)

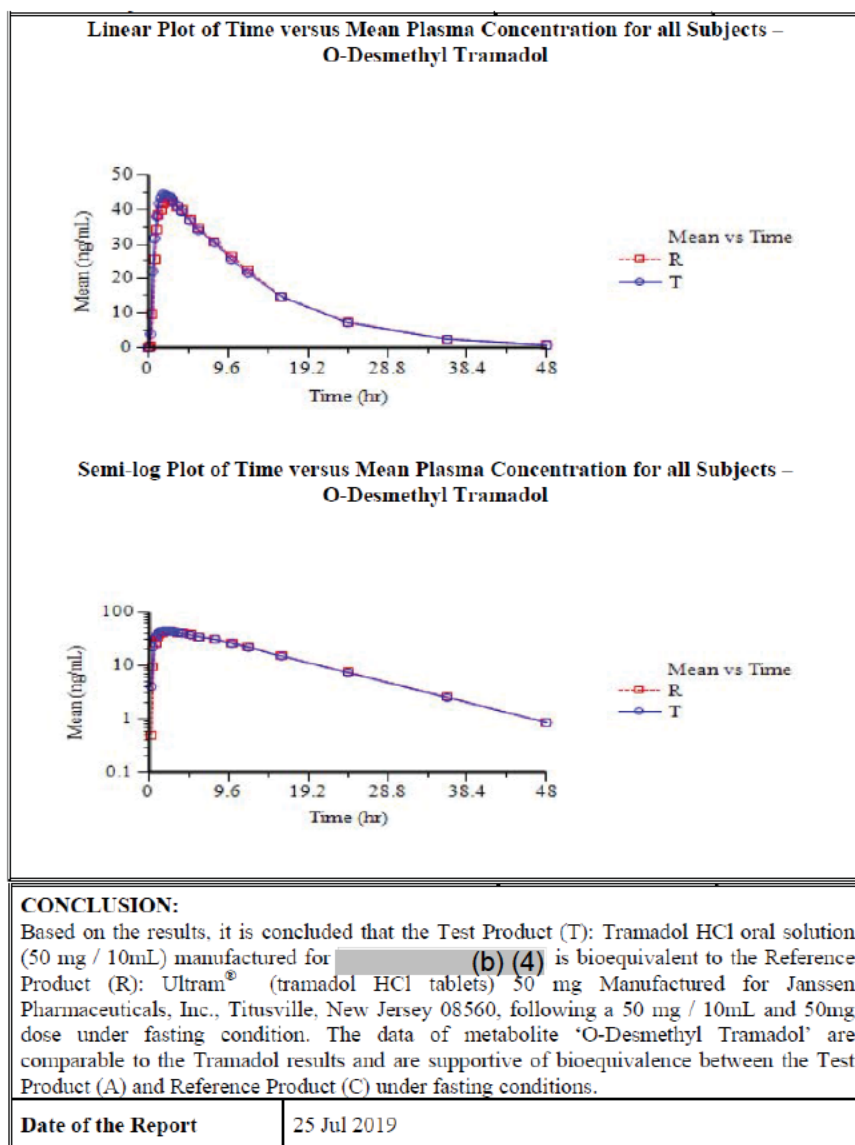
Parameters	Geometric Mean		% Ratio T/R	90% CI		Power	ISCV %
	Test	Reference		Lower	Upper		
C _{max} (ng/mL)	42.7500	40.9927	104.29	99.70	109.08	1.0000	10.8
AUC _{0-t} (hr*ng/mL)	578.4039	580.0828	99.71	96.84	102.66	1.0000	7.0
AUC _{0-inf} (hr*ng/mL)	594.0945	597.8715	99.37	96.41	102.42	1.0000	7.2

Linear Plot of Time versus Mean Plasma Concentration for all Subjects – Tramadol



Semi-log Plot of Time versus Mean Plasma Concentration for all Subjects – Tramadol





Reviewer comments: There are no issues identified with the Applicant's synopsis report.

Additional information pertinent from the main study report:

Bioanalytical laboratory: (b) (4)

RESULTS

1. Summary of PK subject demographics

Table 18A: Summary data for the subjects enrolled in the study

	Age (Years)	Height (cms)	Weight (kg)	BMI (kg/m ²)
Number of subjects	36	36	36	36
Mean	31.44	166.58	63.78	22.99
Minimum	19	155	52.18	19.17
Maximum	42	179	77.15	24.79
SD	5.89	6.29	6.05	1.84
Median	31	167	63.06	23.57

Table 18B: Summary data for the subjects completed the study

	Age (Years)	Height (cms)	Weight (kg)	BMI (kg/m ²)
Number of subjects	33	33	33	33
Mean	31.42	167.00	63.90	22.91
Minimum	19	156	52.18	19.17
Maximum	42	179	77.15	24.79
SD	6.11	5.94	6.24	1.87
Median	31	167	63.08	23.29

Abbreviations: BMI = body mass index, SD = standard deviation

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\report-body-fasting.pdf; p.88/112

2. Individual subject Pharmacokinetic Data of Test Product, Study 197/18, Tramadol

Treatment	Subject	Sequence	Period	Cmax	AUCt	AUCinf	Tmax	Kel	tHalf
				(ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(hr)	(1/hr)	(hr)
T	(b) (6)	TR	1	185.386	2122.099	2154.677	2.250	0.089	7.765
		RT	2	140.855	833.534	864.602	1.750	0.129	5.386
		RT	2	160.385	1298.288	1313.311	2.000	0.124	5.607
		TR	1	184.426	1644.895	1667.385	1.750	0.086	8.090
		TR	1	214.458	2129.459	2185.522	1.500	0.077	9.014
		RT	2	155.224	2309.405	2441.465	2.250	0.058	11.857
		RT	2	153.634	1285.678	1295.907	1.750	0.101	6.890
		TR	1	255.882	2127.305	2167.006	1.750	0.077	9.017
		RT	2	226.374	2274.041	2327.030	1.250	0.082	8.469
		TR	1	220.620	1093.019	1102.106	0.500	0.120	5.779
		TR	1	181.783	1863.482	1891.588	0.750	0.088	7.910
		RT	2	136.219	1237.372	1288.094	2.250	0.149	4.642
		TR	1	204.897	1523.969	1549.915	1.000	0.084	8.220
		RT	2	151.330	1401.592	1424.764	1.500	0.082	8.503
		TR	1	196.877	1795.268	1813.633	1.000	0.097	7.140
		RT	2	186.245	2356.140	2413.102	2.000	0.080	8.676
		TR	1	114.236	895.341	913.443	1.500	0.102	6.768
		RT	2	170.636	1104.430	1133.352	1.250	0.160	4.324
		RT	2	207.547	2364.082	2429.620	2.000	0.071	9.725
		TR	1	158.673	1179.209	1193.524	1.750	0.118	5.857
		TR	1	167.115	1233.190	1247.538	1.750	0.081	8.581
		RT	2	164.843	1609.499	1643.479	1.500	0.083	8.376
		RT	2	143.169	1319.584	1334.299	1.500	0.085	8.140
		TR	1	147.977	1235.634	1260.422	2.000	0.109	6.338
		RT	2	156.024	1514.190	1531.048	2.500	0.097	7.151
		RT	2	208.922	1589.983	1615.890	0.750	0.081	8.580
		TR	1	185.127	1592.203	1605.463	1.500	0.096	7.203
		RT	2	226.476	1817.083	1829.786	1.250	0.098	7.101
		TR	1	194.473	2998.165	3148.003	2.000	0.064	10.772
		RT	2	150.325	1093.168	1107.696	1.250	0.108	6.447
		TR	1	226.346	2029.211	2067.823	1.000	0.077	8.948
		TR	1	227.353	1341.948	1367.937	1.250	0.102	6.818
		RT	2	142.818	1377.069	1394.852	2.000	0.084	8.223
		N		33	33	33	33	33	33
		Mean		180.2017	1623.9252	1658.3115	1.5758	0.0951	7.6460
		SD		33.80524	502.42885	525.96905	0.48608	0.02256	1.63351
		Min		114.236	833.534	864.602	0.500	0.058	4.324
		Median		181.783	1523.969	1549.915	1.500	0.088	7.910
		Max		255.882	2998.165	3148.003	2.500	0.160	11.857
		CV%		18.8	30.9	31.7	30.8	23.7	21.4
		Geometric Mean		177.136	1552.392	1582.924	1.489	0.093	7.471

T: Tramadol hydrochloride oral solution 5 mg/mL

R: Ultram 50 mg tablet

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\16-1-9-documentation-of-statistical-methods-fasting.pdf; p.10/62

Treatment	Subject	Sequence	Period	Cmax	AUCt	AUCinf	Tmax	Kel	tHalf
	(b) (6)			(ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(hr)	(1/hr)	(hr)
R		TR	2	179.891	1837.160	1861.618	1.250	0.092	7.568
		RT	1	149.210	1082.401	1092.291	1.250	0.125	5.542
		RT	1	150.725	1437.271	1462.578	2.750	0.110	6.278
		TR	2	177.073	1888.220	1912.273	1.500	0.094	7.374
		TR	2	188.756	1992.290	2043.656	0.750	0.076	9.141
		RT	1	158.943	2326.309	2485.073	3.000	0.055	12.677
		RT	1	247.669	1282.433	1292.853	1.250	0.099	7.019
		TR	2	238.624	2179.667	2224.202	1.000	0.079	8.802
		RT	1	211.466	2314.536	2391.473	2.500	0.068	10.258
		TR	2	163.727	1175.833	1229.053	1.250	0.142	4.870
		TR	2	180.932	1864.883	1893.652	2.000	0.085	8.189
		RT	1	150.560	1097.391	1105.884	1.500	0.132	5.260
		TR	2	183.170	1578.378	1608.807	1.000	0.088	7.899
		RT	1	153.898	1564.878	1584.218	2.000	0.091	7.583
		TR	2	159.491	1718.987	1740.829	2.250	0.091	7.650
		RT	1	185.118	2104.156	2144.617	1.750	0.087	8.013
		TR	2	122.760	983.279	1004.414	1.750	0.102	6.798
		RT	1	159.106	1276.668	1285.217	1.750	0.143	4.838
		RT	1	192.746	2267.499	2329.982	1.750	0.075	9.240
		TR	2	149.673	1302.939	1322.470	2.000	0.116	5.982
		TR	2	156.588	1144.807	1167.107	1.500	0.105	6.609
		RT	1	178.021	1559.756	1593.173	1.500	0.081	8.513
		RT	1	131.019	1346.711	1362.868	2.250	0.090	7.681
		TR	2	162.881	1382.357	1404.620	1.500	0.116	5.995
		RT	1	163.542	1525.561	1538.432	2.000	0.099	6.991
		RT	1	170.422	1820.068	1869.108	1.250	0.070	9.833
		TR	2	169.599	1623.630	1634.363	1.500	0.108	6.419
		RT	1	175.019	1707.969	1718.811	1.750	0.105	6.604
		TR	2	254.514	4113.894	4404.606	1.250	0.059	11.688
		RT	1	153.107	1158.461	1170.374	1.250	0.123	5.629
		TR	2	179.275	1908.542	1949.557	2.000	0.078	8.851
		TR	2	148.637	1350.707	1380.990	2.250	0.101	6.842
		RT	1	179.809	1576.405	1599.241	1.000	0.082	8.478
		N		33	33	33	33	33	33
		Mean		173.5143	1681.6377	1721.4670	1.6742	0.0959	7.6095
		SD		29.58931	578.06464	624.71658	0.52472	0.02193	1.81820
		Min		122.760	983.279	1004.414	0.750	0.055	4.838
		Median		169.599	1576.405	1599.241	1.500	0.092	7.568
		Max		254.514	4113.894	4404.606	3.000	0.143	12.677
		CV%		17.1	34.4	36.3	31.3	22.9	23.9
		Geometric Mean		171.287	1607.827	1640.202	1.596	0.094	7.412

T: Tramadol hydrochloride oral solution 5 mg/mL

R: Ultram 50 mg tablet

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\16-1-9-documentation-of-statistical-methods-fasting.pdf; p.11/62

3. Individual subject Pharmacokinetic Data of Test Product, Study 197/18, O-Desmethyl Tramadol

Treatment	Subject	Sequence	Period	Cmax (ng/mL)	AUCt (hr*ng/mL)	AUCinf (hr*ng/mL)	Tmax (hr)	Kel (1/hr)	tHalf (hr)
T	(b) (6)	TR	1	44.248	819.666	844.473	2.500	0.075	9.240
		RT	2	80.671	763.734	774.382	1.750	0.125	5.537
		RT	2	72.011	954.859	962.298	2.750	0.109	6.373
		TR	1	40.859	561.530	570.641	1.750	0.089	7.797
		TR	1	33.081	508.746	527.360	2.000	0.071	9.730
		RT	2	19.467	428.240	460.013	3.000	0.057	12.127
		RT	2	40.074	459.151	474.645	2.250	0.097	7.155
		TR	1	75.246	851.780	871.702	1.750	0.079	8.734
		RT	2	15.107	222.565	236.152	1.250	0.082	8.484
		TR	1	79.475	573.807	583.520	0.500	0.108	6.418
		TR	1	11.659	173.430	184.086	3.000	0.078	8.910
		RT	2	51.503	702.081	756.656	3.500	0.132	5.238
		TR	1	21.344	281.199	288.535	1.000	0.080	8.633
		RT	2	41.966	542.383	557.011	1.500	0.081	8.578
		TR	1	46.395	789.820	806.412	1.000	0.085	8.174
		RT	2	35.841	675.704	696.402	2.750	0.078	8.867
		TR	1	51.086	617.428	624.780	2.000	0.094	7.343
		RT	2	68.765	673.386	680.019	1.250	0.131	5.291
		RT	2	51.408	930.525	965.983	2.000	0.071	9.811
		TR	1	51.459	559.915	568.440	2.000	0.120	5.799
		TR	1	68.671	751.498	761.192	1.750	0.095	7.295
		RT	2	33.497	530.191	545.317	1.500	0.077	9.015
		RT	2	36.160	488.985	495.583	2.250	0.089	7.831
		TR	1	71.215	875.978	882.792	1.750	0.106	6.524
		RT	2	56.328	879.661	895.016	3.000	0.089	7.832
		RT	2	53.772	663.606	677.214	1.500	0.079	8.725
		TR	1	42.753	692.491	703.671	2.000	0.090	7.703
		RT	2	60.816	812.406	819.389	2.000	0.103	6.742
		TR	1	9.524	193.900	208.237	5.000	0.059	11.803
		RT	2	60.333	607.118	617.753	1.250	0.118	5.888
		TR	1	44.976	610.333	626.310	1.000	0.077	9.040
		TR	1	52.614	622.392	628.777	1.500	0.098	7.048
		RT	2	54.214	777.326	790.460	2.000	0.085	8.173
		N		33	33	33	33	33	33
		Mean		47.7739	624.1160	638.9461	2.0000	0.0911	7.9352
		SD		19.06335	205.57693	207.12774	0.86603	0.01917	1.64827
		Min		9.524	173.430	184.086	0.500	0.057	5.238
		Median		51.086	622.392	628.777	2.000	0.089	7.832
		Max		80.671	954.859	965.983	5.000	0.132	12.127
		CV%		39.9	32.9	32.4	43.3	21.0	20.8
		Geometric Mean		42.822	579.633	595.390	1.831	0.089	7.772

T: Tramadol hydrochloride oral solution 5 mg/mL

R: Ultram 50 mg tablet

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\16-1-9-documentation-of-statistical-methods-fasting.pdf; p.19/62

Treatment	Subject	Sequence	Period	Cmax (ng/mL)	AUCt (hr*ng/mL)	AUCinf (hr*ng/mL)	Tmax (hr)	Kel (1/hr)	tHalf (hr)
R	(b) (6)	TR	2	43.554	713.567	729.611	3.000	0.083	8.387
		RT	1	70.130	851.190	856.168	2.750	0.110	6.321
		RT	1	70.312	970.917	977.319	4.000	0.113	6.121
		TR	2	33.745	606.383	618.688	1.500	0.086	8.092
		TR	2	32.934	585.903	606.882	2.500	0.073	9.517
		RT	1	21.919	448.236	485.578	5.000	0.054	12.814
		RT	1	65.736	467.383	479.703	1.250	0.101	6.837
		TR	2	62.320	863.372	886.532	1.500	0.077	8.963
		RT	1	11.628	164.138	178.161	2.500	0.072	9.662
		TR	2	61.661	590.035	646.341	1.250	0.106	6.557
		TR	2	11.721	181.036	194.015	2.000	0.079	8.776
		RT	1	61.549	659.482	671.056	1.250	0.117	5.943
		TR	2	22.832	328.899	337.108	2.000	0.080	8.648
		RT	1	39.020	539.428	547.038	2.000	0.094	7.388
		TR	2	37.870	707.355	716.581	2.250	0.092	7.532
		RT	1	36.727	597.305	612.523	2.000	0.081	8.604
		TR	2	53.420	691.935	699.037	2.000	0.098	7.042
		RT	1	65.575	685.822	694.524	2.500	0.127	5.449
		RT	1	49.643	866.927	899.773	2.750	0.072	9.631
		TR	2	50.699	646.966	661.594	2.500	0.108	6.393
		TR	2	67.425	749.418	758.470	1.500	0.095	7.296
		RT	1	31.146	457.337	471.919	1.500	0.074	9.333
		RT	1	32.644	479.895	486.020	2.250	0.096	7.220
		TR	2	60.689	779.915	786.234	2.500	0.104	6.636
		RT	1	61.009	921.029	933.347	3.500	0.096	7.254
		RT	1	42.484	618.535	637.100	2.500	0.075	9.298
		TR	2	41.381	737.860	747.235	2.500	0.097	7.149
		RT	1	51.299	716.766	723.534	2.500	0.101	6.889
		TR	2	7.464	222.473	258.511	10.000	0.043	16.284
		RT	1	74.170	646.369	656.046	2.000	0.123	5.641
		TR	2	40.907	605.825	622.224	2.250	0.078	8.915
		TR	2	47.696	667.086	674.692	2.250	0.096	7.213
		RT	1	61.227	826.363	842.097	1.750	0.085	8.109
		N		33	33	33	33	33	33
		Mean		46.1375	624.0954	639.2625	2.5303	0.0904	8.0580
		SD		18.27749	199.82172	198.04379	1.55216	0.01862	2.11006
		Min		7.464	164.138	178.161	1.250	0.043	5.449
		Median		47.696	646.966	661.594	2.250	0.094	7.388
		Max		74.170	970.917	977.319	10.000	0.127	16.284
		CV%		39.6	32.0	31.0	61.3	20.6	26.2
		Geometric Mean		41.119	580.692	598.418	2.284	0.088	7.843

T: Tramadol hydrochloride oral solution 5 mg/mL

R: Ultram 50 mg tablet

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fasting-study\16-1-9-documentation-of-statistical-methods-fasting.pdf; p.20/62

4.2.2 Food effect Study 198/18

Title: An open label, balanced, randomized, single dose, three treatment, three period, three sequence, crossover, oral food effect and fed Bioequivalence study of Tramadol HCl oral solution (50 mg/10 mL) manufactured for (b) (4), and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects.

Report Date: 8/3/19

The following synopsis report was provided by the Applicant:

Name of Sponsor/Company: (b) (4)	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of the Finished Product: Tramadol HCl Oral Solution(50 mg / 10mL)	Volume:	
Name of the Active Ingredients: Tramadol Hydrochloride	Page:	
Title of Study: An open label, balanced, randomized, single dose, three treatment, three period, three sequence, crossover, oral food effect and fed Bioequivalence study of Tramadol HCl oral solution (50 mg/10 mL) manufactured for (b) (4), and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects.		
Study Number : 198/18		
Investigators:		
Principal Investigator	Dr. A.Venkata Subba Reddy	
Bioanalytical Investigator	(b) (4)	
Pharmacokinetic & Statistical Investigator		
Study Centre (s): Clinical Facility: Actimus Biosciences Private Limited, 4 th Floor, Varun Towers, Kasturiba Marg, Siripuram, Visakhapatnam-530 003, Andhra Pradesh, India Tel: +91-891-6672-000, 100, 200 Fax: +91-891-6672111.		
(b) (4)		
Publication (reference): Not Applicable		
Study Period: Clinical phase: Study Start Date: 27 May 2019 (Period-I Check in) Study Completion Date: 15 Jun 2019 (Last Sample collection date) Bioanalytical phase: (b) (4) (b) (4)		Phase of Development: Bioequivalence Phase Intended for NDA
Objectives: Primary Objective: I. To evaluate the effect of food on the rate and extent of absorption of Tramadol HCl oral solution (50 mg/10 mL) manufactured for (b) (4) in healthy adult human subjects. II. To compare the rate and extent of absorption of Tramadol HCl oral solution (50 mg/10 mL) manufactured for (b) (4) and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects under fed condition. Secondary Objective: To assess the safety and tolerability following oral administration of investigational product.		
Methodology: An open label, balanced, randomized, single dose, three treatment, three period, three sequence, crossover, oral food effect and fed Bioequivalence study in healthy adult human subjects. Subjects underwent screening evaluation to determine eligibility within 28 days prior to the check in of 1 st period. Subjects were confined within the facility from at least 11.00 hours before drug administration to 48.00 hours after drug administration. Subjects were randomized to either 'ABC' or 'BCA or CAB' (where A = Test Formulation under fed condition, B = Test Formulation under fasting condition and C=Reference Formulation under fed condition) and were dosed with 240 mL of water at room temperature in sitting posture.		

Blood samples were drawn from pre-dose (collected within 01 hour prior to drug administration) and up to 48.00 hours post dose. Analysis of Tramadol in plasma concentration was performed by a validated LC-MS/MS analytical method.		
Number of Subjects (Planned and Analysed)		
Planned and Randomized	:	18 healthy, adult, human subjects were randomized and checked-in to the study.
Withdrawal/ Drop out	:	Nil
Details of withdrawal/drop out	:	NA
Completed and Analysed	:	18 subjects completed the study and were analysed.
Diagnosis and Main Criteria for Inclusion:		
Subjects participated in the study were healthy, adult, males between 18-45 years of age; body mass index of 18.50 and 24.90 Kg/(height in m) ² , with body weight at least 50 kgs. Study participants were of normal health as determined by medical history, demographic data (including sex, age, body weight (kg), height (cm) and BMI (kg/m ²), ethnicity, race, vital signs measurements, 12 lead - ECG, chest X-ray, physical examination and laboratory tests performed within 28 days prior to the check-in of 1 st period. Medical examination, Vitals, Breath Alcohol Analysis (BAA), Urine Drug Screening (UDS) were performed on admission day of each period.		
	Test Product (A & B)	Reference Product (C)
Name	Tramadol oral solution 5 mg / mL (50 mg / 10mL)	Tramadol HCl (Ultram [®]) 50 mg/Tab
Strength	50 mg / 10mL (10 mL)	50 mg
Manufactured by/Manufactured for	Manufacturer: (b) (4)	Manufacturer: Janssen Pharmaceuticals Inc.
Lot No.	CL PB525	CL 17GG660
Mfg Date	NA	NA
Expiry Date	09/2019	03/2020
Mode of Administration	Oral	Oral
Duration of Treatment: 27 May 2019 to 15 Jun 2019 (from date of period-I check-in to last study sample collection)		
Period-I : 27 May 2019 to 30 May 2019		
Period-II : 04 Jun 2019 to 07 Jun 2019		
Period-III : 12 Jun 2019 to 15 Jun 2019		
Wash out period: At least 07 days, between each drug administration.		
Blood Sampling Points:		
In each period, a total of 24 blood samples (1 x 05ml each) were collected as per the following schedule:		
Pre-dose (0.00 hour) sample within 01 hour prior to drug administration and the others at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00hrs post dose into 5 mL K ₂ EDTA vacutainers.		
Bioanalytical Method:		
Analytes	Tramadol	O-Desmethyl Tramadol
Analytical Method	LC – MS / MS	LC – MS / MS
Lower Limit of Quantification	(b) (4)	(b) (4)
Calibration Range during Study Sample Analysis		
Criteria for Evaluation:		
Pharmacokinetics:		
Based on the plasma concentrations of Tramadol and O-Desmethyl Tramadol, the pharmacokinetic parameters: C _{max} , AUC ₀₋₄ , AUC _{0-inf} , T _{max} , t _{1/2} and K _{el} were calculated by using "Non-compartmental model" for Treatments Test (A & B) and Reference (C). Pharmacokinetic analysis was done by using Phoenix [®] WinNonlin [®] Software, Version 6.3.		

squares mean for log-transformed pharmacokinetic parameters C_{max}, AUC_{0-4} and AUC_{0-inf} for tramadol conclusion will be drawn for treatment A versus treatment B and treatment A versus treatment C. Absence of food effect on bioavailability of test product will be established if the 90 percent confidence intervals for the ratio of population geometric means between fed and fasted treatments of test product (A Vs B), based on log-transformed data, are contained in the equivalence limits of 80.00 - 125.00% for C_{max}, AUC_{0-4} and AUC_{0-inf}. The test product will be concluded bioequivalent to the reference product under fed condition (A Vs C), if the limits fall within acceptance range (80.00%-125.00%) of the 90% confidence intervals for the difference of means of log-transformed (C_{max}, AUC_{0-4} and AUC_{0-inf}) with respect to Racemic Tramadol. The data of metabolite, 'O-Desmethyl Tramadol' was submitted as supportive evidence.
SUMMARY – CONCLUSIONS SAFETY RESULTS: • All the Subjects vital signs were within normal range in all the periods. • Well-being questionnaire was performed at the time of vital signs monitoring. All the subjects were within normal health status at the time of well-being questionnaire. • Medical examination was performed at check-in and check-out for each study period and all the subjects were found to be in normal health. • The test and reference products were well tolerated by the subjects. • No adverse events were reported during in-house and post study. • All the post study safety assessments performed at the end of the study were evaluated and found to be normal or with no clinical significance. • Serious/Significant adverse events: No serious adverse events reported during the entire duration of the study. Deaths: No deaths reported during the entire duration of the study.
Safety: Vitals (Blood Pressure, Pulse Rate and Oral Temperature) were examined on the day of admission at fitness assessment, prior to administration of the study drug (0.00 hr) and at 1.00, 3.00, 6.00, 10.00, 24.00, 36.00 hours post dose (Within $\pm$ 45 minutes variation) and at the time of check out (48.00 hours post dose). Blood Pressure was measured in Sitting Position.
Statistical Methods: Analysis of Variance: Analysis of Variance (ANOVA) was estimated at alpha (α) 0.05 on the ln-transformed PK Parameters C_{max}, AUC_{0-4} and AUC_{0-inf} using PROCGLM procedure of SAS. The analysis of variance model included sequence, subjects nested within sequence, period and treatment as factors. The significance of the sequence effect at alpha (α) 0.10 was tested using the subjects nested within the sequence as the error term. 90% Confidence Intervals: Consistent with the two one-sided tests for Bioequivalence, 90% confidence intervals for the difference between treatments least-square means were calculated for ln-transformed C_{max}, AUC_{0-4} and AUC_{0-inf}. The confidence intervals were expressed as percentages relative to the LSM of the reference treatments. Ratio Analysis: Ratios of means of each test and reference formulations were estimated using the LSM for ln-transformed C_{max}, AUC_{0-4} and AUC_{0-inf}. The geometric means were reported for the ln-transformed C_{max}, AUC_{0-4} and AUC_{0-inf}. Descriptive Statistics: The descriptive statistics (such as Mean, Standard Deviation, Minimum, Median, Maximum, Coefficient of Variation) for the relevant Pharmacokinetic parameters were estimated for both test and reference formulations. The Geometric Mean and Coefficient of Variation were estimated C_{max}, AUC_{0-4} and AUC_{0-inf}. Arithmetic mean and standard deviation were estimated for C_{max}, AUC_{0-4}, AUC_{0-inf}, T_{max}, $t_{1/2}$ and K_{el}. Criteria for Evaluation: Based on the statistical results of 90% confidence interval for the ratio of the geometric least

PHARMACOKINETIC AND STATISTICAL RESULTS:

The data included subjects who successfully completed the clinical phase. Summarized in Table No's 1A, 2A, 1B, 2B, 1C, 2C, 1D and 2D are the pharmacokinetic and statistical results for Tramadol and O-Desmethyl Tramadol inclusive of data from completed subjects.

Tramadol:**Table 1A: Summary of Pharmacokinetic Data for Tramadol(Bioequivalence)**

	Arithmetic Mean $\pm$ SD (N = 18)	
	Test product (A)	Reference product (C)
# T _{max} (hr)	2.000 (0.500 – 3.500)	1.875 (0.750 – 4.000)
C _{max} (ng/mL)	146.2155 $\pm$ 28.50482	186.6340 $\pm$ 32.86856
AUC ₀₋₄ (hr*ng/mL)	1606.0391 $\pm$ 574.37827	1650.6286 $\pm$ 514.55018
AUC _{0-inf} (hr*ng/mL)	1635.8991 $\pm$ 594.44408	1681.6393 $\pm$ 536.05870
t _{1/2} (hr)	7.3341 $\pm$ 1.19381	7.4220 $\pm$ 1.41923
K _{el} (1/hr)	0.0969 $\pm$ 0.01547	0.0968 $\pm$ 0.01978

Note: # For T_{max} median (min – max)

Tramadol:**Table 2A: Geometric Means and Confidence Intervals for Tramadol[N=18] (Bioequivalence)**

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test (A)	Reference (C)		Lower	Upper		
C _{max} (ng/mL)	143.6218	183.8580	78.12	73.25	83.31	0.9999	11.4
AUC ₀₋₄ (hr*ng/mL)	1515.8015	1580.4555	95.91	92.49	99.45	1.0000	6.4
AUC _{0-inf} (hr*ng/mL)	1541.6540	1607.6616	95.89	92.41	99.51	1.0000	6.6

O-Desmethyl Tramadol:**Table 1B: Summary of Pharmacokinetic Data for O-Desmethyl Tramadol(Bioequivalence)**

	Arithmetic Mean $\pm$ SD (N = 18)	
	Test product (A)	Reference product (C)
# T _{max} (hr)	3.500 (1.750 – 5.000)	2.125 (1.000 – 5.000)
C _{max} (ng/mL)	41.3538 $\pm$ 11.53324	44.7912 $\pm$ 14.05175
AUC ₀₋₄ (hr*ng/mL)	623.1367 $\pm$ 167.54105	626.7567 $\pm$ 143.85018
AUC _{0-inf} (hr*ng/mL)	635.0502 $\pm$ 169.96988	639.9006 $\pm$ 145.57285
t _{1/2} (hr)	7.5593 $\pm$ 1.10155	7.7046 $\pm$ 1.17623
K _{el} (1/hr)	0.0936 $\pm$ 0.01441	0.0920 $\pm$ 0.01428

Note: # For T_{max} median (min – max)

O-Desmethyl Tramadol:**Table 2B: Geometric Means and Confidence Intervals for O-Desmethyl Tramadol [N=18] (Bioequivalence)**

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test (A)	Reference (C)		Lower	Upper		
C _{max} (ng/mL)	39.5430	42.7653	92.47	87.22	98.03	1.0000	10.4
AUC ₀₋₄ (hr*ng/mL)	601.0795	609.9559	98.54	94.43	102.84	1.0000	7.6
AUC _{0-inf} (hr*ng/mL)	612.8940	623.1737	98.35	94.34	102.53	1.0000	7.4

Tramadol:**Table 1C: Summary of Pharmacokinetic Data for Tramadol(Food Effect)**

	Arithmetic Mean $\pm$ SD (N = 18)	
	Test product (A)	Test product (B)
#T _{max} (hr)	2.000 (0.500 – 3.500)	1.875 (0.750 – 3.000)
C _{max} (ng/mL)	146.2155 $\pm$ 28.50482	160.1528 $\pm$ 34.09761
AUC ₀₋₄ (hr*ng/mL)	1606.0391 $\pm$ 574.37827	1577.2434 $\pm$ 585.27217
AUC _{0-inf} (hr*ng/mL)	1635.8991 $\pm$ 594.44408	1610.4305 $\pm$ 616.17364
t _{1/2} (hr)	7.3341 $\pm$ 1.19381	7.6834 $\pm$ 1.51041
K _{el} (1/hr)	0.0969 $\pm$ 0.01547	0.0933 $\pm$ 0.01740

Note: # For T_{max} median (min – max)

Tramadol:**Table 2C: Geometric Means and Confidence Intervals for Tramadol[N=18] (Food Effect)**

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test (A)	Test (B)		Lower	Upper		
C _{max} (ng/mL)	143.6218	156.7631	91.62	85.91	97.71	0.9999	11.4
AUC ₀₋₄ (hr*ng/mL)	1515.8015	1484.1442	102.13	98.49	105.91	1.0000	6.4
AUC _{0-inf} (hr*ng/mL)	1541.6540	1510.5231	102.06	98.36	105.91	1.0000	6.6

O-Desmethyl Tramadol:**Table 1D: Summary of Pharmacokinetic Data for O-Desmethyl Tramadol(Food Effect)**

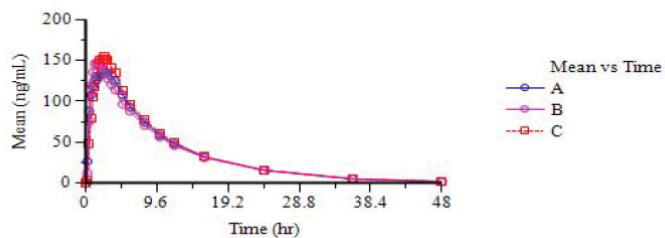
	Arithmetic Mean $\pm$ SD (N = 18)	
	Test product (A)	Test product (B)
#T _{max} (hr)	3.500 (1.750 – 5.000)	2.000 (0.750 – 3.500)
C _{max} (ng/mL)	41.3538 $\pm$ 11.53324	45.6575 $\pm$ 13.95134
AUC ₀₋₄ (hr*ng/mL)	623.1367 $\pm$ 167.54105	635.2980 $\pm$ 181.16193
AUC _{0-inf} (hr*ng/mL)	635.0502 $\pm$ 169.96988	648.0993 $\pm$ 181.51783
t _{1/2} (hr)	7.5593 $\pm$ 1.10155	8.0104 $\pm$ 1.47231
K _{el} (1/hr)	0.0936 $\pm$ 0.01441	0.0890 $\pm$ 0.01489

Note: # For T_{max} median (min – max)

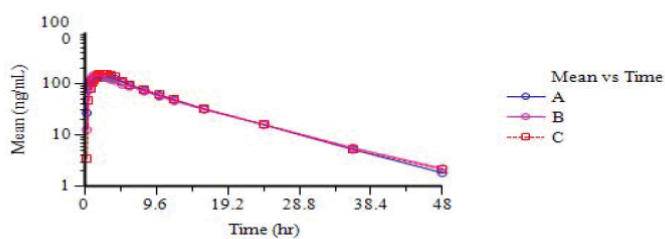
O-Desmethyl Tramadol:**Table 2D: Geometric Means and Confidence Intervals for O-Desmethyl Tramadol[N=18] (Food Effect)**

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test (A)	Test (B)		Lower	Upper		
C _{max} (ng/mL)	39.5430	43.0627	91.83	86.62	97.35	1.0000	10.4
AUC ₀₋₄ (hr*ng/mL)	601.0795	607.1807	99.00	94.86	103.31	1.0000	7.6
AUC _{0-inf} (hr*ng/mL)	612.8940	620.7093	98.74	94.72	102.94	1.0000	7.4

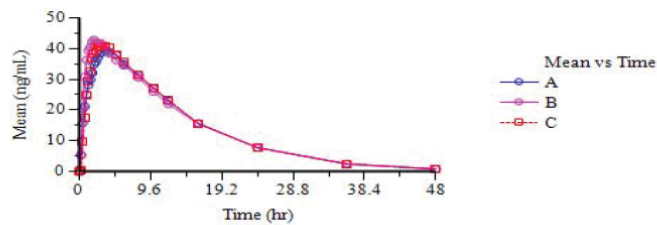
Linear Plot of Time versus Mean Plasma Concentration for all Subjects – Tramadol



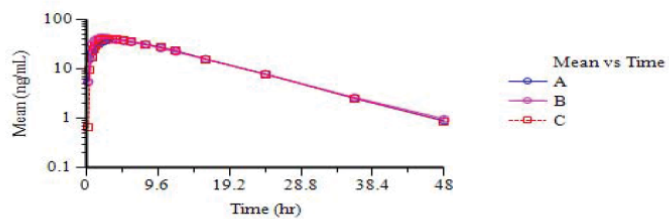
Semi-log Plot of Time versus Mean Plasma Concentration for all Subjects – Tramadol



Linear Plot of Time versus Mean Plasma Concentration for all Subjects – O-Desmethyl Tramadol



Semi-log Plot of Time versus Mean Plasma Concentration for all Subjects – O-Desmethyl Tramadol



CONCLUSION: For Bioequivalence: Based on the C _{max} results, it is concluded that the Test Product (A): Tramadol HCl oral solution (50 mg / 10mL) manufactured for (b) (4) is not bioequivalent to the Reference Product (C): Ultram [®] (tramadol HCl tablets) 50 mg Manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, following a 50 mg / 10mL and 50mg dose under fed conditions. The data of metabolite 'O-Desmethyl Tramadol' are dissimilar from the Tramadol results with respect to C _{max} and are supportive of bioequivalence between the Test Product (A) and Reference Product (C) under fed conditions.	
For Food Effect: Based on the results, it is concluded that the Test Product (A): Tramadol HCl oral solution (50 mg / 10mL) manufactured for (b) (4) administered in fed condition is bioequivalent to the Test Product (B): Tramadol HCl oral solution (50 mg / 10mL) manufactured for (b) (4), administered in fasting condition. The food effect was not observed with the consumption of a high-fat, high calorie meal. The data of metabolite, 'O-Desmethyl Tramadol' were comparable and also demonstrate no food effect with consumption of a high-fat, high calorie meal.	
Date of the Report	03Aug 2019

Reviewer comments: There are no issues identified with the Applicant's synopsis report.

Additional information pertinent from the main study report:

Bioanalytical laboratory: (b) (4)

RESULTS

1. Summary of PK subject demographics

Table 12: Demographics summary

	Age (Years)	Height (cm)	Weight (kg)	BMI (kg/m ²)
Number of subjects	18	18	18	18
Mean (SD)	33.94 (6.68)	169.11 (4.46)	68.19 (5.19)	23.82 (1.13)
Median	36.50	168	68.34	24.26
CV%	19.68	2.64	7.61	4.74
Range	24 - 42	164 - 178	60.60 – 78.11	20.68 – 24.66

Abbreviations: BMI = body mass index, SD = standard deviation

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\report-body-fast-fed.pdf; p.75/128

2. Individual subject Pharmacokinetic Parameters for tramadol: Test Formulation in fed (A) and fasting conditions (B), and, Reference Formulation in fed conditions (C), Study 198/18
Pharmacokinetic Parameters for Test Formulation in Fed Conditions (A): Tramadol

Subject	Sequence	Period	C _{max} (ng/mL)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	T _{max} (hr)	K _{el} (1/hr)	t _{1/2} (hr)
(b) (6)	CAB	2	127.700	1498.419	1527.984	3.500	0.080	8.647
	ABC	1	201.896	2610.556	2667.292	1.000	0.082	8.450
	BCA	3	154.162	1321.675	1345.211	0.750	0.108	6.443
	BCA	3	107.174	1143.566	1167.658	3.500	0.109	6.333
	ABC	1	118.478	1059.861	1078.149	2.750	0.109	6.342
	CAB	2	175.939	2683.649	2781.588	1.250	0.072	9.627
	ABC	1	117.266	882.634	897.590	2.000	0.106	6.565
	CAB	2	114.758	1001.926	1012.657	2.000	0.120	5.762
	BCA	3	116.327	1309.591	1321.230	3.500	0.101	6.860
	ABC	1	173.992	1681.045	1696.934	0.500	0.096	7.198
	CAB	2	168.346	1827.752	1846.084	1.750	0.092	7.546
	BCA	3	172.067	2369.460	2420.614	1.750	0.082	8.430
	ABC	1	140.156	937.924	946.293	0.500	0.125	5.541
	CAB	2	164.167	1637.583	1668.372	2.000	0.109	6.335
	BCA	3	123.795	1417.473	1432.018	2.250	0.102	6.817
	CAB	2	123.932	1512.679	1543.929	2.750	0.080	8.626
	BCA	3	152.656	1555.077	1574.792	3.000	0.091	7.596
	ABC	1	179.068	2457.835	2517.789	3.000	0.078	8.899
N			18	18	18	18	18	18
Mean			146.2155	1606.0391	1635.8991	2.0972	0.0969	7.3341
SD			28.50482	574.37827	594.44408	1.01510	0.01547	1.19381
Min			107.174	882.634	897.590	0.500	0.072	5.541
Median			146.406	1505.549	1535.956	2.000	0.099	7.029
Max			201.896	2683.649	2781.588	3.500	0.125	9.627
CV%			19.5	35.8	36.3	48.4	16.0	16.3
Geometric Mean			143.622	1515.801	1541.654	1.796	0.096	7.244

Pharmacokinetic Parameters for Test Formulation in Fasting Conditions (B): Tramadol

Subject	Sequence	Period	C _{max} (ng/mL)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	T _{max} (hr)	K _{el} (1/hr)	t _{1/2} (hr)
(b) (6)	CAB	3	155.456	1442.957	1463.621	1.750	0.088	7.862
	ABC	2	175.318	2405.017	2451.353	3.000	0.084	8.297
	BCA	1	193.518	1169.010	1189.843	1.000	0.103	6.754
	BCA	1	100.618	1021.447	1033.740	2.000	0.098	7.101
	ABC	2	126.354	1146.753	1157.489	2.000	0.098	7.101
	CAB	3	182.850	2764.422	2929.025	2.750	0.061	11.400
	ABC	2	158.262	1032.825	1044.477	1.000	0.096	7.211
	CAB	3	134.152	923.629	932.847	1.000	0.128	5.405
	BCA	1	143.932	1215.905	1226.708	0.750	0.103	6.710
	ABC	2	145.810	1642.405	1660.856	2.000	0.099	7.031
	CAB	3	215.984	2242.498	2280.351	2.000	0.086	8.098
	BCA	1	171.400	2173.832	2248.340	2.500	0.069	10.046
	ABC	2	123.542	926.551	935.949	1.750	0.124	5.606
	CAB	3	157.115	1396.889	1420.780	2.000	0.111	6.268
	BCA	1	143.677	1388.862	1403.491	1.500	0.095	7.269
	CAB	3	127.807	1354.550	1376.558	2.000	0.086	8.020
	BCA	1	198.454	1645.150	1675.986	0.750	0.075	9.261
	ABC	2	228.501	2497.679	2556.333	0.750	0.078	8.861
N			18	18	18	18	18	18
Mean			160.1528	1577.2434	1610.4305	1.6944	0.0933	7.6834
SD			34.09761	585.27217	616.17364	0.69428	0.01740	1.51041
Min			100.618	923.629	932.847	0.750	0.061	5.405
Median			156.286	1392.876	1412.135	1.875	0.096	7.240
Max			228.501	2764.422	2929.025	3.000	0.128	11.400
CV%			21.3	37.1	38.3	41.0	18.6	19.7
Geometric Mean			156.763	1484.144	1510.523	1.546	0.092	7.551

**Pharmacokinetic Parameters for Reference Formulation in Fed Conditions (C):
Tramadol**

Subject	Sequence	Period	C _{max} (ng/mL)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	T _{max} (hr)	K _{el} (1/hr)	t _{1/2} (hr)
(b) (6)	CAB	1	155.691	1356.673	1377.937	2.250	0.079	8.816
	ABC	3	207.111	2441.748	2488.101	2.500	0.085	8.113
	BCA	2	256.422	1396.514	1422.627	0.750	0.106	6.563
	BCA	2	146.284	1278.793	1291.355	2.000	0.100	6.927
	ABC	3	171.616	1265.835	1276.477	0.750	0.103	6.724
	CAB	1	197.410	2423.548	2540.922	3.000	0.065	10.701
	ABC	3	160.241	1096.481	1107.683	1.000	0.096	7.203
	CAB	1	171.271	954.217	983.647	1.250	0.148	4.677
	BCA	2	152.097	1490.899	1506.667	2.250	0.096	7.257
	ABC	3	206.645	1850.079	1870.354	1.000	0.092	7.519
	CAB	1	234.381	1790.339	1808.648	1.250	0.091	7.654
	BCA	2	206.214	2448.826	2506.405	4.000	0.081	8.546
	ABC	3	124.194	1092.366	1103.980	1.750	0.125	5.533
	CAB	1	206.891	1461.273	1479.943	1.750	0.120	5.762
	BCA	2	205.892	1601.322	1614.095	1.250	0.106	6.553
	CAB	1	180.118	1548.777	1580.683	2.000	0.080	8.652
	BCA	2	177.726	1582.485	1605.405	3.500	0.092	7.540
	ABC	3	199.208	2631.141	2704.577	3.000	0.078	8.856
N			18	18	18	18	18	18
Mean			186.6340	1650.6286	1681.6393	1.9583	0.0968	7.4220
SD			32.86856	514.55018	536.05870	0.95583	0.01978	1.41923
Min			124.194	954.217	983.647	0.750	0.065	4.677
Median			188.764	1519.838	1543.675	1.875	0.094	7.388
Max			256.422	2631.141	2704.577	4.000	0.148	10.701
CV%			17.6	31.2	31.9	48.8	20.4	19.1
Geometric Mean			183.858	1580.455	1607.662	1.740	0.095	7.292

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\16-2-6-individuals-efficacy-response-data-fast-fed-1.pdf; p. 5-7/50

3. Individual subject Pharmacokinetic Parameters for metabolite, O-desmethyl tramadol: Test Formulation in fed (A) and fasting conditions (B), and, Reference Formulation in fed conditions (C), Study 198/18

**Pharmacokinetic Parameters for Test Formulation in Fed Conditions (A):
O-Desmethyl Tramadol**

Subject	Sequence	Period	C _{max} (ng/mL)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	T _{max} (hr)	K _{el} (1/hr)	t _{1/2} (hr)
(b) (6)	CAB	2	50.107	894.785	916.270	3.500	0.083	8.334
	ABC	1	41.856	856.282	883.489	3.500	0.081	8.588
	BCA	3	39.395	415.236	423.799	2.500	0.112	6.209
	BCA	3	53.710	850.419	862.176	3.500	0.095	7.283
	ABC	1	50.432	632.890	638.582	2.750	0.096	7.187
	CAB	2	20.118	423.226	443.312	5.000	0.071	9.804
	ABC	1	48.554	538.615	550.732	2.000	0.107	6.485
	CAB	2	60.386	767.211	772.337	2.750	0.110	6.322
	BCA	3	37.282	573.469	581.143	5.000	0.094	7.378
	ABC	1	47.302	690.113	698.599	3.500	0.095	7.280
	CAB	2	31.011	516.676	525.765	5.000	0.088	7.855
	BCA	3	18.687	359.222	368.019	4.000	0.083	8.354
	ABC	1	43.691	469.176	474.258	1.750	0.129	5.362
	CAB	2	54.079	783.070	789.701	3.000	0.104	6.661
	BCA	3	46.161	712.133	723.628	4.000	0.091	7.596
	CAB	2	35.359	624.858	642.564	5.000	0.080	8.704
	BCA	3	28.341	428.752	436.764	3.500	0.087	7.991
	ABC	1	37.897	680.332	699.767	4.000	0.080	8.675
N			18	18	18	18	18	18
Mean			41.3538	623.1367	635.0502	3.5694	0.0936	7.5593
SD			11.53324	167.54105	169.96988	1.01026	0.01441	1.10155
Min			18.687	359.222	368.019	1.750	0.071	5.362
Median			42.774	628.874	640.573	3.500	0.093	7.487
Max			60.386	894.785	916.270	5.000	0.129	9.804
CV%			27.9	26.9	26.8	28.3	15.4	14.6
Geometric Mean			39.543	601.079	612.894	3.423	0.093	7.482

**Pharmacokinetic Parameters for Test Formulation in Fasting Conditions (B):
O-Desmethyl Tramadol**

Subject	Sequence	Period	C _{max} (ng/mL)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	T _{max} (hr)	K _{el} (1/hr)	t _{1/2} (hr)
(b) (6)	CAB	3	59.548	933.583	952.844	2.500	0.084	8.241
	ABC	2	39.309	797.726	822.078	3.500	0.079	8.805
	BCA	1	42.277	356.847	364.893	1.000	0.103	6.735
	BCA	1	55.695	820.077	835.945	2.500	0.086	8.046
	ABC	2	44.400	610.888	619.528	1.750	0.088	7.870
	CAB	3	17.147	368.517	398.371	3.000	0.056	12.481
	ABC	2	56.947	570.738	579.738	1.000	0.090	7.711
	CAB	3	70.711	856.757	861.635	1.000	0.111	6.249
	BCA	1	39.573	549.065	557.477	0.750	0.090	7.702
	ABC	2	43.840	731.839	743.652	3.500	0.091	7.645
	CAB	3	39.662	591.842	607.100	3.000	0.081	8.522
	BCA	1	16.697	289.043	300.403	3.000	0.071	9.696
	ABC	2	56.989	509.702	516.329	1.750	0.122	5.685
	CAB	3	63.581	781.236	786.677	2.000	0.106	6.514
	BCA	1	46.771	743.839	754.635	2.750	0.092	7.574
	CAB	3	41.128	661.702	675.041	2.000	0.084	8.248
	BCA	1	43.307	536.658	546.070	1.750	0.085	8.135
	ABC	2	44.253	725.306	743.374	2.000	0.083	8.327
N			18	18	18	18	18	18
Mean			45.6575	635.2980	648.0993	2.1528	0.0890	8.0104
SD			13.95134	181.16193	181.51783	0.87085	0.01489	1.47231
Min			16.697	289.043	300.403	0.750	0.056	5.685
Median			44.047	636.295	647.285	2.000	0.087	7.958
Max			70.711	933.583	952.844	3.500	0.122	12.481
CV%			30.6	28.5	28.0	40.5	16.7	18.4
Geometric Mean			43.063	607.181	620.709	1.960	0.088	7.895

**Pharmacokinetic Parameters for Reference Formulation in Fed Conditions (C):
O-Desmethyl Tramadol**

Subject	Sequence	Period	C _{max} (ng/mL)	AUC _t (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	T _{max} (hr)	K _{el} (1/hr)	t _{1/2} (hr)
(b) (6)	CAB	1	54.603	801.000	816.935	4.000	0.085	8.145
	ABC	3	39.111	784.580	809.414	4.000	0.080	8.711
	BCA	2	41.204	416.649	425.589	1.000	0.110	6.304
	BCA	2	50.236	816.955	831.675	2.000	0.090	7.742
	ABC	3	49.904	679.830	687.802	3.000	0.098	7.103
	CAB	1	21.014	393.263	415.723	5.000	0.065	10.613
	ABC	3	47.907	584.806	593.139	1.250	0.091	7.590
	CAB	1	80.352	811.837	825.727	1.500	0.114	6.055
	BCA	2	41.596	654.517	664.025	2.750	0.092	7.507
	ABC	3	44.117	658.768	669.765	2.000	0.088	7.883
	CAB	1	40.005	517.994	526.229	1.250	0.089	7.830
	BCA	2	24.390	418.853	429.806	4.000	0.082	8.455
	ABC	3	44.416	524.876	532.981	2.000	0.121	5.722
	CAB	1	69.683	743.162	759.429	2.000	0.112	6.192
	BCA	2	47.994	732.265	743.830	1.250	0.092	7.563
	CAB	1	41.010	631.770	647.517	2.250	0.081	8.581
	BCA	2	32.385	453.573	461.782	5.000	0.087	7.947
	ABC	3	36.314	656.924	676.841	5.000	0.079	8.743
N			18	18	18	18	18	18
Mean			44.7912	626.7567	639.9006	2.7361	0.0920	7.7046
SD			14.05175	143.85018	145.57285	1.41024	0.01428	1.17623
Min			21.014	393.263	415.723	1.000	0.065	5.722
Median			42.857	655.720	666.895	2.125	0.089	7.786
Max			80.352	816.955	831.675	5.000	0.121	10.613
CV%			31.4	23.0	22.7	51.5	15.5	15.3
Geometric Mean			42.765	609.956	623.174	2.400	0.091	7.620

Source: m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\fed-study\16-2-6-individuals-efficacy-response-data-fast-fed-1.pdf; p. 8-10/50

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