CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211150Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	211150
SDN#	5
Submission Date	12/14/18
Submission Type	*Priority Review*
Brand Name (proposed)	WAKIX
Generic Name	Pitolisant HCl
Dosage Form and Strength	Film coated oral tablets Strengths: 4.45 mg and 17.8 mg
Route of Administration	Oral
Proposed Indication	Excessive daytime sleepiness (EDS) in adult patients with narcolepsy and cataplexy in adult patients with narcolepsy
Applicant	Bioproject Pharma/Harmony Biosciences
Associated IND	IND 111842
PDUFA date	8/14/2019
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OCP Final Signatory	Mehul Mehta Division Director DCP 1

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1. EXECUTIVE SUMMARY

This New Drug Application is for an NME (pitolisant HCL; proposed trade name- WAKIX) submitted by Harmony Biosciences on behalf of Bioproject Pharma for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy and cataplexy in adult patients with narcolepsy.

Pitolisant is a histamine 3 receptor antagonist/inverse agonist which was approved by the European Medicines Agency (EMA) as WAKIX for the treatment of narcolepsy with or without cataplexy in adults in 2016. Pitolisant received Breakthrough Therapy Designation for the treatment of cataplexy in narcolepsy and Fast Track Designation for EDS.

The efficacy and safety of WAKIX is established by several adequate and well-controlled clinical studies conducted in narcolepsy patients. The details are listed in the Medical/Clinical review (Martine Solages *et. al.)*

- Harmony 1: Pivotal Phase 3 efficacy and safety study for excessive daytime sleepiness (EDS)
- Harmony CTP: Pivotal Phase 3 efficacy and safety study for cataplexy
- Harmony Ibis: Phase 3 efficacy and safety study for excessive daytime sleepiness (EDS)
- Harmony III: Open label, long term safety study

Clinical Pharmacology is supported by several clinical studies:

- Six Phase I clinical studies (P02-02, P03-04, P09-11, P14-05, P11-01, and P11-03) evaluating the single dose PK of pitolisant from 5 to 240 mg in healthy subjects;
- Four Phase I clinical studies (P03-03, P04-06, P09-12, and P15-02) evaluating the repeat dose PK of pitolisant from 20 to 50 mg QD in healthy subjects;
- Six clinical studies with nine study parts (P11-03 Parts II and III, P11-10, P03-08, P03-01 Part I, P14-07 Parts I and II, P15-15 Parts I and II), assessing drug interactions with pitolisant in healthy subjects;
- Three clinical studies with PK data from adult (P05-03 and P06-06) and pediatric (P11-11) patients with narcolepsy (ages 6 to <12 years and ages 12 to <18 years);
- Four clinical studies assessing PK in specific populations, including cytochrome P450 (CYP)2D6 poor metabolizers (PMs) (P15-02), elderly subjects (P09-12), subjects with hepatic impairment (P09-14) and subjects with renal impairment (P09-13).

Several pharmacodynamic studies were also conducted:

• Two TQTc (thorough QT/QTc) studies (P09-11 and P14-05);
• A positron emission tomography (PET) study (P14-08; REB 103/2014);
• A human abuse potential (HAP) study (P16-02, INC Research 1008541).

The recommended dose of pitolisant is 35.6 mg to be administered orally once daily in the morning upon waking up. Patients should be titrated to 35.6 mg once daily according to the following schedule:

- Week 1: initiate treatment with a dose of 8.9 mg once daily
- Week 2: increase dose to 17.8 mg once daily
- Week 3: increase to the recommended dose of 35.6 mg once daily

This identical product (film-coated oral tablets) has already been approved by the European Medicines Agency (EMA) as WAKIX® since March 2016 for the treatment of adult patients with narcolepsy with or without cataplexy.

The entire clinical development program including all the efficacy and safety studies and all the clinical pharmacology studies have been conducted in European countries (several countries within eastern and western Europe). Though none of the clinical studies were conducted in U.S patients, the efficacy and safety results are applicable to U.S population because of the similarity of - etiology of the disease, diagnosis of disease and overall progression of disease – in EU and U.S (details in Medical/Clinical review by Martine Solages *et. al.).* Additionally, the pharmacokinetic of WAKIX is likely to be similar in U.S vs. European patients because the PK of pitolisant is known to be not impacted by gender, age, body mass index (BMI) etc. Thus, the results from the development studies are applicable to U.S patients.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA package to support a recommendation of approval for WAKIX. The key review issues with specific recommendations and comments are summarized below:

Key Review Issue	Relevant Clinical Studies	Reviewer Recommendations and Comments
Is the proposed dosing regimen for general patient population acceptable?	• Harmony 1: Pivotal Phase 3 efficacy and safety study for excessive daytime sleepiness (EDS) • Harmony CTP: Pivotal Phase 3 efficacy and safety study for cataplexy • Harmony Ibis: Phase 3 efficacy and safety study for excessive daytime sleepiness (EDS)	The recommended dose of pitolisant is 35.6 mg to be administered orally once daily in the morning upon waking up. Patients should be titrated to 35.6 mg once daily according to the following schedule: • Week 1: initiate treatment with a dose of 8.9 mg (two 4.45 mg tablets) once daily • Week 2: increase dose to 17.8 mg (one 17.8 mg tablet) once daily

	• Additional support for safety via: Harmony III: Open label, long term safety study	• Week 3: increase to the recommended dose of 35.6 mg (two 17.8 mg tablets) once daily The proposed general dosing regimen is supported by several independent clinical studies. The proposed dosing regimen is acceptable.
Are the proposed dose-adjustments for organ impaired patients acceptable?	Hepatic impairment study (# P09-14)	A dedicated hepatic impairment study demonstrated that pitolisant exposures (Cmax and AUC) were generally similar in mild vs. normal healthy. However, moderate had 2-fold increase in AUC as well as prolongation of T1/2. There was no data in severe hepatic impaired subjects. (b) (4) The details are provided in Clinical Pharmacology Questions (Section 3.3). • Mild hepatic impaired= no dose adjustment • Moderate hepatic impaired = titrate the dose for a longer duration (i.e., 2 weeks (b) (4) and cap the dose at 17.8 mg/day • Severe hepatic impaired = contra-indicated
	Renal impairment study (# P09-13)	A dedicated renal impairment study demonstrated that pitolisant exposures (Cmax and AUC) were generally 2-fold higher in all categories of renal impairment (i.e., mild, moderate and severe) vs. normal healthy. There was no data in end stage renal disease subjects. (b) (4) The details are provided in Clinical Pharmacology Questions (Section 3.3). • Mild renal impaired= no dose adjustment • Moderate renal impaired = cap the dose at 17.8 mg/day

		• Severe renal impaired = cap the dose at 17.8 mg/day • ESRD= not recommended
Are there dose adjustments required for poor metabolizers (PMs) of CYP2D6?	Mass Balance Study (# P15-02)	An approximate 2-fold increase in exposure was observed in CYP2D6 poor metabolizers (PMs) as compared to CYP2D6 normal metabolizers (NMs). Additionally, a dedicated drug interaction study with paroxetine (a strong CYP2D6 inhibitor) also resulted in a similar increase in exposure of pitolisant which supports the conclusion that exposures can be expected to be 2 -fold higher in CYP2D6 PMs. The details are provided in Clinical Pharmacology Questions (3.3). • Known CYP2D6 PMs = cap the dose at 17.8 mg/day
Bridge between the to-be-marketed and clinical trial formulations	Pivotal efficacy/safety studies as well as key clinical pharmacology studies were conducted with the final to-be-marketed film-coated tablets.	No additional PK bridging study required.

1.2 Post-Marketing Requirements and Commitments

None currently.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

WAKIX is a selective, orally active antagonist/inverse agonist (Ki of 0.3 nM) of the human histamine 3 (H3) receptor. By binding to presynaptic histaminergic H3 autoreceptors, WAKIX increases the synthesis and release of histamine, a key wake-promoting neurotransmitter. This results in increased histamine transmission in the brain. Increased histamine then binds to excitatory postsynaptic H1 receptors to activate wake-promoting regions in the brain directly, as well as stimulate other wake-promoting neuronal systems.

The key PK characteristics of WAKIX are listed below:

Following oral administration of pitolisant 35.6 mg once daily, the steady state Cmax and AUC is 73 ng/mL (42.9 to 126 ng/mL) and 812 (518 to 1468 ng*hr/mL), respectively. Pitolisant exposure increases proportionally with dose and steady state is reached by day 7.

Absorption
The median time to maximum plasma concentration (Tmax) of pitolisant is 3.5 hours (2 to 5 hours). WAKIX has an oral absorption ~90%. No clinically significant differences in the pharmacokinetics of pitolisant were observed following administration with a high-fat meal.

Distribution
The apparent volume of distribution of pitolisant is approximately 700 L (5 to 10 L/kg). Serum protein binding is approximately 91% to 96%. The blood to plasma ratio of pitolisant is 0.55 to 0.89.

Elimination
After a single dose of 35.6 mg, the median half-life of pitolisant is approximately 20 hours (7.5 to 24.2 hours). The apparent oral clearance (CL/F) of pitolisant is 43.9 L/hr and renal clearance accounts for < 2% of the total clearance of Pitolisant.

Metabolism
Pitolisant is extensively metabolized primarily by polymorphic CYP2D6 and to a lesser extent, by CYP3A4 and Phase 2 glucuronidation. Though there are many circulating metabolites, all the major circulating metabolites were determined to be “inactive”. Additionally, the exposure ratio (i.e., AUC of metabolite/AUC of parent) of all major circulating metabolites is 0.5 or lower.

Excretion
After a single oral radiolabeled pitolisant 17.8 mg dose, approximately 90% of the dose was excreted in urine (< 2% as unchanged parent) and 2.3% in feces.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose of pitolisant is 35.6 mg to be administered orally once daily in the morning upon waking up. Patients should be titrated to 35.6 mg once daily according to the following schedule:

- Week 1: initiate treatment with a dose of 8.9 mg (two 4.45 mg tablets) once daily
- Week 2: increase dose to 17.8 mg (one 17.8 mg tablet) once daily
- Week 3: increase to the recommended dose of 35.6 mg (two 17.8 mg tablets) once daily

2.2.2 Therapeutic individualization

Hepatic Impairment:
A dedicated hepatic impairment study demonstrated that pitolisant exposures (Cmax and AUC) were generally similar in mild vs. normal healthy. However, moderate had 2-fold increase in AUC as well as T1/2. There was no data in severe hepatic impaired subjects. (b) (4) The details are provided in Clinical Pharmacology Questions (3.3).

- Mild hepatic impaired= no dose adjustment
- Moderate hepatic impaired = titrate the dose for a longer duration (i.e., 2 weeks (b) (4) and cap the dose at 17.8 mg/day
- Severe hepatic impaired = contra-indicated

Renal Impairment:
A dedicated renal impairment study demonstrated that pitolisant exposures (Cmax and AUC) were generally 2-fold higher in all categories of renal impairment (i.e., mild, moderate and severe) vs. normal healthy. There was no data in end stage renal disorder subjects. (b) (4) We disagree and have alternate recommendations. The details are provided in Clinical Pharmacology Questions (3.3).

- Mild renal impaired= no dose adjustment
- Moderate renal impaired = cap the dose at 17.8 mg/day
- Severe renal impaired = cap the dose at 17.8 mg/day
- ESRD= not recommended

CYP2D6 Genetic Deficiencies:
An approximate 2-fold increase in exposure was observed in CYP2D6 poor metabolizers (PMs) as compared to CYP2D6 normal metabolizers (NMs). Additionally, a dedicated drug interaction study with paroxetine (a strong CYP2D6 inhibitor) also resulted in a similar increase in exposure of pitolisant which supports the conclusion that exposures can be expected to be 2x -fold higher in CYP2D6 PMs. Therefore, the dose of WAKIX should be capped at 17.8 mg/day in known CYP2D6 PMs. The details are provided in Clinical Pharmacology Questions (3.3).

Drug-Drug Interactions:

Strong CYP2D6 Inhibitors
Concomitant use of pitolisant with paroxetine (a strong CYP2D6 inhibitor) increased pitolisant the Cmax and AUC of pitolisant by 1.5-fold and 2.2-fold, respectively. This may increase the risk of increased adverse events with WAKIX. Therefore, the dose of WAKIX should be reduced by half during concomitant dosing. The details are provided in Clinical Pharmacology Questions (3.3).

Strong CYP3A4 Inducers
Concomitant use of pitolisant with rifampin (strong CYP3A4 inducer) decreased pitolisant Cmax and AUC and by 39% and 48%, respectively. The detailed dose adjustments recommended for WAKIX when co-administered with strong CYP3A4 inducers (e.g., rifampicin, phenytoin etc.) are in Clinical Pharmacology Questions (3.3).

- For patients stable on 8.9 mg/day or 17.8 mg/day: Dose to be increased gradually over a week to reach double the original dose level. Maintain for the duration of use of CYP3A4 inducers.
- For patients stable on the highest dose of 35.6 mg/day: No dose adjustments is recommended

2.3 Outstanding Issues

None currently.

2.4 Summary of Labeling Recommendations

Based on the review, the Office of Clinical Pharmacology made the following labelling recommendations:

- Concrete dose adjustments for patients with hepatic impairments
- Concrete dose adjustments for patients with renal impairments
- Concrete dose adjustments for patients who are known CYP2D6 poor metabolizers (PMs)
- Concrete dose adjustments for patients co-administered with CYP2D6 inhibitors
- Concrete dose adjustments for patients co-administered with CYP3A4 inducers
- Concrete dose steps for patients on oral contraceptives co-administered with WAKIX

The detailed dose-adjustment strategies for all clinical scenarios (listed above) are provide in Section 3.3

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Pitolisant is being developed for the treatment of excessive daytime sleepiness (EDS) and cataplexy in adult patients with narcolepsy. Pitolisant was approved by the European Medicines Agency (EMA) as WAKIX® in March 2016 for the treatment of adult patients with narcolepsy with or without cataplexy. It is planned as film-coated oral tablets at two strengths: 4.45 mg and 17.8 mg.

Pitolisant is a first-in-class, potent, highly selective, histamine 3 (H3) receptor antagonist/inverse agonist, which offers a novel mechanism of action for the treatment of EDS and cataplexy in patients with narcolepsy. It works by enhancing the activity of histaminergic neurons in the brain. Pitolisant binds to H3 receptors and blocks the normal negative feedback mechanism for histamine release, resulting in increased release of this wake promoting neurotransmitter. It also functions as an inverse agonist, resulting in enhanced histamine synthesis and release from presynaptic neurons.

Pitolisant received Orphan Drug Designation by the FDA for the treatment of narcolepsy in May 2010. An investigational new drug (IND) application for pitolisant was filed with the FDA on 27 February 2018, and pitolisant was subsequently granted Fast Track status for the treatment of EDS in patients with narcolepsy and for the treatment of cataplexy in patients with narcolepsy (25 April 2018 FDA letter). Breakthrough Therapy Designation for the treatment of cataplexy in patients with narcolepsy was granted on 27 April 2018, based on preliminary clinical evidence that the safety profile of pitolisant may be superior to the only other approved treatment for narcolepsy with cataplexy (sodium oxybate) (27 April 2018 FDA letter).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Pitolisant is a first-in-class, potent, highly selective, histamine 3 (H3) receptor antagonist/inverse agonist, which offers a novel mechanism of action for the treatment of EDS and cataplexy in patients with narcolepsy.
Active Moieties	Pitolisant is the only active moiety. Though there are many circulating metabolites, all the major circulating metabolites were determined to be “inactive”. Additionally, the exposure

	ratio (i.e., AUC of metabolite/AUC of parent) of all major circulating metabolites is 0.5 or lower.
QT Prolongation	QTc study demonstrated that there was no clinically relevant prolongation of QT interval at the recommended highest dose of 35.6 mg. However, there was a clear and direct correlation of pitolisant exposure with QTc prolongation. Supra-therapeutic single doses of pitolisant (106.8, 142.4, 178 and 213.6 mg) all resulted in increases in QTcF with upper bounds of 90% CI between 12-18 msec.
General Information	
Bioanalysis	Pitolisant and its metabolites concentrations were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as appendix.
Drug exposure at steady state following the therapeutic dosing regimen	The population PK model (developed by sponsor with data from multiple PK studies) demonstrated mean exposures at therapeutic dose of 35.6 mg at steady state levels as follows: - Mean Cmax = ~73 ng/mL - Mean AUC = 812 ng*hr/mL The exposures in CYP2D6 PMs were approximately 2-fold higher.
Dose Proportionality	Pitolisant PK is dose-proportional from 17.8 mg to 213.6 mg
Accumulation Index at steady state	There was approximately 2-fold accumulation of exposure (for both Cmax and AUC) at steady-state
PK in healthy vs. PK in patient	PK of pitolisant in patients was similar to the PK in healthy subjects
Absorption	
• Although an absolute bioavailability study has not been conducted for pitolisant, mass balance study suggests that the absorption of pitolisant is ~90% (because ~90% of oral dose is eliminated via the urine, predominantly as metabolites) • Pitolisant PK is dose-proportional and reaches steady-state by day 7. • The median Tmax of pitolisant is 3.5 hours • Pitolisant has moderate to high inter-subject PK variability (40-60% between subjects).	

Distribution
• Volume of Distribution: 5-10 L/kg. • Plasma Protein Binding: 91-96%
Elimination
• Clearance: Pitolisant has a mean apparent oral clearance (CL/F) of 43.9 L/hr. • Mean effective half-life: 20 hrs. • Metabolism: Pitolisant is primarily metabolized by CYP2D6 and to a lesser extent, by CYP3A4 and Phase 2 glucuronidations. • Excretion: After oral dosing, approximately 90% of the dose was excreted in urine (< 2% as unchanged parent) and 2.3% in feces. • Transporter: In vitro studies suggest that Pitolisant and the major circulating metabolites are unlikely to be substrates or inhibitors of key transporters at clinically relevant concentrations. • Inhibitor/Inducer to CYP enzymes: In vitro studies suggest that Pitolisant and the major circulating metabolites are unlikely to inhibit or induce any key CYP enzymes at clinically relevant concentrations.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The efficacy and safety of WAKIX is established by several adequate and well-controlled clinical studies conducted in narcolepsy patients. The key Phase 3 studies supporting the efficacy and safety are listed below:

- Harmony 1: Pivotal Phase 3 efficacy and safety study for excessive daytime sleepiness (EDS)
- Harmony CTP: Pivotal Phase 3 efficacy and safety study for cataplexy
- Harmony Ibis: Phase 3 efficacy and safety study for excessive daytime sleepiness (EDS)

All the clinical efficacy and safety studies were conducted using a similar study design. All the studies were multicenter, double-blind, placebo-controlled studies with a duration of treatment with pitolisant of 7 or 8 weeks.Progressive individual dose titration was adopted to allow patients to adapt to the waking effects of the drug as well as its potential side effects. In these studies, the starting dose was 4.45 mg or 8.9 mg with dose escalations on week 2 and week 3. At Week 3, the pitolisant dose was titrated to a stable dose based on tolerability and effectiveness, and patients were maintained on this stable dose for the remainder of the study (additional 4-5 weeks at the stable dose). The maximum possible daily dose of pitolisant HCL was 35.6 mg in all studies except one where it was 17.8 mg. These studies collectively demonstrated the efficacy of pitolisant in the treatment of excessive daytime sleepiness and cataplexy in adult patients with narcolepsy. The details of the study design, end-points, study results and efficacy conclusions are in the Medical/Clinical review by Martine Solages *et. al.*

Additionally, dedicated clinical pharmacology studies have been conducted to assess the impact of intrinsic factors on the PK of pitolisant. The results of those studies have led to concrete dosing recommendations in patient subpopulations: renal impaired, hepatic impaired, CYP2D6 poor metabolizers [PMs]). Similarly, dedicated drug-interaction studies led to concrete dosing recommendations in patient concomitantly dosed with CYP2D6 inhibitors and CYP3A4 inducers. In addition, clinical pharmacology studies and concentration-QT analyses provided evidence that there were clinically insignificant QT effects at the highest therapeutic dose and clinically manageable increases in QT at supra-therapeutic doses (i.e., QT increase of 9.8 msec at 2.5X fold over the highest therapeutic dose).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The recommended dose of pitolisant is 35.6 mg to be administered orally once daily in the morning upon waking up. Patients should be titrated to 35.6 mg once daily according to the following schedule:

- Week 1: initiate treatment with a dose of 8.9 mg once daily
- Week 2: increase dose to 17.8 mg once daily
- Week 3: increase to the recommended dose of 35.6 mg once daily

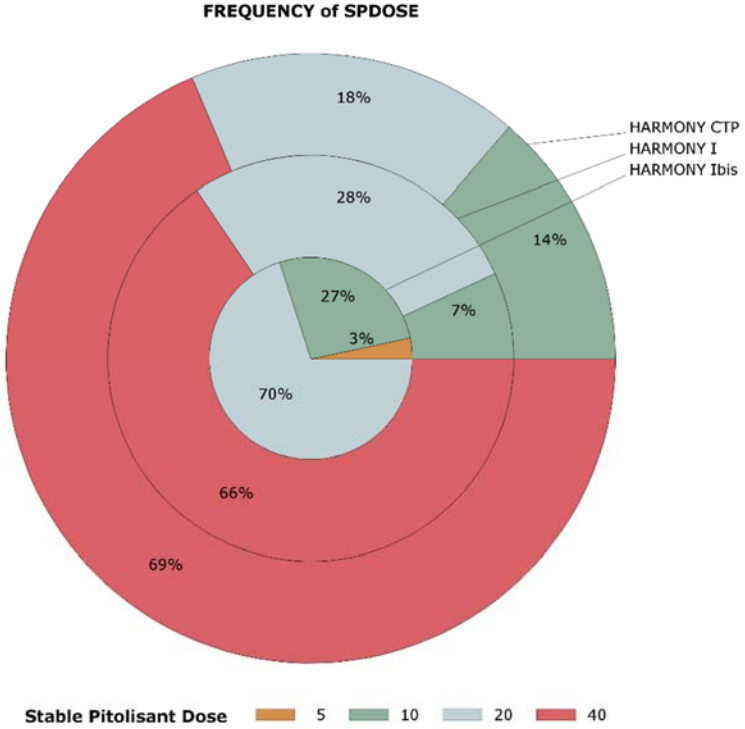
Patients should be monitored for clinical response related to both efficacy and tolerability, as some patients may achieve benefit at lower doses and/or require a lower dose based on tolerability.

In early clinical studies conducted in patients with ADHD (Study P05-07) or narcolepsy (Study P05-03), it was observed that patients starting directly on a dose of 35.6 mg (without any dose titration) had higher incidences of neuropsychiatric adverse events compared to those who started on a dose of 8.9 mg and subsequently titrated to higher doses. In Study P05-03 (Effect of 35.6 mg once-daily pitolisant for 7 days on vigilance in patients with narcolepsy), it was observed that five patients had a plasma level above 150 ng/ml on Day 6-7. Four of these patients experienced adverse events rated moderate or severe in intensity such as sweating nausea, malaise, dryness of the mouth. All occurred at the first day of treatment, except one (sweating) that occurred 3 days after. However, no patient stopped their treatment. The appropriateness of titration schedule for efficacy was informed by the findings from Study P05-03.

Subsequently, the applicant conducted three well-controlled Phase 3 studies that contributed to the safety and efficacy data (key efficacy endpoints of Epworth Sleepiness Scale [ESS], Maintenance of Wakefulness Test [MWT], and cataplexy counts).

In Study HARMONY_Ibis, the maximum dose studied was 17.8 mg (20 mg as salt form). However, in studies HARMONY I and HARMONY CTP, the maximum dose studied was 35.6 mg (40 mg as salt from). Figure 1 shows that a greater percentage of patients were stabilized on the highest dose of 40 mg (salt form) in HARMONY I and HARMONY CTP. Similarly, a greater percentage of patients were stabilized on the highest dose of 20 mg (salt form) in the HARMONY Ibis study. However, two patients were stabilized on 5 mg dose (salt form) in HARMONY Ibis.

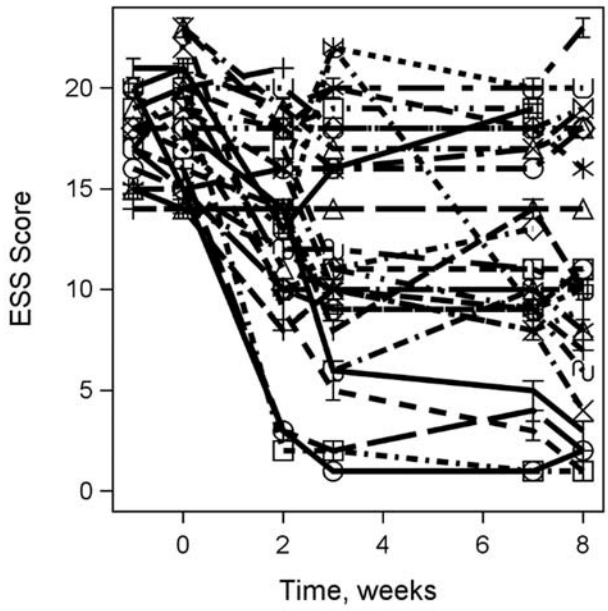
Figure 1. Percentage of patients stabilized at various dose levels in 3 clinical studies (HARMONY CTP, HARMONY I and HARMONY Ibis)



Source: Reviewer's analysis

Data from clinical trials suggest that some patients may see a clinical response during the first few weeks after initiation of therapy, while others may take several weeks up to 8 weeks to achieve an optimal response. Figure 2 shows the ESS score by time (week) in HARMONY I.

Figure 2. ESS score by time (week) in HARMONY I



Source: Reviewer's analysis

Supportive data for the proposed dose level also comes from a positron emission tomography (PET) imaging study of receptor occupancy, which demonstrated that close to 90% of brain H3 receptors were occupied after a 35.6 mg dose (40 mg as salt form) of pitolisant HCl.

The overall risk-benefit profile of pitolisant is detailed in the Medical/Clinical review by Martine Solages *et. al.*

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Dedicated clinical studies have been conducted to assess the effect of hepatic impairment and renal impairment as listed below:

Hepatic impairment study (P09-14): This was a multi-center, open-labeled, parallel group study in 6 subjects with mild hepatic impairment (Child Pugh A), 6 subjects with moderate hepatic impairment (Child Pugh B) and 12 healthy subjects matched for ethnicity, sex, age (±5 years) and BMI (±20%). Each subject received a single dose of pitolisant HCl 20 mg. The Cmax and AUC were generally similar in mild hepatic impaired subjects and healthy control subjects. However, the PK parameters in moderate hepatic impaired differed from healthy control subjects as follows: 30% increase of Cmax, 140% increase in AUC and 2-fold longer

T1/2. The trends in PK were similar for total as well as unbound pitolisant. Severe hepatic impaired subjects were not included in this study.

Table 1: PK of Pitolisant in Subjects with Hepatic Impairment and Matched Normal Subjects

Analyte	Parameter	Healthy Controls n=12	Mild Hepatic Impairment n=6	Moderate Hepatic Impairment n=5 or 6
Pitolisant	C_{max} (ng/mL)	19.1 ± 11.6	20.2 ± 7.17	24.8 ± 9.46
	T_{max} (h)*	2.5 (1.5-4)	2.5 (1-4)	1.75 (1-8)
	AUC_{inf} (ng*h/mL)	327 ± 327	462 ± 450	789 ± 336
	$t_{½}$ (h)	22 ± 12	24 ± 8.9	41 ± 31
	Fu (%)	4.30 ± 1.17	3.93 ± 0.46	6.01 ± 1.76

Source: Sponsor's summary of clinical pharmacology studies

Based on the PK changes observed in the hepatic impairment study, the following dose-adjustments are recommended:

- Mild hepatic impaired= no dose adjustment
- Moderate hepatic impaired = titrate the dose for a longer duration (i.e., 2 weeks (b) (4) and cap the dose at 17.8 mg/day
- Severe hepatic impaired = contraindicated

Renal impairment study (P09-13): This was a multi-center, open-labeled, parallel-group, single-dose study of pitolisant HCl 20 mg administered in 4 subjects with mild renal impairment (estimated glomerular filtration rate [eGFR] of 60 to 80 mL/min/1.73 m^2), 4 subjects with moderate renal impairment (eGFR of 30 to 59 mL/min/1.73 m^2), 4 subjects with severe renal impairment (eGFR of 15 to 29 mL/min/1.73 m^2), and 12 subjects with normal renal function (eGFR > 90 mL/min/1.73m^2). Each subject received a single dose of pitolisant HCl 20 mg. Based on total pitolisant drug levels, mean Cmax and AUC for all categories of renal impaired subjects (mild, moderate and severe) was generally 2-fold higher than the exposure of normal subjects. However, based on the free drug levels, mild and moderate renal impaired subjects had exposure similar to normal subjects while the severe renal impaired subjects had higher exposures (slightly less than 2-fold higher) compared to normal subjects.

Table 2: PK (total and free) of Pitolisant in Subjects with Renal Impairment and Matched Normal Subjects

BF2.649	Renal impairment			
Parameter	*Normal (n=12)*	*Mild (n=4)*	*Moderate (n=4)*	*Severe (n=4)*
C_{max} (ng/mL)	14.37 ± 8.37	31.32 ± 16.57	22.32 ± 15.43	36.76 ± 8.86
Ratio (/normal)		2.18	1.55	2.56
P-value		0.1305 (NS)	0.2028 (NS)	0.0004 ***
AUC_inf (h*ng/mL)	222 ± 175	396 ± 279	443 ± 364	428 ± 221
Ratio (/normal)		1.78	2.00	1.93
P-value		0.1560 (NS)	0.3145 (NS)	0.0760 (NS)
T_{max} (h)	2 [1.5-4]	1.75 [1.5-2]	3.5 [1.5-8]	1.5 [1-2]
$T_{1/2}$ (h)	20 ± 6.5	24 ± 4.5	27 ± 10	24 ± 1.4
Vz/Dose (L)	3950 ± 1850	2990 ± 2620	2300 ± 708	2010 ± 1010
Ratio (/normal)		0.76	0.58	0.51
P-value		0.4283 (NS)	0.1094 (NS)	0.0685 (NS)
Cl/Dose (L/h)	141 ± 91.4	93.9 ± 95.4	63 ± 29.5	57.7 ± 30.9
Ratio (/normal)		0.67	0.45	0.41
P-value		0.3882 (NS)	0.0212 *	0.1003 (NS)
A_e (%)	0.46 ± 0.37	0.31 ± 0.06	1.43 ± 0.87	0.88 ± 0.74
Ratio (/normal)		0.69	3.15	1.92
P-value		0.2408 (NS)	0.1435 (NS)	0.4043 (NS)
Cl_R (L/h)	0.52 ± 0.32	0.30 ± 0.18	1.30 ± 0.97	0.57 ± 0.49
Ratio (/normal)		0.57	2.49	1.08
P-value		0.2345 (NS)	0.2572 (NS)	0.8522 (NS)
f_u (%)	4.80 ± 0.90	3.02 ± 0.55	3.31 ± 0.50	3.72 ± 1.02
Ratio (/normal)		0.63	0.69	0.78
P-value		0.0036 **	0.0105 *	0.0818 (NS)
$C_{max\,u}$ (ng/mL)	0.70 ± 0.41	0.93 ± 0.55	0.76 ± 0.55	1.32 ± 0.28
Ratio (/normal)		1.33	1.09	1.89
P-value		0.3759 (NS)	0.8154 (NS)	0.0140 *
AUC_inf_u (h*ng/mL)	11 ± 8	12 ± 9	15 ± 13	15 ± 7
Ratio (/normal)		1.09	1.36	1.36
P-value		0.7789 (NS)	0.4417 (NS)	0.3562 (NS)

Source: Sponsor's renal impairment study report (P09-13)

We also assessed the total number of subjects with the different degrees of renal impairment who were included in the pivotal efficacy and safety studies (HARMONY 1, HARMONY CTP, HARMONY Ibis) and other studies. As listed below, all the studies consistently had significant proportion of healthy normal subjects and mild renal impaired subjects , ~48% and ~47%, respectively. However, only ~5% of the subjects were moderate renal impaired and no severe renal impaired subjects were ever included in the studies.

Table 3: Number of Patients with Renal Impairment at Baseline in the Clinical efficacy studies

Study	Number of Patients with Mild Renal Impairment	Number of Patients with Moderate Renal Impairment	Number of Patients with Normal Renal Function	Total Number of Patients with Data
HARMONY I (P07-03)	27	4	29	60
HARMONY Ibis (P09-15)	46	5	43	94
HARMONY CTP (P11-05)	52	8	43	103
HARMONY III (P09-10)	48	1	47	96
HARMONY IV (P10-01)	13	0	32	45
All Phase 3 Narcolepsy Studies	186	18	194	398

Source: Sponsor's Response to Clinical Pharmacology Information Request (01 February 2019)

Additionally, the proportion of subjects who were escalated to the highest dose (40 mg/day salt form) as a maintenance dose was similar across the 3 subject types: normal renal, mild renal impaired and moderate renal impaired subjects. In spite of escalation and maintaining at the highest dose, the proportion of subjects having any treatment emergent adverse effects (TEAE) or significant adverse events (SAE) were also similar across 3 subject types: normal renal, mild renal impaired and moderate renal impaired subjects. A representative table for TEAE and SAE is listed below.

Table 4: **Treatment-Emergent Adverse Events and** significant adverse events **by Renal Function Category (HARMONY CTP: P11-05)**

	Mild Renal Impairment (60 to <90 ml/min/1.73m²)		Moderate Renal Impairment (30 to <60 ml/min/1.73m²)		Normal Renal Function (≥90 ml/min/1.73m²)	
	Placebo (N=30)	Pitolisant (N=22)	Placebo (N=4)	Pitolisant (N=4)	Placebo (N=17)	Pitolisant (N=26)
Any TEAE	11 (36.7%)	7 (31.8%)	0	2 (50.0%)	5 (29.4%)	9 (34.6%)
Any SAE	0	0	0	0	0	0

Source: Sponsor's Response to Clinical Pharmacology Information Request (01 February 2019)

Considering the data from the PK changes (total and free) in the dedicated renal impairment study, the information regarding doses and AE's in the subjects from different renal categories in the pivotal efficacy and safety studies and the mass balance information that suggests that pitolisant is extensively metabolized and is primarily eliminated entirely as metabolites (not parent) via the urine (~90% of dose in urine as metabolites)- we recommend the following dose-adjustment strategy for renal impaired patients:

- Mild renal impaired= no dose adjustment

- Moderate renal impaired = cap the dose at 17.8 mg/day
- Severe renal impaired = cap the dose at 17.8 mg/day
- ESRD= not recommended

No alternate dosing regimen is required based on body weight, gender or race.

Figure 3: Box Plot of Dose-Normalized Cmax and AUCinf of Pitolisant by Sex

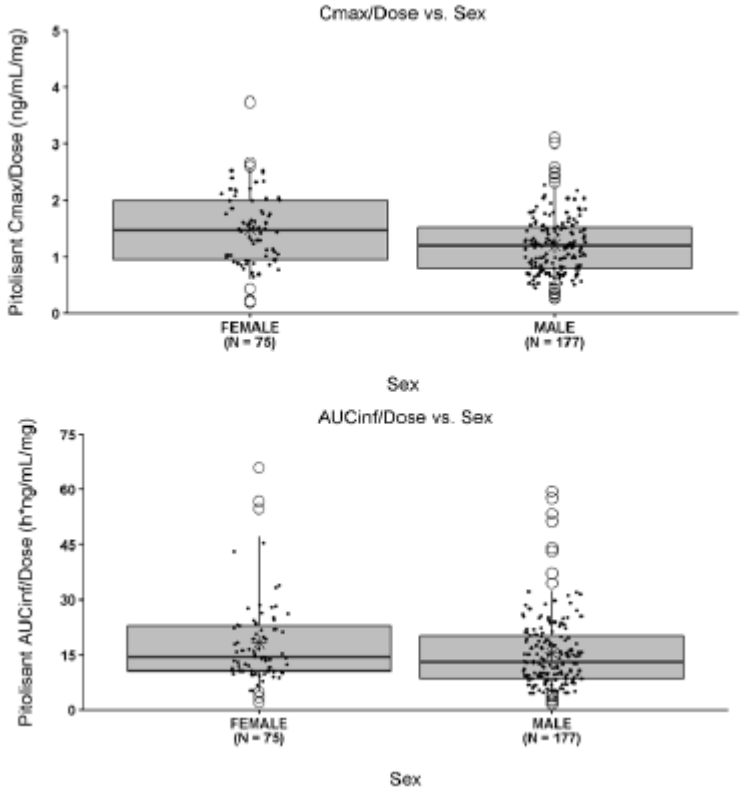


Figure 4: Box Plot of Dose-Normalized Cmax and AUCinf of Pitolisant by BMI

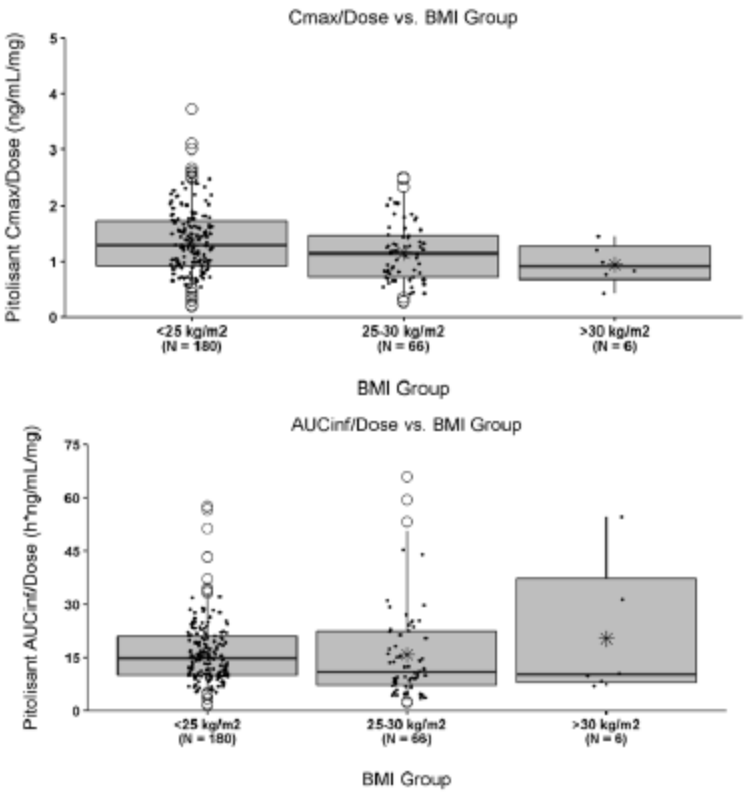
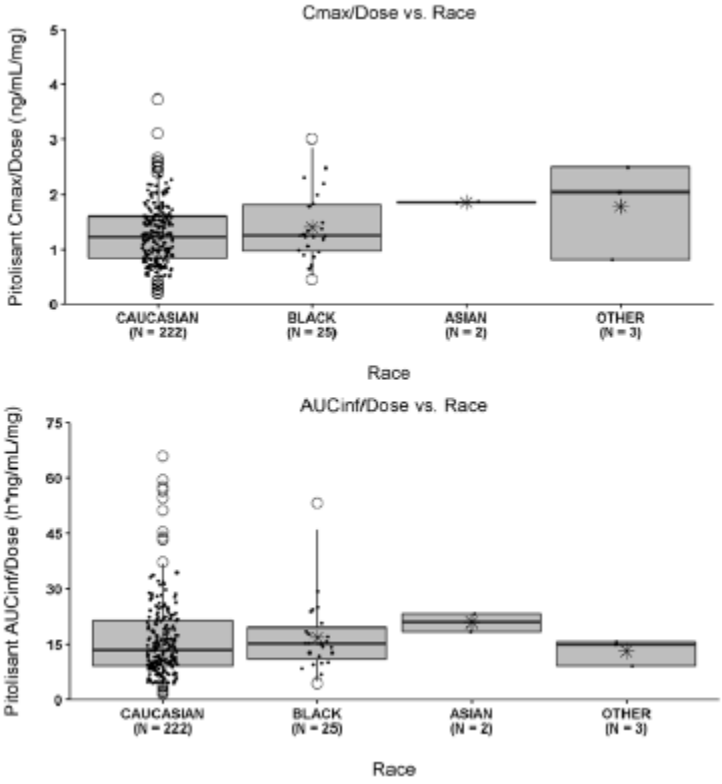


Figure 5: Box Plot of Dose-Normalized Cmax and AUCinf of Pitolisant by Race



Source: Sponsor's Summary of Clinical Pharmacology Studies (2.7.2)

CYP2D6 Genetic Deficiencies:
The PK of pitolisant in PMs of CYP2D6 vs. Normal metabolizers (NMs) of CYP2D6 was assessed in 8 genotyped healthy adult, male subjects in a mass balance clinical study (P15-02). The PK after single dose as well as after steady state (on day 7) at 40 mg dose (in salt form) was used to compare the exposure in PMs (N=3) vs NMs (N=5). CYP2D6 alleles tested and genotyping methods were appropriate for determining CYP2D6 PM and NM status. An approximate 2-fold increase in exposure was observed in CYP2D6 PMs as compared to CYP2D6 NMs. Additionally, a dedicated drug interaction study with paroxetine (a strong CYP2D6 inhibitor) also resulted in a similar increase in exposure of pitolisant which supports the conclusion that exposures can be expected to be 2-fold higher in CYP2D6 PMs.

Table 5: Cmax and AUC after repeat dosing at 40 mg/QD (salt form) in CYP2D6 NMs and PMs

CYP2D6 status	Cmax (ng/mL)	AUC (ng*h/mL)
NMs (N=5)	~73	~812
PMs (N=3)	~153	~1920

The prevalence of PMs is approximately 3-10%, but can vary in difference geographic regions of the world. Considering an approximate 2-fold higher Cmax and AUC in PMs compared to NMs, we recommend capping the dose at 17.8 mg/day in CYP2D6 PMs.

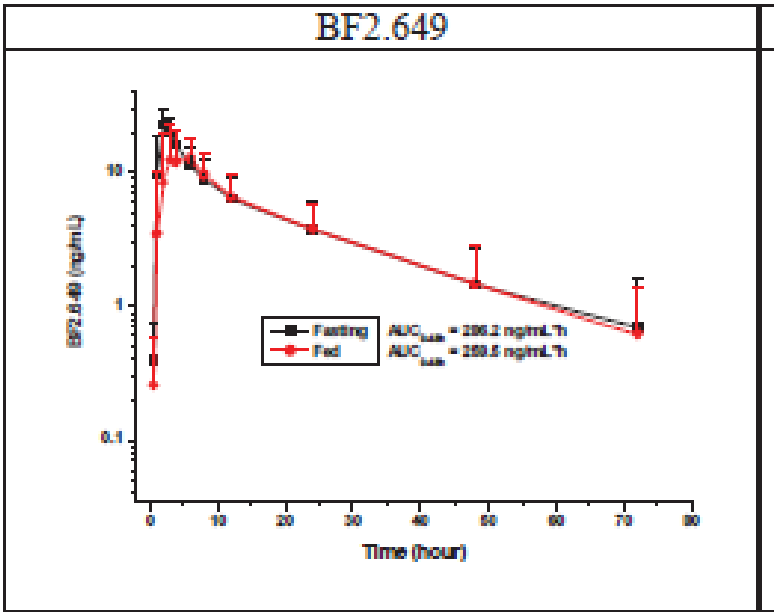
3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Dedicated clinical studies have been conducted to assess the effect of food and other co-administered drugs (i.e., drug-drug interaction) on the PK of pitolisant. The key individual studies and the appropriate dose management strategies are listed below:

Food effect study (P11-03; part I): This was a single-center, randomized two-way cross-over comparative bioavailability study of a single administration of pitolisant administered with or without a high-fat meal. A total of 12 healthy male subjects, (20 to 54 years), received 20 mg pitolisant HCl on 2 occasions, one with a high-fat meal (~963 Kcal, 17% protein, 21% carbohydrates, 62% fat) and one under fasting conditions. Both administrations were separated by a 1-week wash-out period. Serial blood samples were collected in each period over 72 hours post-dose. This study showed that when pitolisant was administered with a high-fat meal, pitolisant Cmax were reduced ~30%, but AUC ratio and 90% CI were within the 80-

125% bioequivalence (BE) criteria. Median Tmax estimates for pitolisant was delayed by 1.5 hr. Thus, food does not cause any clinically relevant effect on the PK of pitolisant and WAKIX can be administered with or without food.

Figure 6: Mean (± standard deviation) pitolisant concentrations measured in 12 healthy male volunteers after a single oral administration at 20 mg in fasting or fed conditions

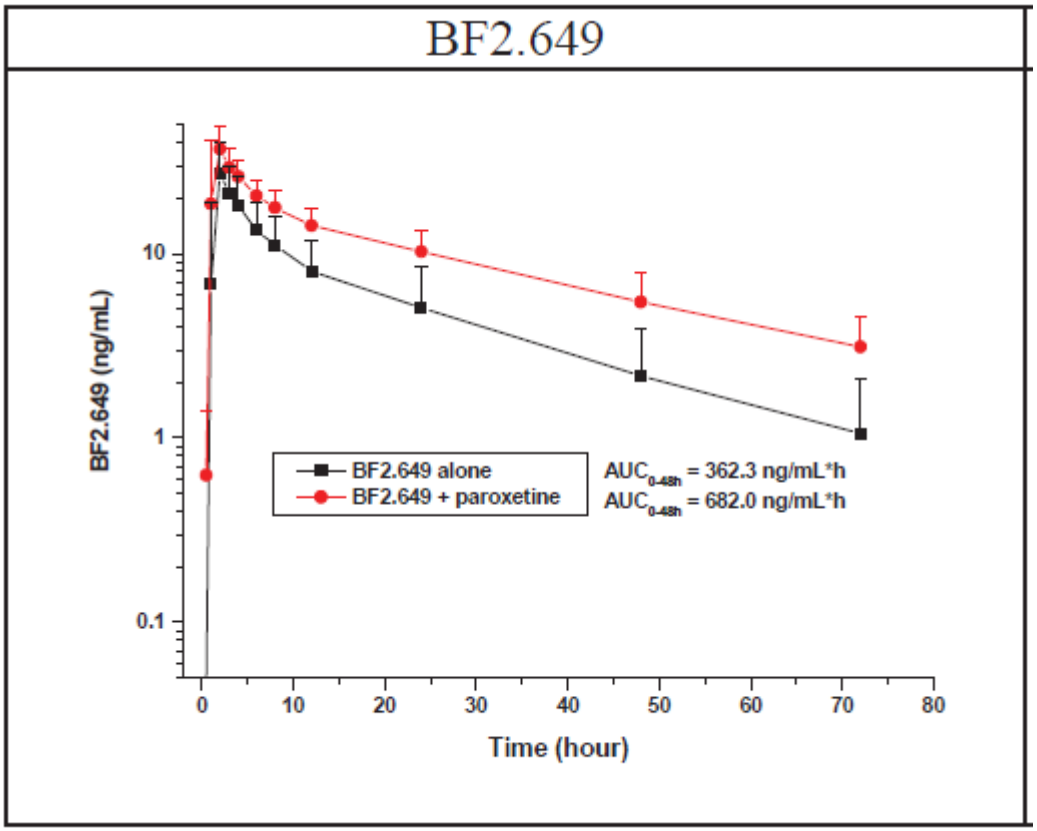


Source: Sponsor's Study Report for Food-Effect (P11-03; part 1)

Drug-Drug Interactions Studies with Pitolisant as a Victim Drug

Effect of paroxetine (CYP2D6 inhibitor) on the PK of pitolisant (P11-03; part III): This study was a comparative bioavailability study of a single administration of pitolisant alone or together with 20 mg paroxetine (at steady state) in a single sequence cross-over design. It was conducted in 18 healthy adult males aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with paroxetine, a potent CYP2D6 inhibitor, at 20 mg QD x 7 days was found to increase the Cmax and AUC of pitolisant by 1.5- and 2.2-fold, respectively. Thus, considering a 2-fold increase in exposure of pitolisant with paroxetine, the clinical dose of WAKIX should be decreased by 50% when co-administrated with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine etc.)

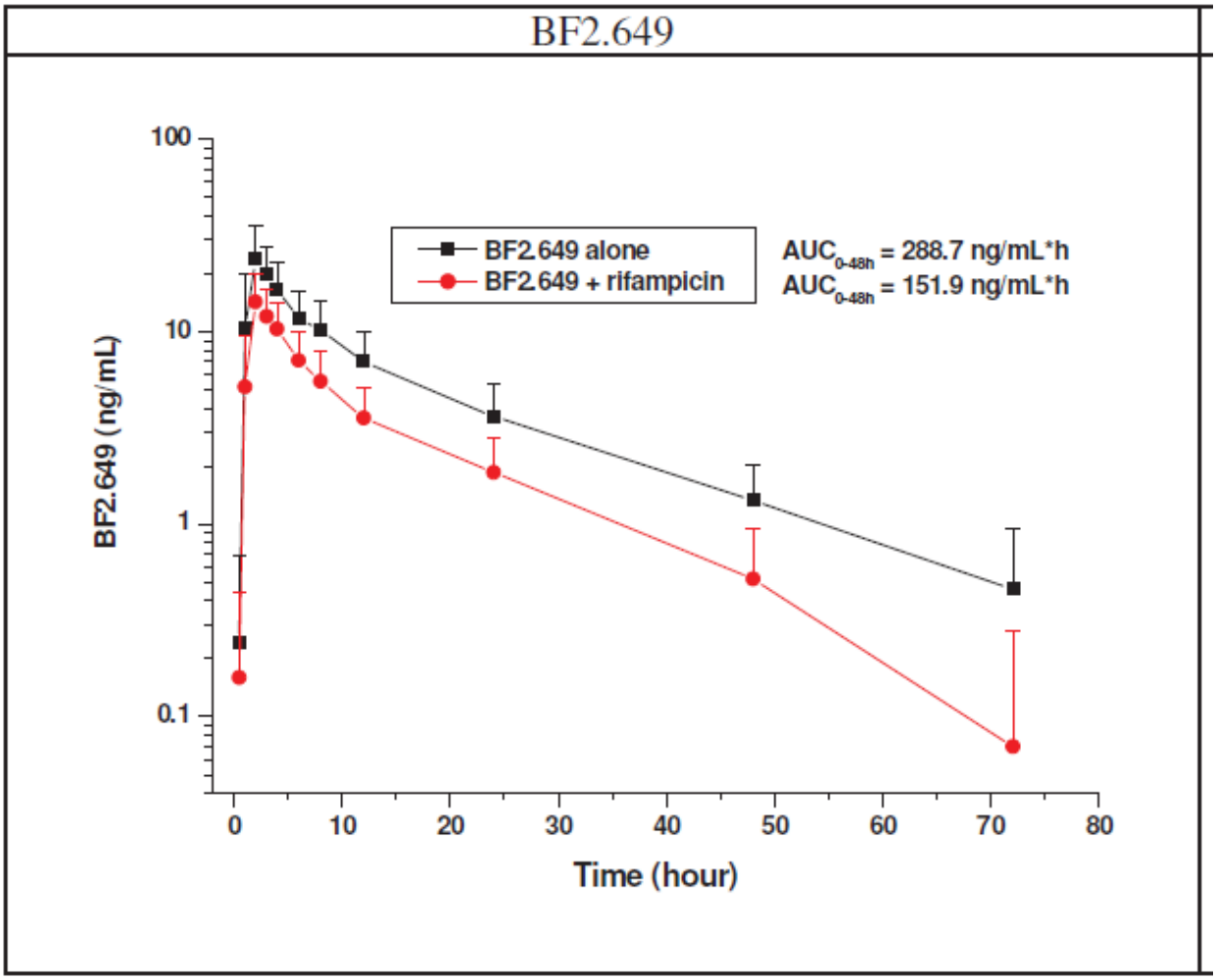
Figure 7: Mean (± standard deviation) Pitolisant concentrations measured in 18 healthy male volunteers after a single oral administration at 20 mg alone or with paroxetine



Effect of rifampicin (CYP3A4 inducer) on the PK of pitolisant (P11-10): This study was a cross-over, single sequence, 2-period study with pitolisant alone as well as pitolisant with rifampicin at steady-state. It was conducted in 18 healthy adults aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with rifampicin, a strong CYP3A4 inducer, at 600 mg QD x 8 days decreased the AUC and Cmax of pitolisant by 48% and 39%, respectively. Therefore, based on the significant reduction in exposure of pitolisant when co-administered with strong CYP3A4 inducers (e.g., rifampicin, phenytoin etc.), the following dose-adjustment strategy is recommended:

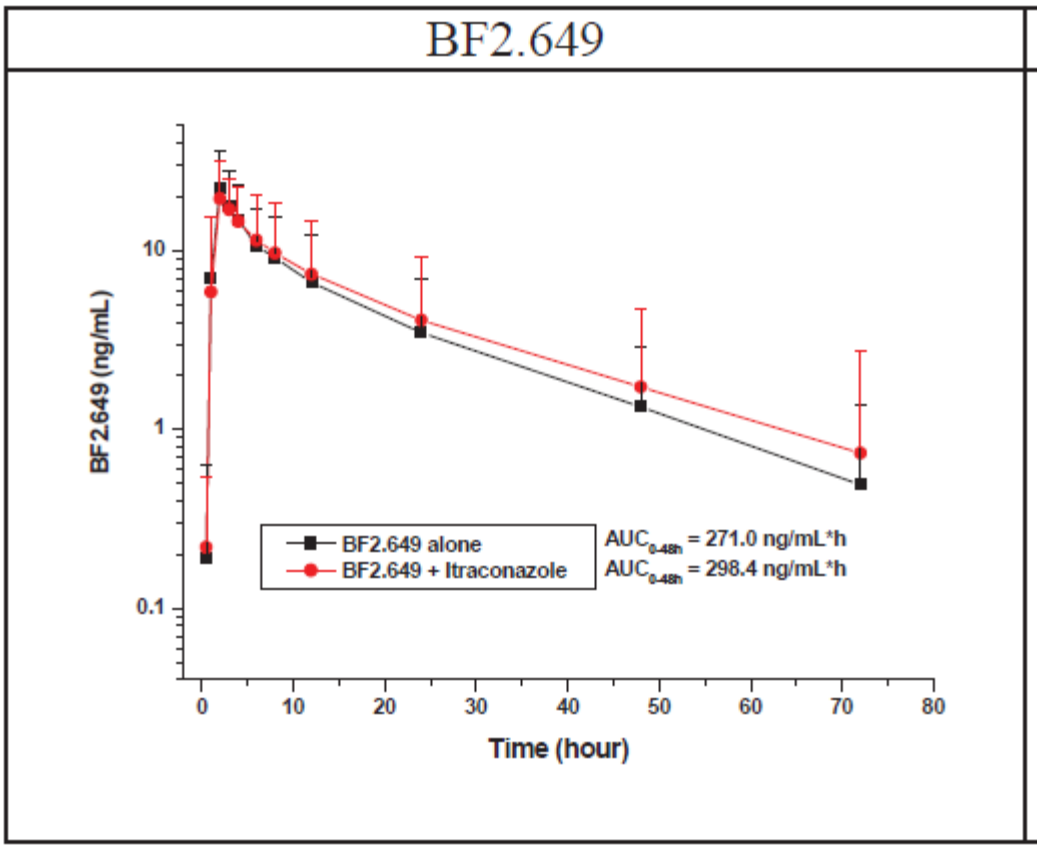
- For patients stable on 8.9 mg/day or 17.8 mg/day: dose to be increased gradually over a week to reach double the original dose level. Maintain for the duration of use of CYP3A4 inducers.
- For patients stable on the highest dose of 35.6 mg/day: No dose adjustments is recommended

Figure 8: Mean (± standard deviation) Pitolisant concentrations measured after a single oral administration at 20 mg alone or with rifampicin.



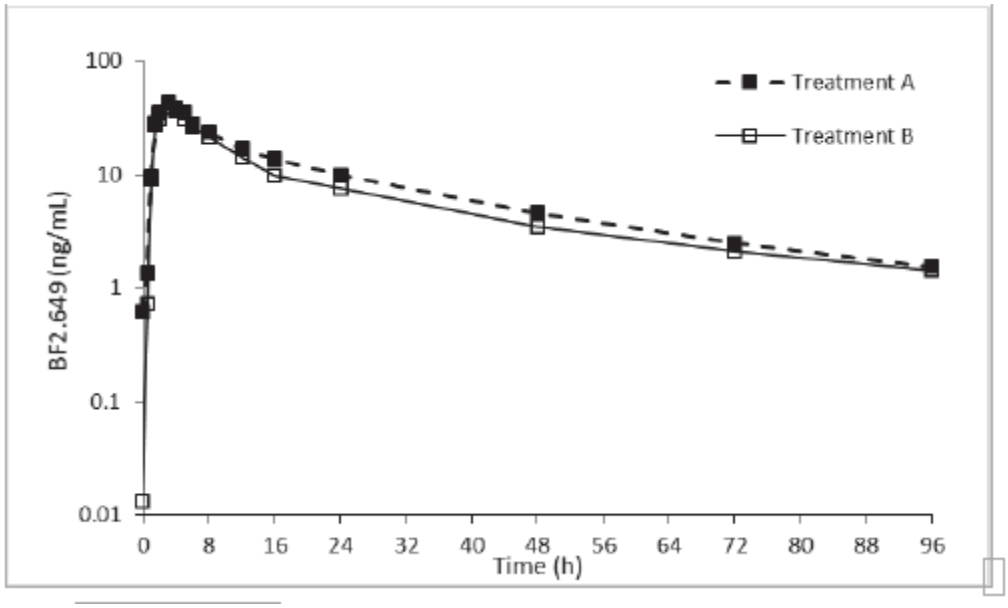
Effect of itraconazole (CYP3A4 inhibitor) on the PK of pitolisant (P11-03; part II): This study was a cross-over, single sequence, 2-period study with pitolisant alone as well as pitolisant with itraconazole at steady-state. It was conducted in 18 healthy adults aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with itraconazole (200 mg QD for 7 days) had negligible effect on the PK of pitolisant. Therefore, no dosage adjustments are needed for WAKIX when co-administered with moderate or potent CYP3A4 inhibitors.

Figure 9: Mean (± standard deviation) Pitolisant concentrations measured after a single oral administration at 20 mg alone or with Itraconazole.



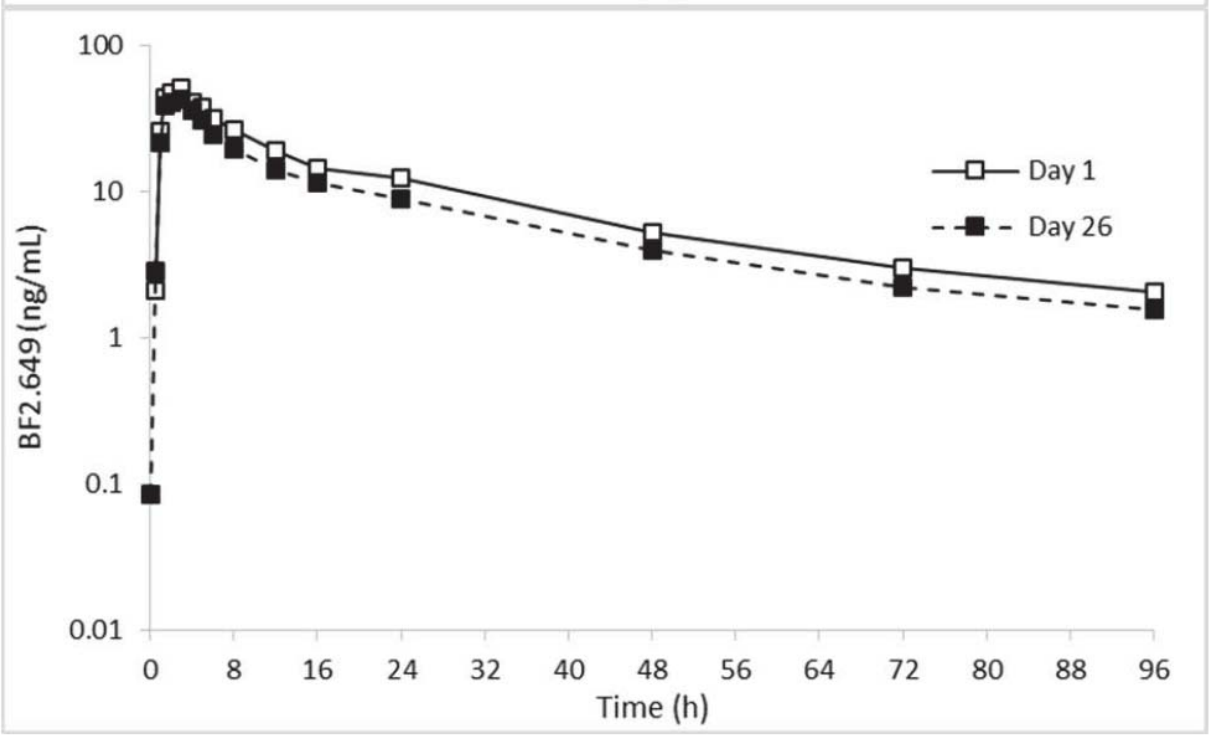
Effect of Sodium Oxybate (approved narcolepsy drug) on the PK of pitolisant (P14-07; part I): This study was an open-label, 2 way cross-over study to evaluate the PK interaction of pitolisant (40 mg salt form) with sodium oxybate (XYREM; 2.25 gm, twice, 3 hrs apart) and vice versa in 16 healthy adult males. Sodium oxybate, which is a commonly administered drug to narcolepsy patients, had minimal effect on the PK of pitolisant. Therefore, no dosage adjustments are needed for WAKIX when co-administered with sodium oxybate.

Figure 10: Mean Pitolisant concentrations measured after a single oral administration at 20 mg alone (Treatment- A) or with Sodium Oxybate (Treatment-B).



Effect of modafinil (approved narcolepsy drug) on the PK of pitolisant (P14-07; part II): This study was an open-label, one sequence, cross-over study to evaluate the PK interaction of single dose pitolisant (40 mg salt form) and a 22-day 200 mg/day modafinil (MODIDOAL200 mg/day for 22 days) and vice versa in 16 healthy adult males. Modafinil, which is a commonly administered drug to narcolepsy patients, had minimal effect on the PK of pitolisant. Therefore, no dosage adjustments are needed for WAKIX when co-administered with modafinil.

Figure 11: Mean Pitolisant concentrations measured after a 40 mg alone (Day 1 PK) or with Modafinil (Day 26 PK).



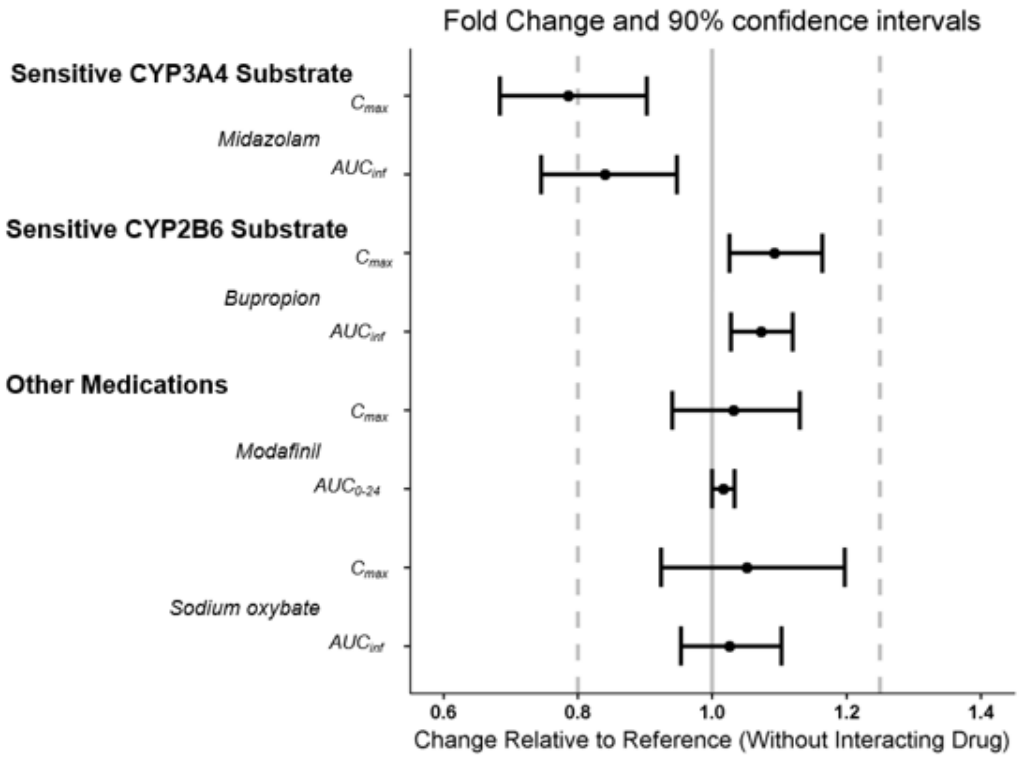
Drug-Drug Interactions Studies with Pitolisant as a Perpetrator drug

Effect of pitolisant on the PK of midazolam (CYP3A4 substrate) (P15-15): A clinical study was conducted to assess the effect of pitolisant on CYP3A4 using Midazolam as a CYP3A4 model substrate. This study showed that pitolisant (17.8 mg QD for 7 days) reduces exposures of midazolam (2.5 mg single dose) about 20%. Because the commonly used oral contraceptives are substrates of CYP3A4, an effect of pitolisant on the PK of oral contraceptives cannot be ruled out. Therefore, administration of pitolisant concomitantly with oral contraceptives may reduce the systemic exposure and the effectiveness of oral contraceptives, Thus, an alternative or additional reliable contraceptive method should be used when taking pitolisant.

Effect of pitolisant on the PK of sodium oxybate and modafinil (approved narcolepsy drugs) (P14-07): Pitolisant 35.6 mg QD had no effect on exposures of sodium oxybate 2.25 g twice, 3 hours apart or modafinil 200 mg daily for 22 days, both of which are commonly administered to narcolepsy patients. Thus, no dosage adjustments are needed to the dose levels of these co-administered drugs (sodium oxybate or modafinil) when taken with Wakix.

Effect of pitolisant on the PK of buproprion (CYP2B6 substrate) (P15-15): A clinical study was conducted to assess the effect of pitolisant on CYP2B6 using bupropion as a CYP2B6 model substrate. This study showed that pitolisant (17.8 mg QD for 7 days) does not affect the PK of bupropion (150 mg single dose) and, therefore, does not induce CYP2B6 metabolism. Therefore, no dosage adjustments are needed for CYP2B6 substrates when they get co-administered with pitolisant.

Figure 12: Effect of Pitolisant on concomitant medications



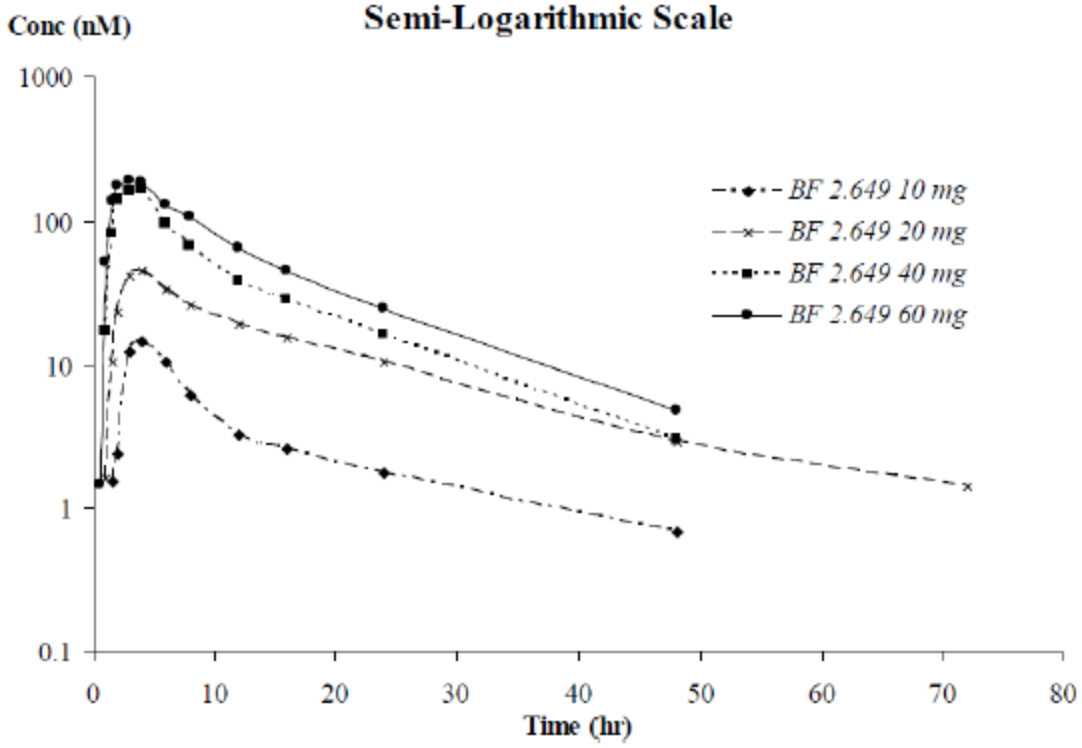
Dots = Geometric LSM ratios, error bars = 90% CI; reference dashed lines are 0.8 and 1.25.
AUC_{inf} = area under the curve from time 0 to time infinity; AUC_{0-24} = area under the curve from time 0 to 24 hours; C_{max} = maximum plasma concentration.

Source: Sponsor's Summary of Clinical Pharmacology

3.3.5 Is the single dose and steady state PK of pitolisant characterized adequately?

Single dose PK of pitolisant was fully characterized in a dedicated single ascending dose study in healthy adult subjects. The doses explored were- 1, 5, 10, 20, 40 and 60 mg of the salt form. Concentration vs. time profile for PK of pitolisant are shown below. The PK parameters and exposures were generally dose-proportional. The details of the PK parameters are in Section 2.1.

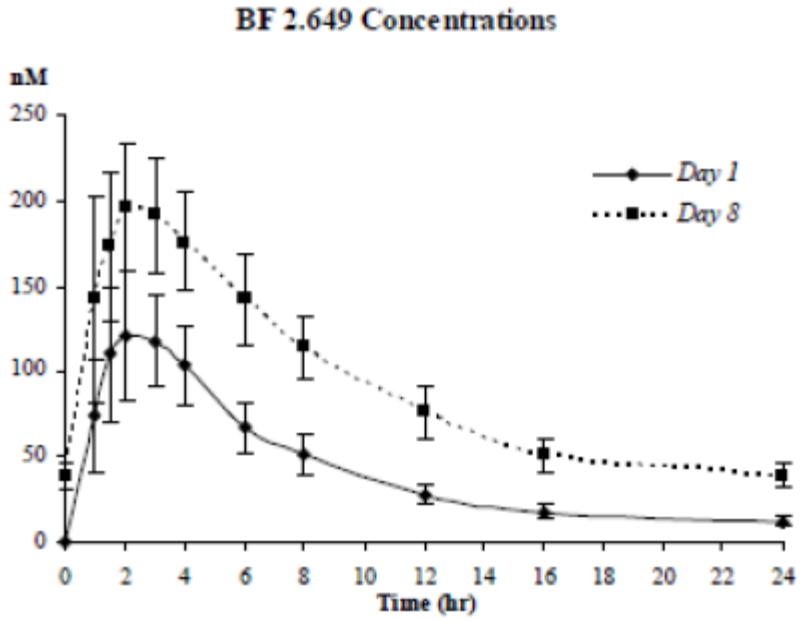
Figure 13: Mean Serum Pitolisant Concentration vs Time Plots for single dose of 10, 20, 40, and 60 mg (as salt form).



Source: Sponsor's Summary of Clinical Pharmacology

The PK of pitolisant at steady state was assessed by a dedicated study at 40 mg (salt form) with daily dosing up to 8 days in healthy adult subjects. Concentration vs. time profile for pitolisant is shown below. As expected, there was an accumulation at steady state and the exposures were generally 2-fold higher at steady state.

Figure 14: Mean Serum Pitolisant Concentration vs Time Profiles on Day 1 and Day 8



Source: Sponsor's Summary of Clinical Pharmacology

Additionally, while full PK profiles have not been collected in adult patients with narcolepsy, sparse sampling was collected in two pilot studies of pitolisant in the treatment of narcolepsy. Those data show that PK of pitolisant in patients is not substantially different from that characterized in healthy subjects.

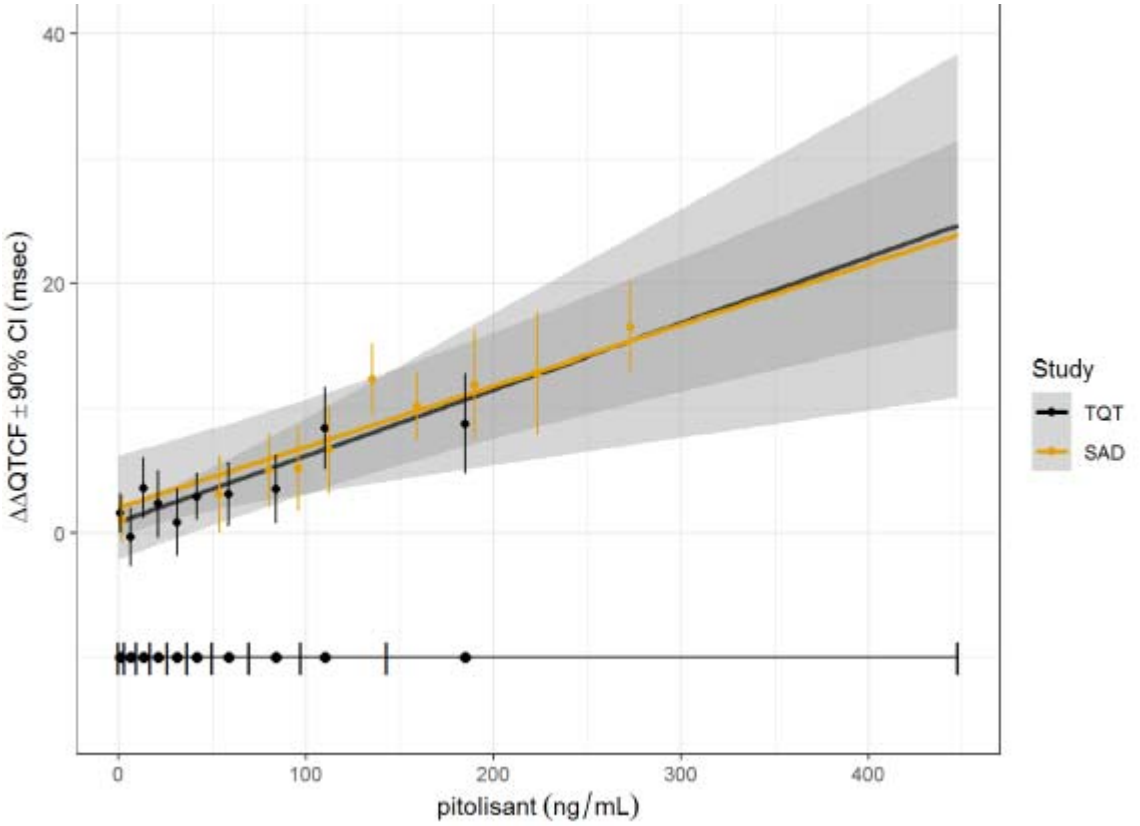
3.3.6 Were there any QT increases observed at therapeutic dose levels or supra-therapeutic dose levels?

The effect of pitolisant was evaluated in clinical studies P09-11 (TQT study) and P14-05 (SAD Study) and the agency performed independent analysis of these data (Darrts- IRT Report, Jose Vicente Ruiz et. al., 3/22/2019). The data analysis suggested that the highest therapeutic dose of 40 mg (salt form) at steady state did not cause any clinically significant QTc prolongation. However, there was a clear and direct correlation of pitolisant exposure with QTc prolongation. At supratherapeutic doses, QTc increases greater than 10 msec are anticipated. The detailed concentration QTc analysis are included in the IRT report.

Table 6: The Point Estimates and the 90% CIs for ΔΔQTcF (ms) increases at therapeutic and supra-therapeutic dose levels

Safety Window	Cmax at steady state (ng/mL)	**ΔΔQTcF (ms) & 90% CI**
Highest therapeutic Dose (i.e., 40 mg in salt form at steady state)	~ 73 ng/mL	4.2 (3.2, 5.2)
2.5-fold over highest therapeutic Dose	~ 175 ng/mL	9.8 (7.7, 11.8)
3.8-fold over highest therapeutic Dose	~ 280 ng/mL	15.5 (12, 18.9)

Figure 15: Goodness-of-fit plot for QTc vs. steady state Cmax



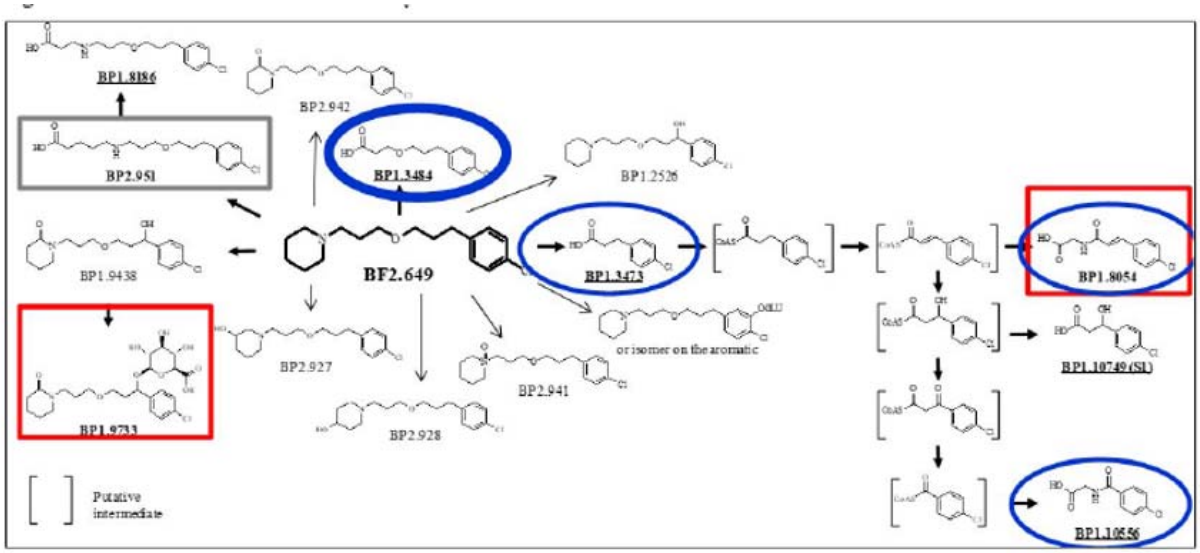
Source: IRT Review (Darrts- IRT Report, Jose Vicente Ruiz et. al., 3/22/2019).

3.3.7 Are the elimination pathways (metabolism and excretion) for pitolisant adequately elucidated via mass balance study?

Dedicated mass balance studies (P11-01 and P15-02) were conducted to elucidate the biotransformation pathways, mechanism of metabolism, circulating levels of drug-related moieties, and the extent of route of elimination/excretion via the urine and feces. Pitolisant is extensively metabolized primarily by CYP2D6 and to a lesser extent, by CYP3A4 and Phase 2 glucuronidation. Though pitolisantt was the major circulating moiety (~50%) in human plasma,

there were several major circulating metabolites- BP2951, BP1.8054, BP1. 9733 etc. However, all the major circulating metabolites were determined to be “inactive”. Additionally, the exposure ratio (i.e., AUC of metabolite/AUC of parent) of all major circulating metabolites is 0.5 or lower. Mass balance study demonstrated that approximately 90% of the dose was excreted in urine (majorly as a mix of a large number of metabolites with < 2% as unchanged parent) and ~2% of dose in feces.

Figure 16: Pitolisant metabolic pathway in Human



Source: Sponsor’s Summary of Clinical Pharmacology

3.3.8 Was the final to-be-marketed formulation (film coated tablet) used in the pivotal efficacy/safety studies and the key clinical pharmacology studies?

Yes, the final to-be-marketed formulation (film coated tablet) was used in the pivotal efficacy/safety studies and the key clinical pharmacology studies. Therefore, no additional bridging PK studies were required.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Pitolisant and its metabolites (BP2.951, BP1.8054, BP1.9733, BP1.3473, BP1.3484, BP1.10556, BP1.0749, and BP1.8186) in serum and pitolisant and BP2.951 in urine were analyzed by high-performance liquid chromatography (HPLC) or ultra-performance LC (UPLC) coupled with tandem mass spectroscopy after solid-phase or solid-liquid phase extraction. The lower limit of quantification was 1 ng/mL, 0.5 ng/mL, or 0.1 ng/mL for pitolisant and BP2.951 in serum; 1 ng/mL or 2 ng/mL for pitolisant and BP2.951 in urine; 1 ng/mL for BP1.8054, BP1.9733, BP1.8186, and BP1.0556 in serum; and 5 ng/mL for BP1.3484 and BP1.3473 in serum. All methods used in human clinical trials were validated in accordance with GLP and GCP regulations. The validated methods used to analyze pitolisant and its metabolites demonstrated reliable and reproducible quantitation of these analytes.

Analyte	Method Description and Performance	
pitolisant (BF2.649)	Method summary/description: An HPLC method followed by MS detection was developed in human serum for the quantitation of pitolisant. Samples were prepared by solid-liquid extraction, and pitolisant was detected by LC-MS/MS. The assay was fully validated for specificity, linearity, accuracy, precision and stability from 1-100 ng/mL and showed that the method is appropriate for the determination of BF2.649 in human serum in the range of the tested doses in clinical studies.	
	Internal standard	(b) (4)
	Limits of quantitation (ng/mL)	1 ng/mL
	Average recovery of drug (% mean)	1 ng/mL: 97%; 5ng/mL: 82%; 25ng/mL: 90%; 100ng/mL: 91%
	Standard curve concentrations (ng/mL)	1, 2.5, 5, 10, 25, 50, 100 ng/mL
	LLOQ	1 ng/mL
	LLOQ intra-batch precision (%CV)	10.1%
	LLOQ inter-batch precision (%CV)	10.7%
	LLOQ intra-batch accuracy (%bias)	-17.0%
	LLOQ inter-batch accuracy (%bias)	-9.1%
	Validated range	1 to 100 ng/mL
	QC intra and inter batch accuracy and precision	
	Intra-day precision (%CV)	≤ 10.1%
	Inter-day precision (%CV)	≤ 10.7%
	Accuracy (%bias)	-9.1% ≤ bias ≤ -5.3%
	Processed extract stability	12 days (nominally +4°C)
	Bench top stability	Up to 24 hours at room temperature in matrix
	Stock stability	7 months at -20°C in DMSO
	Freeze thaw stability	3 cycles at -80°C
	Long term storage stability	1 year at nominally -80°C (study R-B158-1.1442) in matrix
	Assay specificity	No interfering signal observed
	Any/all other relevant parameters	Matrix dilution factor (1/5) in study R-B058-2.649; processed sample extract stability in autosampler for 24 hours at +4°C (study R-B158-1.1442); no matrix effect

Clinical Studies	Analyte	Method Description and Performance	
P03-03 P03-04 P04-06	BP2.951 (metabolite)	Method summary/description: An HPLC method followed by MS/MS detection was developed in human serum for the quantification of BP2.951 for future clinical pharmacokinetic studies. Samples were extracted by solid-liquid matrices, and subjected to LC-MS/MS. The analytical method was fully validated in terms of specificity (no interferences), linearity, accuracy and precision below the guidelines limits for 1-100 ng/mL.	
		Internal standard	(b) (4)
		Limits of quantitation (ng/mL)	1 ng/mL
		Average recovery of drug (% mean)	BP2.951: 1 ng/mL: 87%; 5 ng/mL: 79%; 25 ng/mL: 85%; 100 ng/mL: 94%
		Standard curve concentrations (ng/mL)	1.0, 2.5, 5, 10, 25, 50 and 100 ng/mL
		LLOQ	1 ng/mL
		LLOQ intra-batch precision (%CV)	4.3%
		LLOQ inter-batch precision (%CV)	7.0%
		LLOQ intra-batch accuracy (%bias)	9.0%
		LLOQ inter-batch accuracy (%bias)	5.4%
		Validated range	1 to 100 ng/mL
		QC intra and inter batch accuracy and precision	
		Intra-day precision (%CV)	≤ 4.3%
		Inter-day precision (%CV)	≤ 8.9%
		Accuracy (%bias)	-7.1% ≤ bias ≤ 7.9%
		Processed extract stability	24 hours (nominally +4°C) (study R-B158-1.1442)
		Bench top stability	Up to 24 hours at room temperature
		Stock stability	3 months at -20°C in DMSO
		Freeze thaw stability	3 freeze-thaw cycles at -20°C
		Long term storage stability	1 year at nominally -80°C (study R-B158-1.1442)
		Assay specificity	No interfering signal observed
		Any/all other relevant parameters	Matrix dilution factor (1/5) in study R-B058-2.649; processed sample extract stability in autosampler for 24 hours at +4°C (study R-B158-1.1442); no matrix effect

Analyte	Method Description and Performance	
BP1.8054 (metabolite)	Method summary/description: A UPLC method followed by MS/MS detection was developed in human and rat (Sprague Dawley) serum for the quantitation of BP1.8054 (metabolite). Solid-liquid extraction was used to prepare samples. The analytical method was validated in terms of linearity, accuracy and precision from 1-200 ng/mL. Recovery and matrix effect parameters were satisfying.	
	Internal standard	(b) (4)
	Limits of quantitation (ng/mL)	1 ng/mL
	Average recovery of drug (% mean)	BP1.8054: 1 ng/mL: 90.0%; 5 ng/mL: 80.2%; 10 ng/mL: 92.8%; 20 ng/mL: 81.8%; 50 ng/mL: 94.7%; 100 ng/mL: 84.3%; 200 ng/mL: 90.3%
	Standard curve concentrations (ng/mL)	1.0, 5, 10, 20, 50, 100, and 200 ng/mL
	LLOQ	1 ng/mL
	LLOQ intra-batch precision (%CV)	13.7%
	LLOQ inter-batch precision (%CV)	13.7%
	LLOQ intra-batch accuracy (%bias)	9.2%
	LLOQ inter-batch accuracy (%bias)	1.2%
	Validated range	1 to 200 ng/mL
	QC intra and inter batch accuracy and precision	
	Intra-day precision (%CV)	≤ 13.7%
	Inter-day precision (%CV)	≤ 13.7% (at LLOQ) ≤ 9.7% (above LLOQ)
	Accuracy (%bias)	1.2% ≤ bias ≤ 3.8%
	Stability in DMSO	3 months at -20°C
	Processed extract stability	72 hours at 4°C
	Bench top stability	Up to 24 hours at room temperature
	Stock stability	Up to 93 days at -20°C in DMSO
	Freeze thaw stability	3 cycles at -80°C
	Long term storage stability	Up to 1040 days at -80°C
	Assay specificity	No interfering signal observed
	Any/all other relevant parameters	No matrix effect; no carry over; dilution factor (1/10) validated

Analyte	Method Description and Performance	
BP1.9733 (metabolite)	Method summary/description: A UPLC method followed by MS/MS detection suitable and reliable for routine analysis was developed for the quantitation of BP1.9733 in human and monkey serum. Samples were extracted by solid-liquid matrices. The assay was validated for specificity, linearity, accuracy, precision and stability to quantitate BP1.9733 from 1-1000 ng/mL.	
	Internal standard	(b) (4)
	Limits of quantitation (ng/mL)	1 ng/mL
	Average recovery of drug (% mean)	1 ng/mL: 89.5%; 2.5 ng/mL: 93.9%; 10 ng/mL: 94.9%; 25 ng/mL: 89.3%; 100 ng/mL: 94.1%; 500 ng/mL: 89.3%; 1000 ng/mL: 87.8%
	Standard curve concentrations (ng/mL)	1.0, 2.5, 10, 25, 100, 500 and 1000 ng/mL
	LLOQ	1 ng/mL
	LLOQ intra-batch precision (%CV)	11.1%
	LLOQ inter-batch precision (%CV)	11.1%
	LLOQ intra-batch accuracy (%bias)	4.5%
	LLOQ inter-batch accuracy (%bias)	2.4%
	Validated range	1 to 1000 ng/mL
	QC intra and inter batch accuracy and precision	
	Intra-day precision (%CV)	$\leq$ 11.1%
	Inter-day precision (%CV)	$\leq$ 11.1% (at LLOQ) $\leq$ 5.9% (above LLOQ)
	Accuracy (%bias)	-1.7% $\leq$ bias $\leq$ 2.4%
	Processed extract stability	76 hours at 4°C
	Bench top stability	24 hours at room temperature and +4°C
	Stock stability	98 days at -20°C
	Freeze thaw stability	4 cycles at -80°C
	Long term storage stability	480 days at -80°C
	Assay specificity	No interfering signal observed
	Any/all other relevant parameters	No matrix effect; slight carry over; dilution factor (1/10) validated; incurred sample reanalysis done in P15-15 clinical study

4.2 Individual Study Reports:

1. Hepatic Impairment Study
2. Renal Impairment Study
3. Paroxetine DDI Study
4. Rifampicin DDI Study
5. Midazolam DDI Study
6. Itraconazole DDI Study

CLINICAL PHARMACOLOGY STUDY REVIEW
PK Study in Hepatic Impaired

Study # P09-14	**Study Period:** 5/10/11—11/10/12
NDA 211150 WAKIX	
Title	Pharmacokinetic of 20 mg BF2.649 in single dose, in subjects with normal hepatic function compared to subject with impaired hepatic function.
Objectives:	Primary objective: The primary objective of this study was to investigate the effect of hepatic impairment on the pharmacokinetics of BF2.649 and its main metabolite BP2.951 following single oral dose of 20 mg. Secondary objective: The secondary objective of the study was the evaluation of biological safety and clinical tolerance of BF2.649.

EXECUTIVE SUMMARY:

Hepatic impairment study (P09-14): **This was a multi-center, open-labeled, parallel group study in six subjects with mild hepatic impairment (Child Pugh A), 6 subjects with moderate hepatic impairment (Child Pugh B) and 12 healthy subjects matched for ethnicity, sex, age (±5 years) and BMI (±20%). Each subject received a single dose of pitolisant HCl 20 mg. The Cmax and AUC were generally similar in mild hepatic impaired subjects and healthy control subjects. However, the PK parameters in moderate hepatic impaired differed from healthy control subjects as follows: 30% increase of Cmax, 140% increase in AUC and 2xfold longer T1/2. The trends in PK were similar for total as well as unbound pitolisant. Severe hepatic impaired subjects were not included in this study.**

Based on the PK changes observed in the hepatic impairment study, the following dose-adjustments are recommended:

- **Mild hepatic impaired= no dose adjustment**
- **Moderate hepatic impaired = Titrate the dose for longer duration (i.e., 2 weeks (b) (4)) and cap the dose at 17.8 mg/day**
- **Severe hepatic impaired = contra-indicated**

Study Design:

Study P09-14 was a multi-center, open-labeled, parallel group study in six subjects with mild hepatic impairment (Child Pugh A, Model of End-stage Liver Disease [MELD] score 1 to 9), 6 subjects with moderate hepatic impairment (Child Pugh B, MELD score 2 to 12) and 12 healthy subjects matched for ethnicity, sex, age (±5 years) and BMI (±20%). Each subject received a single dose of pitolisant HCl 20 mg. The primary objective of the study was to investigate the effect of hepatic impairment on the PK of pitolisant and BP2.951. The secondary objective was to evaluate the safety and tolerability of pitolisant.

Serial blood samples were collected at pre-dose and up to 96 hours post-dose for determination of serum pitolisant and BP2.951 using validated assays with LLOQs of 0.1 ng/mL. PK samples were retrospectively quantified for BP1.9733, BP1.8054, BP1.3473, BP1.3484, BP1.8186 and BP1.10556 metabolites from a few subjects using validated assays with LLOQs of 1.0 ng/mL, 1.0 ng/mL, 5.0 ng/mL, 5.0 ng/mL, 1.0 ng/mL and 1.0 ng/mL, respectively.

Urine was collected for up to 24 hours post-dose.

Vital signs and ECGs were collected pre-dose and until 12 hours post dosing and at the times of blood samples, thereafter. PE and laboratory parameters were collected at baseline and at follow-up.

Patients were selected as following:

12 subjects with hepatic dysfunction were stratified according to Child-Pugh Classification:

- Six subjects from 18 years of age with mild hepatic impairment (Child-Pugh A),
- Six subjects from 18 years of age with moderate hepatic impairment (Child-Pugh B).

And 12 healthy subjects with normal hepatic function matched with impaired hepatic function subjects on ethnic group, sex, age (+/- 5 years), and BMI (+/- 20%).

Test product, dose, mode of administration, batch:

Product	BF2.649
Unit dose per day	20 mg (tablet)
Regimen	single oral dose
Mode	Oral

Batch N°: 111 00 11113 (expiration date: 01/12/2011)
111 00 11293 (expiration date: 01/04/2013)

Duration of treatment:
One day.

Pharmacokinetic assessments:

Blood samples were collected on:

- Day 1 at pre-dose, 1h, 1,5h, 2h, 3h, 4h, 6h, 8h, 12h and 16 hours after administration of BF2.649;
- Day 2 at T24h and T36h;
- Day 3 at T48h;
- Day 4 at T72h;
- Day 5 at T96h.

Urine collections:

- Day 1: At pre-dose, [D1T0h – D1T6h[; [D1T6h – D1T12h[; [D1T12h-D2T24h[;
- Day 2 [D2T24h – D3T48h[.

Safety:

Vital signs:

- Blood pressure, Heart rate and oral Temperature: at the screening visit, then on D-1 on D1 at T0h, T2h, T4h, T6h and T12h, on D2 at T24h, D3 at T48h, D4 T72h, D5 T96h and on follow-up visit.
- Oral temperature at screening visit, D-1 and on follow-up visit.
- Body weight: at the screening and at the follow-up visit.

ECG evaluation:

- 12-lead ECG: at the screening visit, then on D-1, on D1 at T0h, T2h, T4h, T6h, and T12h, on D2 at T24h, on D3 at T48h, on D5 T96h and on D4 at T72h and at the follow-up visit.

Bioanalytical methods:

Serum levels of BF2.649 and its metabolite BP2.951 were evaluated using a UHPLC/MS/MS technique developed and validated by Bioprojet-BIOTECH (B258 study). Urine levels of BF2.649 and its metabolites were evaluated using a UHPLC/MS/MS technique developed and validated by Bioprojet-BIOTECH (B256 study). Drugs serum binding were determined by equilibrium dialysis approach. Unbound fraction of BF2.649 and its metabolite BP2.951 in plasma were measured in order to correctly interpret the effect of hepatic function on the BF2.649 clearance.

Statistical methods:

Pharmacokinetics:

Pharmacokinetic parameters for total and unbound drug were estimated for each group: C_{max}, T_{max}, $t_{1/2}$, $AUC_{[0-24]}$, $AUC_{[0-\infty]}$, V/F, Cl/F, protein binding.

Statistical Tests: A one-way analysis of Variance (ANOVA) by considering treatment group as a fixed factor was conducted.

Tolerance:

Individual adverse events were listed and classified by severity and relationship to the drugs. Descriptive statistics were calculated.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Pitolisant and its metabolites		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population:

24 subjects were included: 12 subjects were included in France (5 subjects with impaired hepatic function Child Pugh A, 1 subject with impaired hepatic function Child Pugh B, 6 healthy matched subjects) and 12 subjects were included in Bulgaria (1 subject with impaired hepatic function Child Pugh A, 5 subjects with impaired hepatic function Child Pugh B, 6 healthy matched subjects). All the subjects completed the study.

Study population (N = 24):

- 100 % were Caucasian volunteers.
- 75% were male, 25% were female.
- The age ranged from 49 to 74 years with a mean of 58.9 ± 7.0 years.
- The height ranged from 156 cm to 184 cm with a mean of 168.6 ± 8.1 cm.
- The weight ranged from 59 to 105 kg with a mean of 78.04 ± 11.82 kg.
- The BMI ranged from 22.5 to 31.3 kg/m² with a mean of 27.37 ± 2.91 kg/m².

All subjects were non smokers (83.3%) or smokers of not more than 10 cigarettes a day (16.7%). 29.2% of the subjects were alcohol consumers (mean consumption of 10.1 ± 9.3 g/day). 62.5% of the subjects were caffeine consumers (≤ 4 cups/day).

All the subjects in the impaired hepatic function group had a pertinent medical or surgical history: according to the protocol, all subjects had hepatobiliary disorders (mainly cirrhosis).

Among the subjects with impaired hepatic function, Child-Pugh score was of 5.0 in class A and 7.0 in class B.

3/12 subjects in the healthy matched subjects group had a medical or surgical history (mainly appendectomy).

Table 9.5-1 – Main baseline characteristics – Included set (n = 24)

		Impaired hepatic function (Case)			Healthy matched subjects (Control)			
Demography	Statistic	Child Pugh A (N=6)	Child Pugh B (N=6)	Total (N=12)	Child Pugh A (N=6)	Child Pugh B (N=6)	Total (N=12)	Overall (N=24)
Age (years)	N	6	6	12	6	6	12	24
	Mean±SD	61.8±8.4	55.8±3.8	58.8±7.0	62.0±8.4	55.8±5.1	58.9±7.4	58.9±7.0
	Min/Median/Max	49/63.0/74	51/55.0/62	49/57.5/74	49/64.0/70	51/54.5/64	49/58.0/70	49/57.5/74
Gender								
- Male	N(%)	4(66.7)	5(83.3)	9(75.0)	4(66.7)	5(83.3)	9(75.0)	18(75.0)
- Female	N(%)	2(33.3)	1(16.7)	3(25.0)	2(33.3)	1(16.7)	3(25.0)	6(25.0)
Height (cm)	N	6	6	12	6	6	12	24
	Mean±SD	167.67±8.96	172.83±9.26	170.3±9.1	169.05±8.87	165.00±4.73	167.0±7.1	168.6±8.1
	Min/Median/Max	156.0/168.50/178.0	160.0/174.50/184.0	156/172.0/184	158.0/168.75/180.0	160.0/164.00/171.0	158/166.8/180	156/168.8/184
Weight (kg)	N	6	6	12	6	6	12	24
	Mean±SD	78.50±14.15	85.92±16.04	82.21±14.93	72.83±5.78	74.92±5.71	73.88±5.58	78.04±11.82
	Min/Median/Max	59.0/77.00/97.0	65.5/89.50/105.0	59.0/82.50/105.0	62.0/74.00/78.0	65.0/76.25/80.0	62.0/75.25/80.0	59.0/76.50/105.0
BMI (kg/m²)	N	6	6	12	6	6	12	24
	Mean±SD	27.72±2.66	28.50±2.50	28.11±2.50	25.62±3.10	27.63±3.23	26.63±3.20	27.37±2.91
	Min/Median/Max	23.3/28.00/31.3	24.4/29.40/31.0	23.3/28.70/31.3	22.5/24.45/30.8	23.6/27.95/30.9	22.5/25.35/30.9	22.5/27.70/31.3
Ethnic origin								
- Caucasian	N(%)	6(100.0)	6(100.0)	12(100.0)	6(100.0)	6(100.0)	12(100.0)	24(100.0)
Child-Pugh score	N	6	6	12	NA			
	Mean±SD	5.0±0.0	7.0±0.0	6.0±1.0				
	Min/Median/Max	5/5.0/5	7/7.0/7	5/6.0/7				

Inclusion Crietria:

All subjects with impaired hepatic function included in the study had to meet all of the following criteria for inclusion in the study:

- Patients > 18 years old with stable impaired hepatic function classified Child-Pugh A or Child-Pugh B.
- Hepatic dysfunction due to hepatocellular disease (not secondary to other diseases) as documented by medical history, physical examination, laboratory tests and liver biopsy results indicating the presence of hepatic cirrhosis. It was possible to recommend the use of non-invasive alternative to liver biopsy, such as results from Fibrotest and /or Fibroscan.
- Stable Hepatic dysfunction e.g. no clinical significant change in disease status within the last 30 days documented by recent medical history, including no worsening of clinical signs of hepatic impairment or no worsening of total Bilirubin or Prothrombin time>50%.
- Stable treatment regimen or dose of medication.
- Patients with body mass index (weight/height^2) in the range 18 to 32 kg/m^2 (inclusive).
- Laboratory parameters within the normal range, unless the Investigator considered an abnormality to be clinically irrelevant; with the exception of all biological parameters affected by hepatic impairment. However, the following parameters had to be within the following limits:
  - ASAT and ALAT < 3ULN,
  - Alkaline Phosphatases < 2ULN,
  - Haemoglobin > 10g/dL,
  - Platelets > 50G/L.
- Normal 12-lead ECG or judged not clinically significant by investigator with QTc< 470 ms.
- If female, subject had to use an effective contraception method according to the investigator, except if she was sterilized for more than 3 months or postmenopausal. Menopause is defined as over the age of 60 years, or between 45 and 60 years being amenorrheic for at least 2 years with plasma FSH level > 30 UI/L.
- If smoker, smoking less than 10 cigarettes/day and able to stop smoking during several days covering the hospitalization time.
- Normal eating habits.
- Be able to understand and willing to sign the informed consent form.
- For the French site, be registered with the French Social Security in agreement with the French Law on biomedical experimentation.
- Subject not participating in another study or being in a follow–up period for another study.

All healthy subjects included in the study had to meet all of the following criteria for inclusion in the study:

- Healthy subjects > 18 years old with normal hepatic function matched with impaired hepatic function subjects on ethnic group, sex, age (+/- 5 years), and BMI (+/- 20%). Liver function tests, albumin and prothrombin time should be within the normal ranges.
- Be certified as healthy by a comprehensive clinical assessment (detailed medical history, and a complete physical examination) and laboratory investigations (haematological and blood chemistry tests, and urinalysis), the results of which were within the normal range or judged not clinically significant by the investigator.
- Normal vital signs after 10 minutes resting in supine position: 95 mmHg < systolic blood pressure < 140 mmHg, 45 mmHg < diastolic blood pressure < 90 mmHg; 40 bpm < heart rate < 100 bpm.
- Normal 12-lead ECG or judged not clinically significant by investigator with QTc < 450 ms for women or < 430 ms for men.
- If female, subject had to use an effective contraception method according to the investigator, except if she was sterilized for more than 3 months or postmenopausal. Menopause is defined as over the age of 60 years, or between 45 and 60 years being amenorrheic for at least 2 years with plasma FSH level > 30 UI/L.
- Be non-smoker or if smoker, smoking less than 10 cigarettes/day and able to stop smoking during several days covering the hospitalization time.
- Normal eating habits.

Exclusion Criteria:

All subjects with impaired hepatic function included in the study had not to meet any of the following non inclusion criteria:

- Other underlying diseases that could alter Child Pugh components like metastatic cancer to the brain or peritoneal surface or cancer cachexia (hypoalbuminemia, encephalopathy, ascites).
- Hepatocellular carcinoma confirmed by alpha-fetoprotein rate >50 mg/dL no longer than 3 months before inclusion.
- Signs of encephalopathy (grade 1 to 4 e.g. moderate to severe).
- Presence of clinical ascites (slight to severe).
- Drug addicts patients treated with methadone or buprenorphine.
- Presence of clinical ascites and/or pleural effusion. According to the investigator's judgment, small ascites radiologically detected but not clinically relevant could be accepted.
- Severe hepatic encephalopathy, (Grade > 2, portal systemic encephalopathy score).
- Recent history of gastrointestinal bleeding due to oesophageal varices. According to the investigator's judgment, patient who had oesophageal varices could be included if surgically treated by ligation or sclerosis and with a prophylactic treatment by non-selective β-blockers (e.g., propranolol) and after checking by echography.
- History of hepatic cytolysis due to medication.
- Known HIV infection.
- Renal impairment as measured by creatinine clearance < 75 mL/min.
- History of gastrointestinal, renal disorders or any surgery which put them at risk in the opinion of the investigator.
- History of allergy or hypersensitivity to one drug (abnormal drug reaction, idiosyncrasy or asthma).
- If female, pregnancy (defined as positive β-HCG blood test) or breast feeding women.
- Chronic abuse of alcohol leading to addiction and impossibility for subject to stop consumption during the study.
- Excessive consumption of caffeine containing beverages (more than 6 cups of coffee per day or equivalent).
- Presence of concomitant pathology requiring intake of any drugs or substances known to be inhibitors or inductors of CYP enzymes – mainly CYP3A4 and CYP2D6 within 14 days or 5 half lives prior to dosing (e.g: St-john wort, rifampicin, efavirenz, etc).
- Who had previously participated in a study during the last 3 months.
- Who had donated blood in the two months preceding the initiation of the study or who would donate blood during the study or within the three months following the study completion.
- Who had received blood or plasma derivatives in the three months preceding the initiation of the study.
- Who, in the judgment of the investigator, was likely to be non-compliant or uncooperative during the study.
- Who had forfeited their freedom by administrative or legal award or who was under guardianship.
- Who could not be contacted in case of emergency.

All healthy subjects included in the study had not to meet any of the following non inclusion criteria:

- Subject with a history of gastrointestinal, renal, cardiovascular, neurological, endocrine or psychiatric disorders, or any other condition which, in the opinion of the investigator, would jeopardize the safety of the subject, or impact the validity of the study results.
- History of allergy or hypersensitivity to one drug (abnormal drug reaction, idiosyncrasy or asthma).
- Acute or chronic disease within 1 month before inclusion.
- Known or suspected HIV, HBV and HCV infection.

PK Results

PHARMACOKINETIC RESULTS

Circulating levels of BF2.649 and of its metabolite BP2.951 showed a significant exposure of subjects receiving BF2.649.

Pharmacokinetic parameters of BF2.649 and its major metabolite BP2.951 in healthy volunteers and subjects with impaired hepatic function, after administration of single 20 mg BF2.649 dose were analyzed and did not show any significant differences between normal and patients with mild hepatic impairment.

BF2.649 pharmacokinetic parameters such as T_{max}, $t_{1/2}$, $AUC_{[0-\infty]}$, Vz/Dose, Cl/Dose, fu showed significant difference between normal volunteers and patients with moderate hepatic impairment.

BF2.649		*Hepatic impairment*		
Parameter		*Normal (n=12)*	*Mild (n=6)*	*Moderate (n=5 or 6)*
AUC_inf (h*ng/mL)		327 ± 327	462 ± 450	789 ± 336
	Ratio (/normal)		1.41	2.41
	P-value		0.4768 (NS)	0.0189 *
T_{max} (h)		2.5 [1.5-4]	2.5 [1-4]	1.75 [1-8]
$T_{1/2}$ (h)		22 ± 12	24 ± 8.9	41 ± 31
Vz/Dose (L)		3640 ± 2090	2880 ± 1790	1950 ± 464
	Ratio (/normal)		0.79	0.54
	P-value		0.4590 (NS)	0.0199 *
Cl/Dose (L/h)		137 ± 164	96.9 ± 97.0	30.7 ± 15.7
	Ratio (/normal)		0.71	0.22
	P-value		0.5938 (NS)	0.0476 *
f_u (%)		4.30 ± 1.17	3.93 ± 0.46	6.01 ± 1.76
	Ratio (/normal)		0.91	1.40
	P-value		0.3738 (NS)	0.0344 *
AUC_inf_u (h*ng/mL)		15 ± 20	17 ± 16	50 ± 30
	Ratio (/normal)		1.13	3.33
	P-value		0.8521 (NS)	0.0127 *
$Vz/Dose_u$ (L)		90600 ± 55700	70900 ± 37900	35200 ± 13900
	Ratio (/normal)		0.78	0.39
	P-value		0.4485 (NS)	0.0064 **
$Cl/Dose_u$ (L/h)		3470 ± 4390	2290 ± 1930	607 ± 508
	Ratio (/normal)		0.66	0.17
	P-value		0.4405 (NS)	0.0464 *

Statistical significance (p-value) for unpaired data: NS = not significant; * $p<0.05$; ** $p<0.01$

BP2.951,pharmacokinetics in mild or moderate hepatic impairment compared to healthy volunteers were not statistically different except for C_{max} values statistically different between normal volunteers and patients with moderate hepatic impairment.

BP2.951		*Hepatic impairment*		
Parameter		*Normal (n=11 or 12)*	*Mild (n=6)*	*Moderate (n=4 to 6)*
C_{max} (ng/mL)		12.33 ± 2.10	9.95 ± 3.52	4.63 ± 5.47
	Ratio (/normal)		0.81	0.38
	P-value		0.0883 (NS)	0.0169 *

Statistical significance (p-value) for unpaired data: NS = not significant; * $p<0.05$; ** $p<0.01$

Analyte	Parameter	Healthy Controls n=6	Mild Hepatic Impairment n=6	Moderate Hepatic Impairment n=5 or 6
BP1.8054	C_{max} (ng/mL)	27.3 ± 16.6	5.26[b]	9.33 ± 15.6
	T_{max} (h) [a]	1.5 (1.5-3)	2.0[b]	16.0 (1.5-24.0)
	AUC_{inf} (ng*h/mL)	135 ± 44	116[b]	244[b]
	$t_{½}$ (h)	8.9 ± 3.4	29.3[b]	10.2[b]
BP1.9733	C_{max} (ng/mL)	4.16 ± 1.36	0.94[b]	1.07 ± 1.42
	T_{max} (h) [a]	2.5 (2-3)	3[b]	4 (2-72)
	AUC_{inf} (ng*h/mL)	49.3 ± 14.9	40.7[b]	39.3 ± 15.7
	$t_{½}$ (h)	18.8 ± 11.1	45.5	62.6 ± 32.0
BP1.3473	C_{max} (ng/mL)[c]	NA	5.55-22.75	
BP1.3484	C_{max} (ng/mL)[c]	NA	BLOQ-11.0	
BP1.8186	C_{max} (ng/mL)[c]	NA	BLOQ-BLOQ	
BP1.10556	C_{max} (ng/mL)[c]	NA	BLOQ-12.8	

[a] median (min-max)
[b] n=1
[c] min-max
NA=not available, BLOQ=below the limit of quantification
Data presented as arithmetic mean ± standard deviation, unless otherwise specified

Appears this way on original

Safety Results

Was there any death or serious adverse events?

SAFETY RESULTS

During the overall study period, 5/24 (20.8%) subjects reported the occurrence of 6 adverse events. 4 were treatment emergent adverse events (TEAEs):

- 2/6 (33.3%) subjects reported 3 TEAEs in the impaired hepatic function Child Pugh A group,
- 1/6 (16.7%) subject reported 1 TEAE in the healthy subject matched with impaired hepatic function Child Pugh A group.

No TEAE occurred in the impaired hepatic function Child Pugh B and healthy subject matched with impaired hepatic function Child Pugh B groups.

All TEAEs were of mild intensity and were resolved before the end of the study.

The relationship to study drug seemed possibly related for one TEAE: one episode of headache reported in the impaired hepatic function Child Pugh A group.

The relationship to study drug seemed related for one TEAE: one episode of dysgeusia reported in the impaired hepatic function Child Pugh A group.

The relationship to study drug seemed not related for 2 TEAEs: one episode of vertigo reported in the impaired hepatic function Child Pugh A group and one episode of abdominal distension reported in the healthy subject matched with impaired hepatic function Child Pugh A group.

No serious adverse events were reported during this study.

No clinically relevant findings were observed in clinical examination laboratory parameters, vital signs or ECG parameters.

☐ Yes ☑ No ☐ NA

Overall Sponsor Conslusions

CONCLUSION

This study was carried out in 24 subjects. 12 subjects in France, (5 subjects with impaired hepatic function Child-Pugh A, 1 subject with impaired hepatic function Child-Pugh B, 6 healthy matched subjects) and 12 subjects in Bulgaria (1 subject with impaired hepatic function Child-Pugh A, 5 subjects with impaired hepatic function Child-Pugh B, 6 healthy matched subjects). All the subjects completed the study.

No serious adverse events were reported during this study. 4 emergent adverse events were reported:
3 in the impaired hepatic function Child Pugh A group and 1 in the healthy subject matched with hepatic function Child Pugh A group.

No clinically relevant findings were observed in clinical examination laboratory parameters, vital signs or ECG parameters.

Circulating levels of BF2.649 and of its metabolite BP2.951 show a significant exposure of subjects receiving BF2.649.

Pharmacokinetic parameters of BF2.649 and its major metabolite BP2.951 in healthy volunteers and subjects with impaired hepatic function, after administration of single 20 mg BF2.649 dose were analyzed and did not show any significant differences between healthy subjects and patients with mild hepatic impairment.

BF2.649 pharmacokinetic parameters such as T_{max}, $t_{1/2}$, $AUC_{[0-\infty]}$, Vz/Dose, Cl/Dose, fu showed significant difference between normal volunteers and patients with moderate hepatic impairment.

BP2.951 pharmacokinetic parameters, in mild or moderate hepatic impairment compared to healthy volunteers, were not statistically different except for C_{max} values statistically different between healthy subjects and patients with moderate hepatic impairment.

Reviewer Comments and Conclusions

This was a multi-center, open-labeled, parallel group study in six subjects with mild hepatic impairment (Child Pugh A), 6 subjects with moderate hepatic impairment (Child Pugh B) and 12 healthy subjects matched for ethnicity, sex, age (±5 years) and BMI (±20%). Each subject received a single dose of pitolisant HCl 20 mg. The Cmax and AUC were generally similar in mild hepatic impaired subjects and healthy control subjects. However, the PK parameters in moderate hepatic impaired differed from healthy control subjects as follows: 30% increase of Cmax, 140% increase in AUC and 2xfold longer T1/2. The trends in PK were similar for total as well as unbound pitolisant. Severe hepatic impaired subjects were not included in this study.

Based on the PK changes observed in the hepatic impairment study, the following dose-adjustments are recommended:

- **Mild hepatic impaired= no dose adjustment**
- **Moderate hepatic impaired = Titrate the dose for longer duration (i.e., 2 weeks instead of 1 week) and cap the dose at 17.8 mg/day**
- **Severe hepatic impaired = contra-indicated**

CLINICAL PHARMACOLOGY STUDY REVIEW
PK Study in Renal Impaired

Study # P09-13	**Study Period:** 3/6/11—26/11/12
NDA 211150 WAKIX	
Title	Pharmacokinetics of 20 mg BF2.649 in single dose, in subjects with normal renal function compared to subject with impaired renal function.
Objectives:	Primary objective: The primary objective of this study was to investigate the effect of renal impairment on the pharmacokinetics of BF2.649 and its main metabolite BP2.951 following single oral dose of 20 mg. Secondary objective: The secondary objective of the study is the evaluation of biological and clinical safety of BF2.649.

EXECUTIVE SUMMARY:

Renal impairment study (P09-13): **This was a multi-center, open-labeled, parallel-group, single-dose study of pitolisant HCl 20 mg administered in 4 subjects with mild renal impairment (estimated glomerular filtration rate [eGFR] of 60 to 80 mL/min/1.73 m2), 4 subjects with moderate renal impairment (eGFR of 30 to 59 mL/min/1.73 m2), 4 subjects with severe renal impairment (eGFR of 15 to 29 mL/min/1.73 m2), and 12 subjects with normal renal function (eGFR > 90 mL/min/1.73m2). Each subject received a single dose of pitolisant HCl 20 mg. Based on total pitolisant drug levels, mean Cmax and AUC for all categories of renal impaired subjects (mild, moderate and severe) was generally 2xfold higher than the exposure of normal subjects. However, unbound pitolisant drug levels were also assessed for the individual subject in this study. Based on the free drug levels, mild and moderate renal impaired subjects had exposure similar to normal subjects while only the severe renal impaired subjects had higher exposures (slightly less than 2 Xfold higher) compared to normal subjects.**

Considering the data from the PK changes (total and free) in the dedicated renal impairment study, the information regarding doses and AE's in the subjects from different renal categories in the pivotal efficacy and safety studies and the mass balance information that suggests that pitolisant is extensively metabolized and is primarily eliminated entirely as metabolites (not parent) via the urine (~90% of dose in urine as metabolites)- we recommend the following dose-adjustment strategy for renal impaired patients:

- **Mild renal impaired= no dose adjustment**
- **Moderate renal impaired = cap the dose at 17.8 mg/day**
- **Severe renal impaired = cap the dose at 17.8 mg/day**

Study Design:

Methodology:

This was an open, parallel group study in subjects with normal renal function compared to those with renal dysfunction.

Twenty four subjects were to be stratified according to renal function by using assessment of glomerular filtration rate (GFR) as defined by MDRD formula as follows:

- Four subjects from 18 to 75 years of age with mild impaired renal function defined by GFR between 60 and 89 ml/min (STAGE 2 according to the international classification of chronic kidney disease),
- Four subjects from 18 to 75 years of age with moderate impaired renal function defined by GFR between 30 and 59 ml/min (STAGE 3 according to the international classification of chronic kidney disease),
- Four subjects from 18 to 75 years of age with severe impaired renal function defined by GFR between 15 and 29 ml/min (STAGE 4 according to the international classification of chronic kidney disease),
- Twelve healthy subjects with normal renal function defined by GFR>90 ml/min with no proteinuria (<0.15g/L determined by urinalysis) matched with impaired renal function subjects on ethnic group, sex, age (+/- 5 years), and BMI (+/- 20%).

Number of subjects:
Planned: 24 subjects
Included: 25 subjects

Test product, dose, mode of administration, batch:

Product	BF2.649
Unit dose per day	20 mg (tablet)
Regimen	single oral dose
Mode	Oral

Batch N°: 111 00 11113 (expiration date: 01/12/2011)
111 00 11293 (expiration date: 01/04/2013)

Duration of treatment:
One day.

Pharmacokinetic assessments:

Blood samples were collected on:

- Day 1 at pre-dose, 1h, 1,5h, 2h, 3h, 4h, 6h, 8h, 12h and 16 hours after administration of BF2.649;
- Day 2 at T24h and T36h;
- Day 3 at T48h;
- Day 4 at T72h;
- Day 5 at T96h.

Urine collections:

- Day 1: At pre-dose, [D1T0h – D1T6h[; [D1T6h – D1T12h[; [D1T12h-D2T24h[;
- Day 2 [D2T24h – D3T48h[.

Safety:

Vital signs:

- Blood pressure, Heart rate and oral Temperature: at the screening visit, then on D-1 on D1 at T0h, T2h, T4h, T6h and T12h, on D2 at T24h, D3 at T48h, D4 T72h, D5 T96h and on follow-up visit.
- Oral temperature at screening visit, D-1 and on follow-up visit.
- Body weight: at the screening and at the follow-up visit.

ECG evaluation:

- 12-lead ECG: at the screening visit, then on D-1, on D1 at T0h, T2h, T4h, T6h, and T12h, on D2 at T24h, on D3 at T48h, on D5 T96h and on D4 at T72h and at the follow-up visit.

Bioanalytical methods:

Serum levels of BF2.649 and its metabolite BP2.951 were evaluated using a UHPLC/MS/MS technique developed and validated by Bioprojet-BIOTECH (B258 study). Urine levels of BF2.649 and its metabolites were evaluated using a UHPLC/MS/MS technique developed and validated by Bioprojet-BIOTECH (B256 study). Drugs serum binding were determined by equilibrium dialysis approach. Unbound fraction of BF2.649 and its metabolite BP2.951 in plasma were measured in order to correctly interpret the effect of hepatic function on the BF2.649 clearance.

Statistical methods:

Pharmacokinetics:

Pharmacokinetic parameters for total and unbound drug were estimated for each group: C_{max}, T_{max}, $t_{1/2}$, $AUC_{[0\text{-}24]}$, $AUC_{[0\text{-}\infty]}$, V/F, Cl/F, protein binding.
Statistical Tests: A one-way analysis of Variance (ANOVA) by considering treatment group as a fixed factor was conducted.

Tolerance:

Individual adverse events were listed and classified by severity and relationship to the drugs. Descriptive statistics were calculated.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Pitolisant and its metabolites		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population:

POPULATION / STUDY OUTCOME:

25 subjects were included:

13 subjects were included in France (2 subjects with stage 2 impaired renal function, 3 subjects with stage 3 impaired renal function and 1 subject with stage 4 impaired renal function, 7 healthy matched subjects) and 12 subjects were included in Bulgaria (2 subjects with stage 2 impaired renal function, 1 subject with stage 3 impaired renal function and 3 subjects with stage 4 impaired renal function, 6 healthy matched subjects).

One subject was withdrawn from the study for consent withdrawal and was replaced.

In the Included population (N = 25):

- 100 % were Caucasian volunteers.
- 84% were male, 16% were female.
- The age ranged from 35 to 70 years with a mean of 53.2 ± 10.6 years.
- The height ranged from 158 cm to 184 cm with a mean of 174.2 ± 6.3 cm.
- The weight ranged from 57 to 98 kg with a mean of 81.26 ± 11.37 kg.
- The BMI ranged from 21.1 to 31.6 kg/m² with a mean of 26.69 ± 2.95 kg/m².

In the Pharmacokinetic population (N=24):

- 100 % were Caucasian volunteers.
- 83.3% were male, 16.7% were female.
- The age ranged from 35 to 70 years with a mean of 52.9 ± 11.0 years.
- The height ranged from 158 cm to 180 cm with a mean of 173.8 ± 6.1 cm.
- The weight ranged from 57 to 98 kg with a mean of 80.6 ± 11.12 kg.
- The BMI ranged from 21.1 to 31.6 kg/m² with a mean of 26.61 ± 2.98 kg/m².

All subjects were non smokers (84%) or smokers of not more than 10 cigarettes a day (16%). 32% of the subjects were alcohol consumers (mean consumption of 8.3 ± 6.1 g/day). 92% of the subjects were caffeine consumers (≤ 6 cups/day).

As expected, all the subjects in the impaired renal function group had a pertinent medical or surgical history:

- 11/12 subjects had renal and urinary disorders (mainly glomerulonephritis chronic, renal failure and renal failure chronic).
- 11/12 subjects had vascular disorders (mainly hypertension).
- 7/12 subjects had metabolism and nutrition disorders.

Among the subjects with impaired renal function, Glomerular filtration mean score was of 64.4 (±6.4) mL/min in stage 2, 48.9 (± 6.4) mL/min in stage 3 and 24.0 (± 3.9) mL/min in stage 4.

4/13 subjects in the normal renal function group had a surgical history (appendectomy). No medical history was reported.

Table 9.5-1 – Main baseline characteristics – Included set (n = 25)

		Impaired renal function (Case)				Normal renal function (Control)				
Demography	Statistic	Stage 2 (N=4)	Stage 3 (N=4)	Stage 4 (N=4)	Total (N=12)	Stage 2 (N=4)	Stage 3 (N=5)	Stage 4 (N=4)	Total (N=13)	Overall (N=25)
Age (years)	N	4	4	4	12	4	5	4	13	25
	Mean±SD	56.5±11.3	54.5±10.5	49.0±12.2	53.3±10.8	55.5±13.2	55.6±8.9	47.8±11.6	53.2±10.9	53.2±10.6
	SEM	5.6	5.2	6.1	3.1	6.6	4.0	5.8	3.0	2.1
	Min/Median/Max	44/57.5/67	41/56.0/65	35/49.5/62	35/54.0/67	39/56.5/70	41/58.0/63	35/48.5/59	35/56.0/70	35/56.0/70
Gender										
Male	N(%)	4(100.0)	3(75.0)	3(75.0)	10(83.3)	4(100.0)	4(80.0)	3(75.0)	11(84.6)	21(84.0)
Female	N(%)	0(0.0)	1(25.0)	1(25.0)	2(16.7)	0(0.0)	1(20.0)	1(25.0)	2(15.4)	4(16.0)
Height (cm)	N	4	4	4	12	4	5	4	13	25
	Mean±SD	173.13±6.12	174.00±6.16	170.75±10.24	172.6±7.2	176.63±4.50	175.40±6.88	175.25±4.86	175.7±5.2	174.2±6.3
	SEM	3.06	3.08	5.12	2.1	2.25	3.08	2.43	1.4	1.3
	Min/Median/Max	164.0/175.75/177.0	165.0/176.00/179.0	158.0/172.50/180.0	158/176.0/180	170.0/178.25/180.0	167.0/177.00/184.0	169.0/176.00/180.0	167/178.0/184	158/176.0/184
Weight (kg)	N	4	4	4	12	4	5	4	13	25
	Mean±SD	80.38±5.79	88.50±10.02	74.63±17.73	81.17±12.55	82.63±8.75	86.20±7.29	74.00±13.98	81.35±10.68	81.26±11.37
	SEM	2.90	5.01	8.86	3.62	4.38	3.26	6.99	2.96	2.27
	Min/Median/Max	74.0/80.75/86.0	76.0/90.00/98.0	57.0/72.50/96.5	57.0/82.75/98.0	70.0/85.75/89.0	77.0/87.00/97.0	63.0/70.00/93.0	63.0/83.50/97.0	57.0/83.50/98.0
BMI (kg/m²)	N	4	4	4	12	4	5	4	13	25
	Mean±SD	26.83±1.49	29.18±2.38	25.30±3.61	27.10±2.91	26.43±1.67	28.10±2.79	23.98±3.37	26.32±3.05	26.69±2.95
	SEM	0.75	1.19	1.81	0.84	0.84	1.25	1.69	0.85	0.59
	Min/Median/Max	24.6/27.45/27.8	26.5/29.30/31.6	22.8/23.95/30.5	22.8/27.45/31.6	24.2/26.70/28.1	24.6/28.70/31.2	21.1/23.05/28.7	21.1/26.20/31.2	21.1/27.20/31.6
Ethnic origin										
Caucasian	N(%)	4(100.0)	4(100.0)	4(100.0)	12(100.0)	4(100.0)	5(100.0)	4(100.0)	13(100.0)	25(100.0)

Inclusion Crietria:

All subjects with impaired renal function included in the study had to meet all of the following criteria for inclusion in the study:

- Subjects from 18 to 75 years of age, with impaired renal function (MDRD between 15 and 89 mL/min), medically stable since 3 months.
- With body mass index (weight/height^2) in the range 18 to 32 kg/m^2 (inclusive).
- Equilibrated blood pressure with or without treatment.
- Normal 12-lead ECG or judged not clinically significant by investigator.
- No clinically significant abnormalities on physical examination or laboratory tests, other than those commonly observed for subject's degree of renal impairment.
- If female, subject had to use an effective contraception method according to the investigator, except if she was sterilized for more than 3 months or postmenopausal. Menopause is defined as over the age of 60 years or between 45 and 60 years being amenorrheic for at least 2 years with plasma FSH level > 30 UI/L.
- If smoker, smoking less than 10 cigarettes/day and able to stop smoking during several days covering the hospitalization time.
- Be able to understand and willing to sign the informed consent form.
- For the French site, be registered with the French Social Security in agreement with the French Law on biomedical experimentation.
- Subject not participating in another study or being in a follow–up period for another study.

All healthy subjects included in the study had to meet all of the following criteria for inclusion in the study:

- Healthy subjects with normal renal function (MDRD > 90 mL/min) and no proteinuria (< 0.15 g/L determined by urinalysis) matched with impaired renal function subjects on ethnic group, sex, age (+/- 5 years), and BMI (+/- 20%).
- Be certified as healthy by a comprehensive clinical assessment (detailed medical history and a complete physical examination) and laboratory investigations (haematological and blood chemistry tests and urinalysis), the results of which were within the normal range or judged not clinically significant by the investigator.
- Normal vital signs after 10 minutes resting in supine position: 95 mmHg < systolic blood pressure < 140 mmHg, 45 mmHg < diastolic blood pressure < 90 mmHg; 40 bpm < heart rate < 100 bpm.
- Normal 12-lead ECG or judged not clinically significant by investigator with 120 ms < PR < 220 ms, QRS < 120 ms, QTc ≤ 430 ms for men and QTc ≤ 450 ms for women.
- If female, subject had to use an effective contraception method according to the investigator, except if she was sterilized for more than 3 months or postmenopausal. Menopause is defined as over the age of 60 years or between 45 and 60 years being amenorrheic for at least 2 years with plasma FSH level > 30 UI/L.
- Be non-smoker or if smoker, smoking less than 10 cigarettes/day and able to stop smoking during several days covering the hospitalization time.
- Normal eating habits.
- Be able to understand and willing to sign the informed consent form.
- Be registered with the French Social Security in agreement with the French Law on biomedical experimentation.
- Subject had not to participate in another study or being in a follow–up period for another study.

Exclusion Criteria:

All subjects with impaired renal function included in the study had not to meet any of the following non inclusion criteria:

- Subject with a history of hepatic, cardiovascular (including conduction disturbance) or psychiatric disorder or any other condition which, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of study results.
- Subjects with evidence of liver disease (ALAT or ASAT > 2 ULN or total bilirubin > 2,2 ULN)
- Presence of concomitant pathology requiring intake of any drugs or substances known to be inhibitors or inductors of CYP enzymes – mainly CYP3A4 and CYP2D6 - within 14 days before inclusion (e.g: corticosteriods, St-john wort, rifampin, efavirenz, etc). For antihypertensive drugs, only strong inhibitors/inductors of CYP enzymes were prohibited.
- Presence of metabolic or ionic disorders not controlled by adapted treatment such as hyperkaliemia (defined as kaliemia > 5.5mmol/L), hypocalcemia (defined as calcemia < 2.2 mmol/L) or hypoalbuminemia.
- Presence of significant anemia not controlled by erythropoietin which could be a contra-indication to blood sampling.
- Presence of nephrotic syndrome.
- Renal transplantation.
- History of allergy or hypersensitivity to one drug (abnormal drug reaction, idiosyncrasy or asthma).
- If female, pregnancy (defined as positive β-HCG blood test) or breast feeding women,
- Chronic abuse of alcohol leading to addiction and impossibility for subject to stop consumption during the study.
- Excessive consumption of caffeine containing beverages (more than 6 cups of coffee per day or equivalent).
- Practice or likely to practice strenuous physical activities (sports).
- Who previously participated in a study during the last 3 months.
- Who had a positive urine drug screen.
- Who donated blood in the two months preceding the initiation of the study or who would donate blood during the study or within the three months following the study completion.
- Who received blood or plasma derivatives in the three months preceding the initiation of the study.
- Who, in the judgment of the investigator, was likely to be non-compliant or uncooperative during the study.
- Who forfeited their freedom by administrative or legal award or who was under guardianship.
- Who could not be contacted in case of emergency.

All healthy subjects included in the study had not to meet any of the following non inclusion criteria:

- Subject with a history of renal, cardiovascular, gastrointestinal, hepatic, neurological, endocrine or psychiatric disorders or any surgery which puts them at risk in the opinion of the investigator.
- History of allergy or hypersensitivity to one drug (abnormal drug reaction, idiosyncrasy or asthma).
- Acute or chronic disease within 1 month before inclusion.
- Regular use of drugs, sedatives, hypnotics, tranquilizers or other addictive agents.
- Any treatment within 14 days before inclusion or within 5 times the elimination half-life of that drug, whichever the longest, including treatment which could lead to inhibition or induction of CYP enzymes – mainly CYP3A4 and CYP2D6 and with the exception of hormonal contraception and menopausal hormone replacement therapy.
- Known or suspected HIV, HBV and HCV infection.
- If female, pregnancy (defined as positive β-HCG blood test) or breast feeding women.
- History or evidence of acute or chronic abuse of alcohol (more than 30g per day) or acute intoxication in the month preceding inclusion.
- Excessive consumption of caffeine containing beverages (more than 6 cups of coffee per day or equivalent).

PK Results

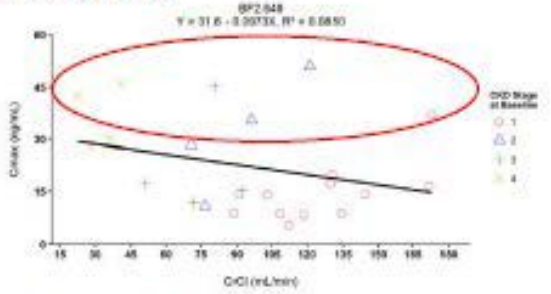
Pharmacokinetic parameters of BF2.649 and its major metabolite BP2.951 in healthy volunteers and subjects with impaired renal function, after administration of single 20 mg BF2.649 dose.
Median plus range are presented for T_{max}; harmonic means ± SDs are presented for $T_{1/2}$ and arithmetic means ± SDs for other parameters. Subscript "u" stands for unbound drug.

BF2.649		*Renal impairment*		
	Normal	*Mild*	*Moderate*	*Severe*
Parameter	*(n=12)*	*(n=4)*	*(n=4)*	*(n=4)*
C_{max} (ng/mL)	14.37 ± 8.37	31.32 ± 16.57	22.32 ± 15.43	36.76 ± 8.86
Ratio (/normal)		2.18	1.55	2.56
P-value		0.1305 (NS)	0.2028 (NS)	0.0004 ***
AUC_inf (h*ng/mL)	222 ± 175	396 ± 279	443 ± 364	428 ± 221
Ratio (/normal)		1.78	2.00	1.93
P-value		0.1560 (NS)	0.3145 (NS)	0.0760 (NS)
T_{max} (h)	2 [1.5-4]	1.75 [1.5-2]	3.5 [1.5-8]	1.5 [1-2]
$T_{1/2}$ (h)	20 ± 6.5	24 ± 4.5	27 ± 10	24 ± 1.4
Vz/Dose (L)	3950 ± 1850	2990 ± 2620	2300 ± 708	2010 ± 1010
Ratio (/normal)		0.76	0.58	0.51
P-value		0.4283 (NS)	0.1094 (NS)	0.0685 (NS)
Cl/Dose (L/h)	141 ± 91.4	93.9 ± 95.4	63 ± 29.5	57.7 ± 30.9
Ratio (/normal)		0.67	0.45	0.41
P-value		0.3882 (NS)	0.0212 *	0.1003 (NS)
A_e (%)	0.46 ± 0.37	0.31 ± 0.06	1.43 ± 0.87	0.88 ± 0.74
Ratio (/normal)		0.69	3.15	1.92
P-value		0.2408 (NS)	0.1435 (NS)	0.4043 (NS)
Cl_R (L/h)	0.52 ± 0.32	0.30 ± 0.18	1.30 ± 0.97	0.57 ± 0.49
Ratio (/normal)		0.57	2.49	1.08
P-value		0.2345 (NS)	0.2572 (NS)	0.8522 (NS)
f_u (%)	4.80 ± 0.90	3.02 ± 0.55	3.31 ± 0.50	3.72 ± 1.02
Ratio (/normal)		0.63	0.69	0.78
P-value		0.0036 **	0.0105 *	0.0818 (NS)
$C_{max\,u}$ (ng/mL)	0.70 ± 0.41	0.93 ± 0.55	0.76 ± 0.55	1.32 ± 0.28
Ratio (/normal)		1.33	1.09	1.89
P-value		0.3759 (NS)	0.8154 (NS)	0.0140 *
AUC_inf $_u$ (h*ng/mL)	11 ± 8	12 ± 9	15 ± 13	15 ± 7
Ratio (/normal)		1.09	1.36	1.36
P-value		0.7789 (NS)	0.4417 (NS)	0.3562 (NS)
Vz/Dose $_u$ (L)	87400 ± 53400	97100 ± 70200	72500 ± 31500	53500 ± 18100
Ratio (/normal)		1.11	0.83	0.61
P-value		0.7738 (NS)	0.6079 (NS)	0.2411 (NS)
Cl/Dose $_u$ (L/h)	3180 ± 2600	3020 ± 2560	1950 ± 933	1520 ± 516
Ratio (/normal)		0.95	0.61	0.48
P-value		0.9139 (NS)	0.3761 (NS)	0.0560 (NS)

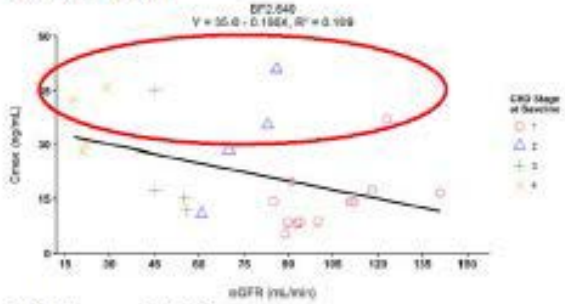
Statistical significance (p-value) for unpaired data: NS = not significant; * $p<0.05$; ** $p<0.01$; *** $p<0.001$
Note: More powerful statistical analysis will be described in another report, independent of this study.

Figure 13: Relationship Between CrCL or eGFR and Pitolisant PK Parameters (P09-13)

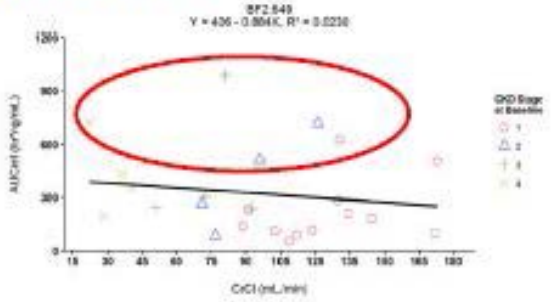
C_{max} vs CrCL



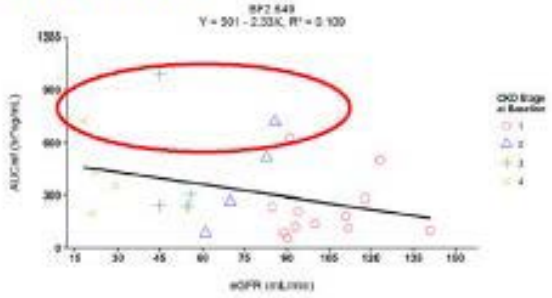
C_{max} vs eGFR



AUC_{inf} vs CrCL



AUC_{inf} vs eGFR



BP2.951	Renal impairment			
Parameter	*Normal (n=12)*	*Mild (n=4)*	*Moderate (n=4)*	*Severe (n=4)*
C_{max} (ng/mL)	11.86 ± 3.95	14.75 ± 5.43	10.55 ± 7.24	19.08 ± 13.19
Ratio (/normal)		1.24	0.89	1.61
P-value		0.2654 (NS)	0.6453 (NS)	0.3560 (NS)
AUC_inf (h*ng/mL)	80 ± 28	110 ± 47	112 ± 60	156 ± 74
Ratio (/normal)		1.38	1.40	1.95
P-value		0.1463 (NS)	0.3619 (NS)	0.1311 (NS)
T_{max} (h)	1.5 [1.5-2]	1.5 [1-1.5]	1.5 [1.5-6]	1.5 [1.5-2]
$T_{1/2}$ (h)	11 ± 12	11 ± 12	23 ± 14	17 ± 6.7
Vz/Dose (L)	5940 ± 2580	5200 ± 3710	6890 ± 1480	4390 ± 3360
Ratio (/normal)		0.88	1.16	0.76
P-value		0.6642 (NS)	0.4987 (NS)	0.2312 (NS)
Cl/Dose (L/h)	275 ± 90.7	207 ± 87.3	209 ± 88.8	172 ± 133
Ratio (/normal)		0.75	0.76	0.63
P-value		0.2129 (NS)	0.2312 (NS)	0.1013 (NS)
A_e (%)	7.49 ± 2.01	5.20 ± 0.73	4.33 ± 0.66	2.17 ± 1.06
Ratio (/normal)		0.69	0.58	0.29
P-value		0.0556 (NS)	0.0117 *	0.0003 ***
Cl_R (L/h)	21.59 ± 5.34	11.67 ± 3.62	10.81 ± 4.37	3.44 ± 1.44
Ratio (/normal)		0.54	0.50	0.16
P-value		0.0059 **	0.0042 **	9 E-08 ***
f_u (%)	43.19 ± 4.66	37.57 ± 2.09	39.57 ± 2.12	36.35 ± 4.73
Ratio (/normal)		0.87	0.92	0.84
P-value		0.0465 *	0.1821 (NS)	0.0328 *
$C_{max\,u}$ (ng/mL)	5.22 ± 2.15	5.58 ± 2.17	4.10 ± 2.60	7.39 ± 5.90
Ratio (/normal)		1.07	0.79	1.42
P-value		0.7769 (NS)	0.4036 (NS)	0.5185 (NS)
AUC_inf_u (h*ng/mL)	35 ± 13	42 ± 20	45 ± 26	58 ± 29
Ratio (/normal)		1.20	1.29	1.66
P-value		0.4484 (NS)	0.5063 (NS)	0.2070 (NS)
$Vz/Dose_u$ (L)	14000 ± 6640	14000 ± 10400	17300 ± 3210	13100 ± 11800
Ratio (/normal)		1.00	1.24	0.94
P-value		0.9982 (NS)	0.3531 (NS)	0.8527 (NS)
$Cl/Dose_u$ (L/h)	656 ± 278	557 ± 242	533 ± 223	509 ± 464
Ratio (/normal)		0.85	0.81	0.78
P-value		0.5365 (NS)	0.4359 (NS)	0.4451 (NS)

Statistical significance (p-value) for unpaired data: NS = not significant; * p<0.05; ** p<0.01; *** p<0.001
Note: More powerful statistical analysis will be described in another report, independent of this study.

Safety Results

Was there any death or serious adverse events?

☐ Yes ☐ No

☐ NA

SAFETY RESULTS

During the overall study period, 8/25 (32%) subjects reported the occurrence of 11 adverse ever treatment emergent adverse events (6 in the impaired renal function group and 4 in the healthy mat group):

- 1/4 (25%) subject reported 1 treatment emergent adverse events (TEAEs) in the impaired re (stage 2) group,
- 2/4 (50%) subjects reported 3 TEAEs in the impaired renal function (stage 3) group,
- 2/4 (50%) subjects reported 2 TEAEs in the impaired renal function (stage 4) group,
- 2/5 (40%) subjects reported 3 TEAEs in the healthy subject matched with impaired renal functi group,
- 1/4 (25%) subject reported 1 TEAE in the healthy subject matched with impaired renal functi group.

No TEAEs occurred in the healthy subject matched with impaired renal function (stage 2) group.

All TEAEs were of mild or moderate intensity and were resolved before the end of the study.

The relationship to study drug seemed possibly related for 2 TEAEs: one episode of insomnia and on erythema, all reported in the healthy subject matched with impaired renal function (stage 3) group.

No relationship to study drug was noted for 8 TEAEs: one episode of influenza reported in the im function (stage 2) group, 2 episodes of hypoglycaemia and 1 episode of musculoskeletal stiffness rej impaired renal function (stage 3) group, 1 episode of headache and 1 episode of circulatory collapse the impaired renal function (stage 4), 1 episode of skin reaction reported in the healthy subject m impaired renal function (stage 3) group and 1 episode of atrioventricular block first degree rep healthy subject matched with impaired renal function (stage 4) group.

No serious adverse events were reported during this study.

No clinically relevant findings were observed in clinical examination laboratory parameters, vital si parameters.

Overall Sponsor Conslusions

CONCLUSION

This study was carried out in 25 subjects. 13 subjects in France (2 subjects with stage 2 impaired renal function, 3 subjects with stage 3 impaired renal function and 1 subject with stage 4 impaired renal function, 7 healthy matched subjects) and 12 subjects were included in Bulgaria (2 subjects with stage 2 impaired renal function, 1 subject with stage 3 impaired renal function and 3 subjects with stage 4 impaired renal function, 6 healthy matched subjects). One subject was withdrawn from the study for consent removal and was replaced.

No serious adverse events were reported during this study. 10 emergent adverse events were reported:
6 in the impaired renal function group and 4 in the healthy matched subject group. 2 adverse events seemed possibly related to study drug administration (one episode of insomnia and one episode of erythema reported in the healthy subject matched with impaired renal function (stage 3) group).

No clinically relevant findings were observed in clinical examination laboratory parameters, vital signs or ECG parameters.

Circulating levels of BF2.649 and of its metabolite BP2.951 showed a significant exposure of subjects receiving BF2.649. No statistically significant difference in most PK parameters was observed in renal insufficient patients compared to healthy volunteers for BF2.649.

Cmax and AUC are anyway approximately increased by a factor 2.5. No half-life increase has been noted in this study. Consequently it is not mandatory to adapt the dosing regimen by starting by lower doses in patients with a renal impaired function and thus particularly because the drug has a good safety profile in the range of the exposures observed. Anyway in order to improve tolerability and to avoid the occurrence of a too marked and strong effect in patients, it seems reasonable to start treatment with the half of the recommended dose i.e 10 mg (instead of 20 mg), then to increase after 7 treatment days to the 20 mg daily dose. It is not recommended to dose patients suffering from renal impairment with higher daily dose than 20 mg. This dose could be then potentially adapted and reduced either to 15 mg or 10 mg daily, if needed based on clinical symptoms and efficacy.

Reviewer Comments and Conclusions

This was a multi-center, open-labeled, parallel-group, single-dose study of pitolisant HCl 20 mg administered in 4 subjects with mild renal impairment (estimated glomerular filtration rate [eGFR] of 60 to 80 mL/min/1.73 m2), 4 subjects with moderate renal impairment (eGFR of 30 to 59 mL/min/1.73 m2), 4 subjects with severe renal impairment (eGFR of 15 to 29 mL/min/1.73 m2), and 12 subjects with normal renal function (eGFR > 90 mL/min/1.73m2). Each subject received a single dose of pitolisant HCl 20 mg. Based on total pitolisant drug levels, mean Cmax and AUC for all categories of renal impaired subjects (mild, moderate and severe) was generally 2xfold higher than the exposure of normal subjects. However, unbound pitolisant drug levels were also assessed for the individual subject in this study. Based on the free drug levels, mild and moderate renal impaired subjects had exposure similar to normal subjects while only the severe renal impaired subjects had higher exposures (slightly less than 2 Xfold higher) compared to normal subjects.

Considering the data from the PK changes (total and free) in the dedicated renal impairment study, the information regarding doses and AE's in the subjects from different renal categories in the pivotal efficacy and safety studies and the mass balance information that suggests that pitolisant is extensively metabolized and is primarily eliminated entirely as metabolites (not parent) via the urine (~90% of dose in urine as metabolites)- we recommend the following dose-adjustment strategy for renal impaired patients:

- **Mild renal impaired= no dose adjustment**
- **Moderate renal impaired = cap the dose at 17.8 mg/day**
- **Severe renal impaired = cap the dose at 17.8 mg/day**

CLINICAL PHARMACOLOGY STUDY REVIEW
Drug Interaction Study—Pitolisant & Paroxetine (CYP2D6 inhibitor)

Study # P11-03; part III	**Study Period:** 8/8/11---9/29/11
NDA 211150 WAKIX	
Title	A three part study to assess the potential impact of concomitant food effect (Study Part I), drug-drug interaction of itraconazole (Study Part II), and paroxetine (Study Part III) on the relative bioavailability of BF2.649 in healthy male subjects (Study Part III)
Objectives:	**Primary objective:** The primary objective of the study was to assess whether single dose BF2.649 (20 mg) oral bioavailability and main PK parameters were modified by concomitant administration of paroxetine leading to an extensive inhibition of CYP2D6. **Secondary objective:** The secondary objective of the study was to assess safety and tolerability of BF2.649 after single oral administration of 20 mg BF2.649 administered alone or after multiple dose of paroxetine in healthy male subjects.

EXECUTIVE SUMMARY:

Effect of paroxetine (CYP2D6 inhibitor) on the PK of pitolisant (P11-03; part III): This study was a comparative bioavailability study of a single administration of pitolisant alone or together with 20 mg paroxetine (at steady state) in a single sequence cross-over design. It was conducted in 18 healthy adult males aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with paroxetine, a potent CYP2D6 inhibitor, at 20 mg QD x 7 days was found to increase the Cmax and AUC of pitolisant by 1.5x and 2.2x, respectively. Thus, considering a 2X fold increase in exposure of pitolisant with paroxetine, the clinical dose of WAKIX should be decreased by 50% when co-administrated with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine etc.)

Study Design:

Methodology:

The study was divided in 3 successive parts. In this clinical report, only results of Part III are presented.

The study was a comparative bioavailability study of a single administration of BF2.649 administered alone or together with paroxetine at steady-state according to a one sequence cross-over design.

A total of 18 subjects received BF2.649 on 2 occasions, either alone or with concomitant administration of paroxetine at steady-state.

Number of subjects (planned and analyzed):

Planned	:	18	Completed the trial	:	18
Screened/enrolled	:	25	In PK analysis	:	18
Included	:	19	In safety analysis	:	19

Diagnosis and main criteria for inclusion:

The study was carried out in 18 healthy male volunteers, aged 18 to 55 years old and with a body mass index (BMI) between 18 and 30 kg/m^2.

Duration of treatment:

Single dose of BF2.649 on two occasions (Day 1 and Day 14).

Paroxetine *q.d.* from Day 8 to Day 16.

Dosage regimen:

Single dose of 20 mg on 2 occasions for BF2.649 (Day 1 and Day 14)

Multiple dose for paroxetine (20 mg for 8 days and 10 mg for 1 day). Administration was performed in ambulatory conditions from Day 8 to Day 13 and on Day 16.

Test product(s), dose and mode of administration, batch number:

Product and Formulation:	BF2.649 / Tablet 20 mg
Batch number:	1120011158
Expiry date:	01/12/2011
Mode of administration:	Oral
Dosage/regimen:	Single dose of 20 mg on 2 occasions

Test product(s), dose and mode of administration, batch number:

Product and Formulation:	Paroxetine / Tablet 20 mg
Batch number:	600
Expiry date:	04/2014
Mode of administration:	Oral
Dosage/regimen:	Multiple dose (20 mg for 8 days and 10 mg for 1 day)

Each subject was administered the following treatments (oral route):

- **Day 1:** 1* 20 mg BF2.649 tablet,
- **Day 8 to Day 13 inclusive:** 1* 20 mg paroxetine tablet once daily,
- **Day 14:** 1* 20 mg BF2.649 tablet + 1* 20 mg paroxetine tablet,
- **Day 15:** 1* 20 mg paroxetine tablet once daily,
- **Day 16:** ½* 20 mg paroxetine tablet once daily.

Subjects under fasted conditions swallowed the appropriate tablet containing BF2.649 or paroxetine with 240 mL of water at room temperature. Subjects were dosed whilst standing or semi-recumbent and they were not allowed to lie flat for 4 h post-dose, except for study procedures or if clinically indicated.

All paroxetine and BF2.649 administrations were performed in fasted conditions.

On Day 14, BF2.649 and paroxetine were given concomitantly.

Criteria for evaluation:

Efficacy / PD:

Not applicable.

PK:

On Day 1 and Day 14, blood samples for evaluation of BF2.649 (main compound) and BP2.951 (metabolite) concentrations were collected pre-dose and at 0.50, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00, 48.00 and 72.00 h post-dose.

Safety:

Monitoring for the occurrence of AEs. Changes in physical examination, vital signs (blood pressure and pulse rate), ECG and clinical laboratory tests (biochemistry, hematology, and urinalysis).

Statistical methods:

PD:

Not applicable.

PK:

All serum concentrations were summarized by day.

The derived PK parameters were listed by subject and summarized by day.

The effect of paroxetine on the PK parameters of BF2.649 and BP2.951 was evaluated based on $AUC_{0-\infty}$, AUC_{0-t} and C_{max} by ANOVA using a mixed effect model applied to log transformed PK parameters with treatment as fixed effects and subject as random effect. For each parameter, a point estimate for the ratio of geometric means (BF2.649 (BP2.951) + paroxetine / BF2.649 (BP2.951) alone) was obtained by calculating the difference of least square means on the logarithmic scale and subsequent back transformation with the anti-log function. Likewise, 90% CI for the ratios was obtained and a point estimate for the ratio of geometric means BF2.649 (BP2.951) + paroxetine / BF2.649 (BP2.951) alone was obtained by least square means.

The analysis of t_{max} was based on the non-parametric Wilcoxon signed rank test.

Safety:

All safety parameters (ECG, vital signs, AEs, etc.) were summarized by day and time point (where appropriate).

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Pitolisant and its metabolites		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population:

A total of 19 male subjects aged between 21 and 55 years old and with a BMI ranging from 19.9 to 29.8 kg/m^2 participated to this study as presented next.

Table 11.2.1 - 1 Summary of demographic data

N		19
Age (Years)	Mean (SD)	39.5 (10.0)
	Min - Max	21 - 55
Height (cm)	Mean (SD)	177.7 (6.1)
	Min - Max	167 - 190
Weight (kg)	Mean (SD)	76.09 (11.68)
	Min - Max	57.4 – 94.1
BMI (kg/m2)	Mean (SD)	24.08 (3.34)
	Min - Max	19.9 – 29.8

Source: Tables 14.1.1-1.

Inclusion Crietria:

All subjects included in the study had to meet all of the following criteria for inclusion in the study.

1. Male healthy volunteers 18 to 55 years of age,
2. Light smokers (less than 5 cigarettes per day) or subjects who were non-smokers. No smoking (or use of smoking substitute *e.g.* nicotine patch) was permitted from screening throughout the study,
3. Male subjects with a body weight of at least 50 kg and a body mass index (BMI) calculated as weight in kg/height (in m^2) from 18 to 30 kg/m^2 at screening,
4. Able to communicate well with the Investigator and research staff and to comply with the requirements of the entire study,
5. Provision of written informed consent to participate as shown by a signature on the volunteer's consent form,
6. Normal arterial blood pressure (BP) and pulse rate or, if abnormal, considered not clinically significant by the principal Investigator. These were measured after resting for 5 min,*
7. Registered with the French Social Security in agreement with the French law on biomedical experimentation. [10, 11]

*Normal BP was taken to be [100–150] mmHg systolic and [45–90] mmHg diastolic. Normal pulse rate was taken to be [40-100] bpm.

Exclusion Criteria:

All the subjects included in the study did not meet the following exclusion criteria:

1. On direct questioning and physical examination had evidence of any clinically significant acute or chronic disease, including known or suspected HIV, HBV or HCV infection,
2. Previously received BF2.649,

3. Had any clinically significant abnormality following review of pre-study laboratory tests (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and alkaline phosphatase (ALP) had to be within normal ranges), vital signs, full physical examination and ECG,
4. Were within the exclusion period defined in the National Register for Healthy Volunteers of the French Ministry of Health,
5. Forfeited their freedom by administrative or legal award or who were under guardianship,
6. Unwilling to give their informed consent,
7. Presented a positive laboratory test for Hepatitis B surface antigen (HbsAg), or anti-HIV 1/2 or anti- HCV antibodies,
8. Had a history of allergy, intolerance or photosensitivity to any drug,
9. Had a history of serious allergy, asthma, allergic skin rash or sensitivity to any drug,
10. Were known or suspected alcohol or drug abusers (more than 14 units of alcohol per week, one unit = 8 g or about 10 mL of pure alcohol),
11. Drank more than 8 cups daily of beverage containing caffeine,
12. Presented a positive laboratory test for urine drug screening (opiates, cocaine, amphetamine, cannabis, benzodiazepines),
13. Had undergone surgery or had donated blood within 12 weeks prior to the start of the study,
14. Had taken any prescribed or over the counter drug (including antacid drug), with the exception of paracetamol (up to 3 g per day) within 2 weeks prior to the first dose administration,
15. Presented any clinical condition or prior therapy which, in the opinion of the Investigator, made the subject unsuitable for the study,
16. Participated to any clinical trial with an investigational drug in the past 3 months preceding study entry.

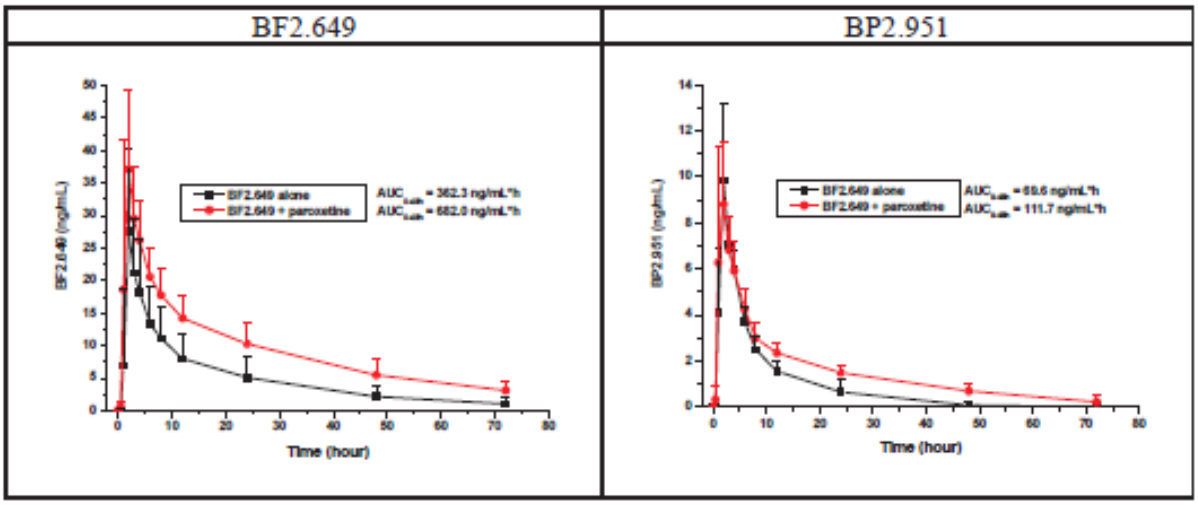
PK Results

A summary of the BF2.649 (parent drug) and BP2.951 (major metabolite) pharmacokinetic results obtained is provided below:

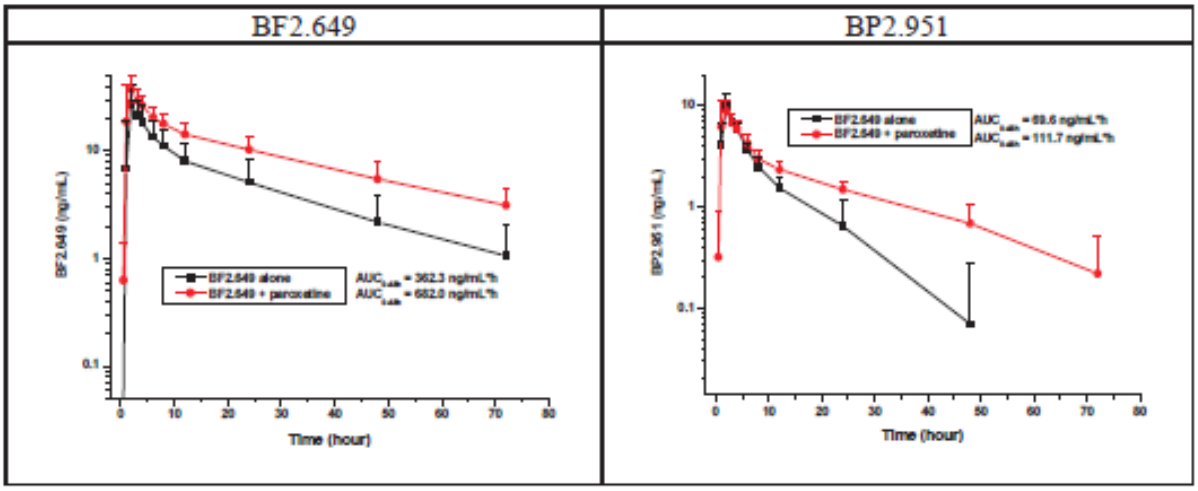
PK parameters	BF2.649		BP2.951	
Day	BF2.649 alone	BF2.649 + paroxetine	BF2.649 alone	BF2.649 + paroxetine
C_{max} (ng/mL) Mean ± SD CV%	28.40 ± 11.48 40.4	40.99 ± 15.99 39.0	10.14 ± 2.94 29.0	9.84 ± 3.56 36.2
T_{max} (h) Mean ± SD CV%	2.3 ± 1.0 44.1	1.9 ± 0.6 32.9	2.2 ± 0.5 23.7	1.9 ± 0.6 32.9
$AUC_{0-\tau}$ (ng/mL.h) Mean ± SD CV%	362 ± 198 54.7	682 ± 197 28.9	70 ± 19 27.2	112 ± 23 21.0
$AUC_{0-\infty}$ (ng/mL.h) Mean ± SD CV%	396 ± 233 58.8	802 ± 253 31.6	71 ± 22 30.3	128 ± 27 21.0
λ_z (1/h) Mean ± SD CV%	0.040 ± 0.009 21.6	0.029 ± 0.007 24.1		
$T_{1/2}$ (h) Mean ± SD CV%	18.2 ± 3.9 21.4	24.7 ± 4.9 19.9		
Clss/F (mL/h) Mean ± SD CV%	65561 ± 33285 50.8	27706 ± 9595 34.6		
Vdss/F (mL) Mean ± SD CV%	1638000 ± 758412 46.3	936389 ± 204819 21.9		

Mean (± standard deviation) BF2.649 or BP2.951 concentrations measured in 18 healthy male volunteers after a single oral administration of BF2.649 dosed at 20 mg alone or with paroxetine

Linear coordinates



Semi-logarithmic coordinates



Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Overall Sponsor Conslusions

Safety and tolerability was good with paroxetine.

Reviewer Comments and Conclusions

<u>Effect of paroxetine (CYP2D6 inhibitor) on the PK of pitolisant (P11-03; part III):</u> This study was a comparative bioavailability study of a single administration of pitolisant alone or together with 20 mg paroxetine (at steady state) in a single sequence cross-over design. It was conducted in 18 healthy adult males aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with paroxetine, a potent CYP2D6 inhibitor, at 20 mg QD x 7 days was found to increase the Cmax and AUC of pitolisant by 1.5x and 2.2x, respectively. Thus, considering a 2X fold increase in exposure of pitolisant with paroxetine, the clinical dose of WAKIX should be decreased by 50% when co-administrated with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine etc.)

CLINICAL PHARMACOLOGY STUDY REVIEW
Drug Interaction Study—Pitolisant & Rifampicin (CYP3A4 inducer)

Study # P11-10	**Study Period:** 4/26/12---6/19/12
NDA 211150 WAKIX	
Title	A study to assess the potential impact of drug-drug interaction of rifampicin on the relative bioavailability of BF2.649 in healthy male subjects
Objectives :	**Primary objective:** The primary objective of the study was to assess whether single dose BF2.649 (20 mg) oral bioavailability and main PK parameters were modified by concomitant administration of rifampicin leading to an extensive induction of CYP3A4 and CYP2C8/C9 activity **Secondary objective:** The secondary objective of the study was to assess safety and tolerability of BF2.649 after single oral administration of 20 mg BF2.649 administered alone or after multiple dose of rifampicin in healthy male subjects

EXECUTIVE SUMMARY:

Effect of rifampicin (CYP3A4 inducer) on the PK of pitolisant (P11-10): This study was a cross-over, single sequence, 2-period study with pitolisant alone as well as pitolisant with rifampicin at steady-state. It was conducted in 18 healthy adults aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with rifampicin, a strong CYP3A4 inducer, at 600 mg QD x 8 days decreased the AUC and Cmax of pitolisant by 48% and 39%, respectively. Therefore, based on the significant reduction in exposure of pitolisant when co-administered with strong CYP3A4 inducers (e.g., rifampicin, phenytoin etc.), the following dose-adjustment strategy is recommended:

- **For patients stable on 8.9 mg/day or 17.8 mg/day: Dose to be increased gradually over a week to reach double the original dose level. Maintain for the duration of use of CYP3A4 inducers.**
- **For patients stable on the highest dose of 35.6 mg/day: No dose adjustments is recommended**

Study Design:

Methodology:

The study was a cross-over, single sequence, two period, open label, single dose (on 2 occasions) study in 18 subjects in order to have at least 16 evaluable. Subjects received BF2.649 on 2 occasions, one alone and one after multiple dose administration of rifampicin.

Number of subjects (planned and analyzed):

Planned	:	18	Completed the trial	:	18
Screened/enrolled	:	27	In PK analysis	:	19
Included	:	19	In safety analysis	:	18

Diagnosis and main criteria for inclusion:

The study was carried out in 18 healthy volunteers, aged 18 to 55 years old and with a body mass index (BMI) between 18 and 30 kg/m^2.

Duration of treatment:

Single dose of BF2.649 on 2 occasions (Day 1 and Day 14).

Rifampicin *q.d.* from Day 8 to Day 15.

Dosage regimen:

Single dose of 20 mg on 2 occasions for BF2.649 (Day 1 and Day 14)

Multiple dose for rifampicin (600 mg q.d. for 8 days from Day 8 to Day 15) ➔ ambulatory administration from Day 8 to Day 13

Test product(s), dose and mode of administration, batch number:

Product and Formulation:	BF2.649 tablet
Batch number:	1218212116
Expiry or retest date:	01/04/2013
Mode of administration:	Oral
Dosage/regimen:	Single dose of 20 mg on 2 occasions (Day 1 and Day 14)

Reference/Comparator product(s), dose and mode of administration, batch number:

Product and Formulation:	Rifadine®
Batch number:	A1165
Expiry or retest date:	10/2014
Mode of administration:	Oral
Dosage/regimen:	Once daily for 8 days (Day 8 to Day 15)

Criteria for evaluation:

Efficacy / PD:

Not applicable.

PK:

On Day 1 and Day 14, blood samples for evaluation of BF2.649 (main compound) and BP2.951 concentrations were collected pre-dose and at 0.50, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 h post-dose.

Safety:

Monitoring for the occurrence of AEs. Changes in physical examination, vital signs (body temperature, O_2 saturation at ambient room air, blood pressure and pulse rate), ECG, and clinical laboratory tests (biochemistry, hematology, and urinalysis)

Statistical methods:

Efficacy / PD:

Not applicable.

PK:

All serum concentrations were summarized by treatment or by day where appropriate.

The derived PK parameters were listed by subject and summarized by treatment or by day where appropriate.

The effect of rifampicin on the PK parameters of BF2.649 and BP2.951 was evaluated based on $AUC_{0-\infty}$, AUC_{0-t} and C_{max} by ANOVA using a mixed effect model applied to log transformed PK parameters with treatment as fixed effects and subject as random effect. For each parameter, a point estimate for the ratio of geometric means (BF2.649 (BP2.951) + rifampicin / BF2.649 (BP2.951) alone) was obtained by calculating the difference of least square means on the logarithmic scale and subsequent back transformation with the anti-log function. Likewise, 90% CI for the ratios were obtained and a point estimate for the ratio of geometric means BF2.649 (BP2.951) + rifampicin / BF2.649 (BP2.951) alone were obtained by least square means.

The analysis of t_{max} was based on the non-parametric Wilcoxon signed rank test and was carried out.

Safety:

All safety parameters (ECG, vital signs, AEs, etc.) were summarized by day and time point (where appropriate).

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Pitolisant and its metabolites		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population:

A total of 19 male subjects aged between 23 and 54 years old and with a BMI ranging from 18.1 to 29.3 kg/m^2 participated to this study as presented in Table 11.2.1 - 1 .

Table 11.2.1 - 1 Summary of demographic data (safety population)

	N	All
		19
Age (Years)	Mean (SD)	35.6 (9.1)
	Min - Max	23 - 54
Height (cm)	Mean (SD)	178.2 (8.1)
	Min - Max	160 – 193
Weight (kg)	Mean (SD)	75.8 (11.3)
	Min - Max	57.7 – 92.7
BMI (kg/m²)	Mean (SD)	23.9 (3.5)
	Min - Max	18.1 – 29.3

Inclusion Crietria:

The study was performed on healthy males in good general condition, who met all the inclusion criteria and none of the exclusion criteria presented in Sections 9.3.1 and 9.3.2.

All the volunteers selected in this study belonged to the (b) (4) volunteers' panel. They were therefore entered and identified in the national register of the French Ministry of Health by their name, surname, date and place of birth. For all these subjects, the list of the trials in which they participated in the past, as well as the exclusion period after the last trial and the total amount of the fees earned during the last twelve months preceding this study were available.

All subjects gave their written informed consent at screening.

9.3.1 Inclusion criteria

All subjects included in the study had to meet all of the following criteria for inclusion in the study:

1. Male healthy volunteers 18 to 55 years of age,
2. Light smokers (less than 5 cigarettes per day) or subjects who were non-smokers,
3. Male subjects with a body weight of at least 50 kg and a body mass index (BMI) calculated as weight in kg/height (in m^2) from 18 to 30 kg/m^2 at screening,
4. Able to communicate well with the Investigator and research staff and to comply with the requirements of the entire study,
5. Provision of written informed consent to participate as shown by a signature on the volunteer consent form,
6. Normal arterial blood pressure (BP) and pulse rate or, if abnormal, considered not clinically significant by the principal Investigator. These were measured after resting for 5 minutes (min),*
7. Registered with the French Social Security in agreement with the French law on biomedical experimentation. (6 ,7)

*Normal BP was taken to be [100–150] mmHg systolic and [45–90] mmHg diastolic. Normal pulse rate was taken to be [40-100] bpm.

Exclusion Criteria:

None of the exclusion criteria had to be met unless, after discussion between the Investigator and the Sponsor, it was concluded that any deviation would not have been of clinical significance. The deviation and date of agreement had to be documented in the CRF.

All the subjects included in the study did not meet the following exclusion criteria:

1. Who on direct questioning and physical examination had evidence of any clinically significant acute or chronic disease, including known or suspected HIV, HBV or HCV infection,
2. Who previously received BF2.649 as reported during subject's interview,

3. With any clinically significant abnormality following review of pre-study laboratory tests (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and alkaline phosphatase (ALP) must be within normal ranges), vital signs, full physical examination and ECG,
4. Who were within the exclusion period defined in the National Register for Healthy Volunteers of the French Ministry of Health
5. Who forfeited their freedom by administrative or legal award or who were under guardianship,
6. Unwilling to give their informed consent,
7. Who had a positive laboratory test for Hepatitis B surface antigen (HbsAg), or anti-HIV 1/2 or anti- HCV antibodies,
8. Who had a history of allergy (serious or not), allergic skin rash, asthma, intolerance, sensitivity or photosensibility to any drug,
9. Who were known or suspected alcohol or drug abusers (more than 14 units of alcohol per week, one unit = 8 g or about 10 mL of pure alcohol),
10. Who drank more than 8 cups daily of beverage containing caffeine,
11. Who had a positive laboratory test for urine drug screening (opiates, cocaine, amphetamine, cannabis, benzodiazepines),
12. Who underwent surgery or had donated blood within 12 weeks prior to the start of the study,
13. Who had taken any prescribed or over the counter drug (including antacid drug), with the exception of paracetamol (up to 3 g per day) within 2 weeks prior to the first dose administration,
14. Who had any clinical condition or prior therapy which, in the opinion of the Investigator, made the subject unsuitable for the study,
15. Who participated to any clinical trial with an investigational drug in the past 3 months preceding study entry.

All exclusion and inclusion criteria must be observed.

9.3.3 Removal of subjects from therapy or assessment

In accordance with the Declaration of Helsinki, subjects were free to withdraw from the study at any time should they wish so.

The following reasons were accepted for study discontinuation:

- Withdrawal of subject consent, or loss to follow-up, or inability to remain under medical observation including post study examination,
- Non-compliance or major deviation from the protocol,
- Appearance of a Serious Adverse Event (SAE),
- Any other situation where, in the opinion of the Investigator, continuation of the study would not be in the interest of the subject,
- Discontinuation of the study by the Sponsor.

PK Results

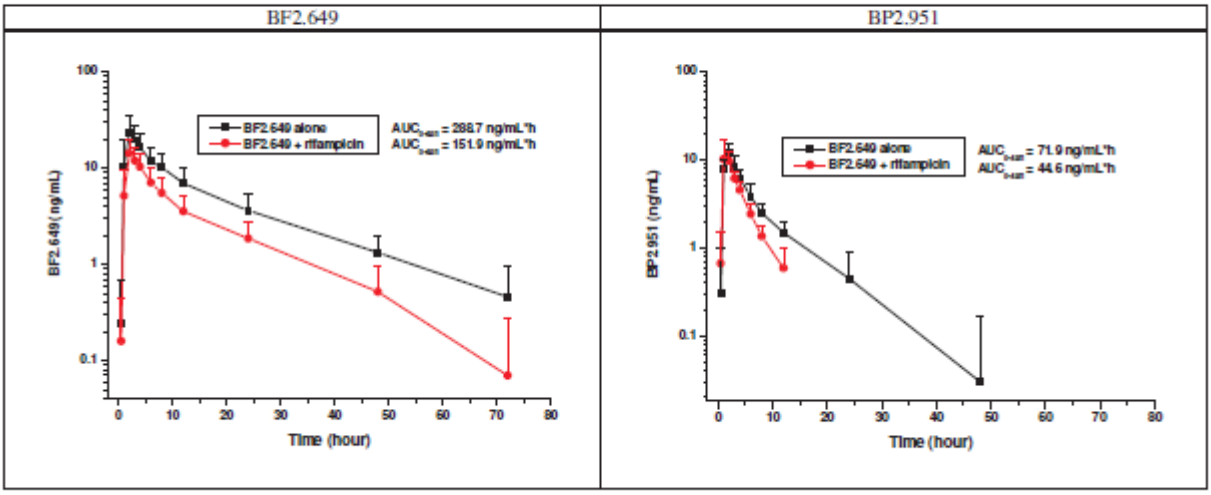
SUMMARY OF PHARMACOKINETIC RESULTS

A summary of the BF2.649 (parent drug) and BP2.951 (major metabolite) pharmacokinetic results obtained is provided below:

PK parameters	BF2.649		BP2.951	
Day	BF2.649 alone	BF2.649 + rifampicin	BF2.649 alone	BF2.649 + rifampicin
C_{max} (ng/mL) Mean ± SD CV%	24.93 ± 11.01 44.2	14.74 ± 5.74 39.0	11.67 ± 3.18 27.3	12.24 ± 5.72 46.7
T_{max} (h) Mean ± SD CV% Median [Min-Max]	2.3 ± 0.6 25.2 2.0 [1.0-3.0]	1.9 ± 0.5 25.0 2.0 [1.0-3.0]	1.9 ± 0.2 12.1 2.0 [1.0-2.0]	1.6 ± 0.5 31.1 2.0 [1.0-2.0]
$AUC_{0-\tau}$ (ng/mL.h) Mean ± SD CV%	289 ± 123 42.6	152 ± 68 44.6	71 ± 21 29.2	45 ± 11 25.3
$AUC_{0-\infty}$ (ng/mL.h) Mean ± SD CV%	303 ± 132 43.5	156 ± 72 45.8	70 ± 22 30.8	44 ± 11 24.1
λ_z (1/h) Mean ± SD CV%	0.047 ± 0.009 18.8	0.061 ± 0.012 20.1	0.149 ± 0.068 46.0	0.278 ± 0.050 18.1
$T_{1/2}$ (h) Mean ± SD CV% Median [min-max]	15.2 ± 2.8 18.7 14.5 [10.9-21.2]	11.9 ± 2.5 20.9 11.9 [8.7-17.9]	5.8 ± 2.9 50.6 5.5 [2.6-13.7]	2.6 ± 0.4 16.2 2.5 [1.7-3.5]
Clss/F (mL/h) Mean ± SD CV%	78667 ± 33378 42.4	151844 ± 62799 41.4		
Vdss/F (mL) Mean ± SD CV%	1656111 ± 604033 36.5	2465000 ± 729208 29.6		

Mean (± standard deviation) BF2.649 or BP2.951 concentrations measured in 18 healthy male volunteers after a single oral administration of BF2.649 dosed at 20 mg alone or with rifampicin

Semi-logarithmic coordinates



Results:

Efficacy / PD:

Not applicable.

PK:

Co-administration of rifampicin, a potent CYP3A4 and CYP2C8/C9 inductor, with BF2.649 (single dose of 20 mg) in 18 healthy male subjects:

- Induced a significant decrease of rate of absorption and extent of exposure of the BF2.649 (39%, 47% and 48% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ geometric means, respectively); the 90% CIs being excluded from the reference range [0.8000-1.2500].
- Didn't modify the rate of appearance (C_{max}) of the metabolite BP2.951, the 90% CI being included in the reference range [0.8000-1.2500] and induced a decrease of extent of exposure of BP2.951 (38% and 37% for AUC_{0-t} and $AUC_{0-\infty}$ geometric means, respectively) with 90% CIs completely excluded from the reference interval [0.8000-1.2500].
- Had no impact on median t_{max} value (2.0 hours for both BF2.649 and BP2.951 in both treatment conditions)
- Induced an increase of about 20% of the geometric mean of metabolite:parent AUC ratio.

PK analysis details are included in a separate report (Appendix 16.5).

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Safety:

A total of 19 healthy male subjects were included and 18 of them completed the study without relevant deviation. Only 4 AEs were recorded throughout the study duration. 3 of them were TEAEs (2 with BF2.649 and 1 with rifampicin alone). 1 was observed on Day 2 (after BF2.649 alone), 1 was observed on Day 4 (after BF2.649 alone), and 1 was observed on Day 9 (after rifampicin alone). Two (2) of the 3 TEAEs were not related either to BF2.649 or to rifampicin. The only AE related to BF2.649 was a dizziness sensation reported in the hours following the administration of BF2.649 alone (Day 1). This AE was of mild intensity and resolved spontaneously. The three other AEs consisted in conjunctivitis (2 cases) and constipation (1 case). No other relevant change in any safety parameters was observed.

Overall Sponsor Conslusions

Conclusions:

Safety and tolerability of single oral dose of 20 mg BF2.649 given alone or after induction of CYP3A4 and CYP2C8/C9 activity induced by multiple dose of rifampicin was very good.

Based on the study results, rifampicin a potent inducer of CYP3A4 and CYP2C8/C9 activities, increased BF2.649 metabolism, leading to a approximately 2-fold decrease of mean BF2.649 exposure (i.e., decrease of about 47% of geometric mean of AUC_{0-t}).

Reviewer Comments and Conclusions

<u>Effect of rifampicin (CYP3A4 inducer) on the PK of pitolisant (P11-10)</u>: This study was a cross-over, single sequence, 2-period study with pitolisant alone as well as pitolisant with rifampicin at steady-state. It was conducted in 18 healthy adults aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with rifampicin, a strong CYP3A4 inducer, at 600 mg QD x 8 days decreased the AUC and Cmax of pitolisant by 48% and 39%, respectively. Therefore, based on the significant reduction in exposure of pitolisant when co-administered with strong CYP3A4 inducers (e.g., rifampicin, phenytoin etc.), the following dose-adjustment strategy is recommended:

- **For patients stable on 8.9 mg/day or 17.8 mg/day: Dose to be increased gradually over a week to reach double the original dose level. Maintain for the duration of use of CYP3A4 inducers.**
- **For patients stable on the highest dose of 35.6 mg/day: No dose adjustments is recommended**

CLINICAL PHARMACOLOGY STUDY REVIEW
Drug Interaction Study—Pitolisant & Midazolam (CYP3A4 substrate)

Study # P15-15	**Study Period:** 2/2/16---4/13/16
NDA 211150 WAKIX	
Title	A two-part, open label, one sequence, cross-over pharmacokinetic study to evaluate : Part I: At steady-state, the pitolisant (40 mg) interaction (as inducer) on both a single dose of midazolam (Buccolam® 2.5 mg) and of bupropion (Zyban® L.P. 150 mg) in eighteen healthy male volunteers. Part II: The probenecid (Benemide®), a UDP-glucuronosyltransferases inhibitor, interaction on a 40 mg pitolisant single oral dose in eighteen healthy male volunteers.
Objectives :	**Primary objectives:** The primary objectives of this study part were: - To evaluate at steady-state the PK interaction of 40 mg pitolisant (as inducer) with a 2.5 mg midazolam single dose, in 18 healthy male volunteers. - To evaluate at steady-state the PK interaction of 40 mg pitolisant (as inducer) with a 150 mg bupropion single dose, in 18 healthy male volunteers. **Secondary objective:** The secondary objective was to evaluate the pitolisant tolerability when administered concomitantly with midazolam and bupropion in healthy male volunteers.

EXECUTIVE SUMMARY:

Effect of pitolisant on the PK of midazolam (CYP3A4 substrate) (P15-15): A clinical study was conducted to assess the effect of pitolisant on CYP3A4 using Midazolam as a CYP3A4 model substrate. This study showed that pitolisant (17.8 mg QD for 7 days) reduces exposures of midazolam (2.5 mg single dose) about 20%. Because the commonly used oral contraceptives are substrates of CYP3A4, an effect of pitolisant on the PK of oral contraceptives cannot be ruled out. Therefore, administration of pitolisant concomitantly with oral contraceptives may reduce the systemic exposure and the effectiveness of oral contraceptives, Thus, an alternative or additional reliable contraceptive method should be used when taking pitolisant.

Study Design:

9.1 OVERALL STUDY DESIGN

This study part was an open label, single center, one sequence cross-over study, to evaluate PK characteristics of single oral dose of both 2.5 mg midazolam and 150 mg bupropion when given alone or with 40 mg oral dose of BF2.649 at steady-state. The study was run in healthy male subjects with a body mass index (BMI) between 18 (inclusive) and 30 kg/m² (inclusive).

9.2 DISCUSSION OF THE STUDY DESIGN

Biotransformation of BF2.649 into its main metabolite BP2.951 is driven by both CYP2D6 and CYP3A4. Another possible enzymatic pathway in pitolisant metabolism is UGT2B7 substrates. The ability of BF2.649 to induce the catalytic activity of several isoforms of CYP450 has been assessed in *in vitro* studies. A weak induction for CYP2B6 isoform has been observed.

The aim of this study part was to evaluate the impact of pitolisant, as potential inducer of both CYP3A4 and CYP2B6, by assessing midazolam and bupropion and their respective major metabolite PK, when given alone or combined with pitolisant under steady-state conditions.

Number of patients (planned and analyzed):

Planned	:	18 completed subjects	Completed the trial	:	18
Screened/enrolled	:	35	In PK analysis	:	19
Included	:	19	In safety analysis	:	19

Diagnosis and main criteria for inclusion:

The study was carried out in 19 healthy male volunteers, aged 18 to 50 years old and with a BMI between 18 and 30 kg/m^2.

Duration of treatment:

Subjects had 14 days of treatment: on Day 1, Day 3 and from Day 7 to Day 18.

Dosage regimen:

Each subject received:

- on Day 1: a 2.5 mg midazolam single oral dose,
- on Day 3: a 150 mg bupropion single oral dose,
- from Day 7 to Day 12: a 40 mg pitolisant single oral dose,
- on Day 13: a 40 mg pitolisant single oral dose combined with a 2.5 mg midazolam single oral dose,
- on Day 14: a 40 mg pitolisant single oral dose,
- on Day 15: a 40 mg pitolisant single oral dose combined with a 150 mg bupropion single oral dose,
- from Day 16 to Day 18: a 40 mg pitolisant single oral dose.

Test product, dose and mode of administration, batch number:

Product and Formulation:	Pitolisant, 20 mg tablets
Batch number:	5008
Expiry date:	07/2017
Mode of administration:	Oral
Dosage/regimen:	1 administration of 40 mg of pitolisant per day from Day 7 to Day 18.

Test product, dose and mode of administration, batch number:

Product and Formulation:	Midazolam, 2.5 mg/0.5 mL oro-mucosal solution
Batch number:	1505015
Expiry date:	10/2016
Mode of administration:	Oral
Dosage/regimen:	2 single administrations of 2.5 mg of midazolam one on Day 1 and one on Day 13.

Criteria for evaluation:

Efficacy / PD:
Not applicable.

PK:
On Day 1 and Day 13, blood samples were collected for midazolam and its major circulating metabolite (1-hydroxymidazolam) levels determinations at pre-dose, then 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 h post-dose (n = 26).

On Day 3 and Day 15, blood samples were collected for bupropion and its major circulating metabolite (6-hydroxybupropion) levels determinations at pre-dose, then 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0 h post-dose (n = 34).

From Day 10 to Day 18, blood samples were collected for pitolisant and major metabolites (BP2.951, BP1.8054 and BP1.9733 levels determinations at pre-dose (n = 9).

The following PK parameters of pitolisant and its major metabolites (BP2.951, BP1.8054 and BP1.9733), midazolam and its major circulating metabolite (1-hydroxymidazolam), bupropion and its major circulating metabolite (6-hydroxybupropion) were determined: C_{max}, t_{max}, $t_{1/2}$, AUC_{0-t} and $AUC_{0-\infty}$.

Safety:
Monitoring for the occurrence of AEs. Changes in physical examination, vital signs (blood pressure and HR), ECG and clinical laboratory tests (biochemistry, hematology, and urinalysis) between screening and EOS.

Statistical methods:

PD:
Not applicable.

PK:
For each compound of interest, all serum concentrations were summarized by treatment and day. The derived PK parameters were listed by subject and summarized by treatment and day.

The effect of pitolisant on the PK parameters of midazolam and its related metabolite (1-hydroxymidazolam) was evaluated based on $AUC_{0-\infty}$, AUC_{0-t} and C_{max} by ANOVA using a mixed effect model applied to log transformed PK parameters with treatment as fixed effects and subject as random effect. For each parameter, a point estimate for the ratio of GM ([midazolam + BF2.649] / midazolam alone) was obtained by calculating the difference of least square means on the logarithmic scale and subsequent back transformation with the anti-log function. Likewise, 90% CI for the ratios were obtained and a point estimate for the ratio of GM ([midazolam + BF2.649] / midazolam alone) was obtained by least square means.

Statistical methods (continued):

PK (continued):
The effect of pitolisant and all related metabolites on the PK parameters of bupropion and its related metabolite (6-hydroxybupropion) was evaluated based on $AUC_{0-\infty}$, AUC_{0-t} and C_{max} by ANOVA using a mixed effect model applied to log transformed PK parameters with treatment as fixed effects and subject as random effect. For each parameter, a point estimate for the ratio of GM ([bupropion + BF2.649] / bupropion alone) was obtained by calculating the difference of least square means on the logarithmic scale and subsequent back transformation with the anti-log function. Likewise, 90% CI for the ratios were obtained and a point estimate for the ratio of GM ([bupropion + BF2.649] / bupropion alone) was obtained by least square means.

The analysis of t_{max} was based on the non-parametric analysis.

Safety:
All safety parameters (ECG, vital signs, AEs, etc.) were presented by using individual data listing and descriptive statistics. All these parameters were summarized by treatment, day and time point (where appropriate).

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Pitolisant and its metabolites		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Study Population:

A total of 19 male subjects (18 Caucasian and 1 black) aged between 19 and 50 years old and with a BMI ranging from 18.7 to 27.9 kg/m^2 participated to this study as presented in Table 8.

Table 8 Summary of demographic data

		Safety Analysis Set
Age (years)	**N**	19
	Mean (SD)	34.7 (9.5)
Height (cm)	**N**	19
	Mean (SD)	175.4 (8.6)
Weight (kg)	**N**	19
	Mean (SD)	71.72 (11.08)
BMI (kg/m²)	**N**	19
	Mean (SD)	23.24 (2.54)

Inclusion Crietria:

All subjects included in the study had to meet all of the following criteria for inclusion in the study. They were:

1. Healthy male volunteers 18 to 50 years of age,
2. Light smokers (less than 5 cigarettes per day) or non-smokers. No smoking (or use of smoking substitute e.g. nicotine patch) was permitted from screening throughout the study,
3. Able to communicate well with the Investigator and research staff and to comply with the requirements of the entire study,
4. Provision of written informed consent to participate as shown by a signature on the volunteer consent form,
5. Normal arterial BP and heart rate (HR), normal physical examination, normal 12-lead electrocardiogram (ECG) recording and normal laboratory tests or, if abnormal, considered as not clinically significant by the principal Investigator,
6. Registered with the French Social Security in agreement with the French law on biomedical experimentation [1,4,5],
7. Body weight of at least 50 kg and a BMI calculated as weight in kg/(height in m2) from 18 to 30 kg/m2 at screening.

Exclusion Criteria:

All the subjects included in the study did not have to meet the following non-inclusion criteria.

Non included subjects were subjects:

1. Who on direct questioning and physical examination had evidence of any clinically significant acute or chronic disease,
2. Who were within the exclusion period defined in the National Register for Healthy Volunteers of the French Ministry of Health,
3. Who forfeited their freedom by administrative or legal award or who were under guardianship,
4. Unwilling to give their informed consent,
5. Who had a positive laboratory test for Hepatitis B surface antigen (HbsAg), or anti-human immunodeficiency virus (HIV) 1/2 or anti-Hepatitis C virus (HCV) antibodies,
6. Who had a history of allergy, allergic skin rash, asthma, intolerance, sensitivity or photosensitivity to any drug,
7. Who had history or current gastrointestinal, hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs,
8. Who had history of seizure disorder or epilepsy,
9. Who had a history of anorexia nervosa or bulimia,
10. Who had a history of alcoholism or drug abuse or were suspected alcohol or drug abusers (more than 14 units of alcohol per week, one unit = 8 g or about 10 mL of pure alcohol),
11. Who drank daily more than 8 cups of beverage containing caffeine,
12. Who had a positive laboratory test for urine drug screening (opiates, cocaine, amphetamines, cannabinoids, barbiturates and benzodiazepines),
13. Who had undergone surgery or had donated blood within 8 weeks prior to the start of the study,
14. Who had taken any prescribed or over the counter drug (including antacid drug), with the exception of paracetamol (up to 3 g per day) within 2 weeks prior to the first dose administration,
15. Who had any clinical condition or prior therapy which, in the opinion of the Investigator, made the subject unsuitable for the study,
16. Who would have received more than 4500 € as indemnities for his participation in biomedical research within the last 12 months, including the indemnities for the present study.

PK Results

Figure 2 **Mean midazolam serum concentrations *vs.* time profiles after single oral administration of 2.5 mg midazolam without (Day 1) or with (Day 13) co-administration of BF2.649 (upper: lin-lin scale; lower: lin-log scale)**

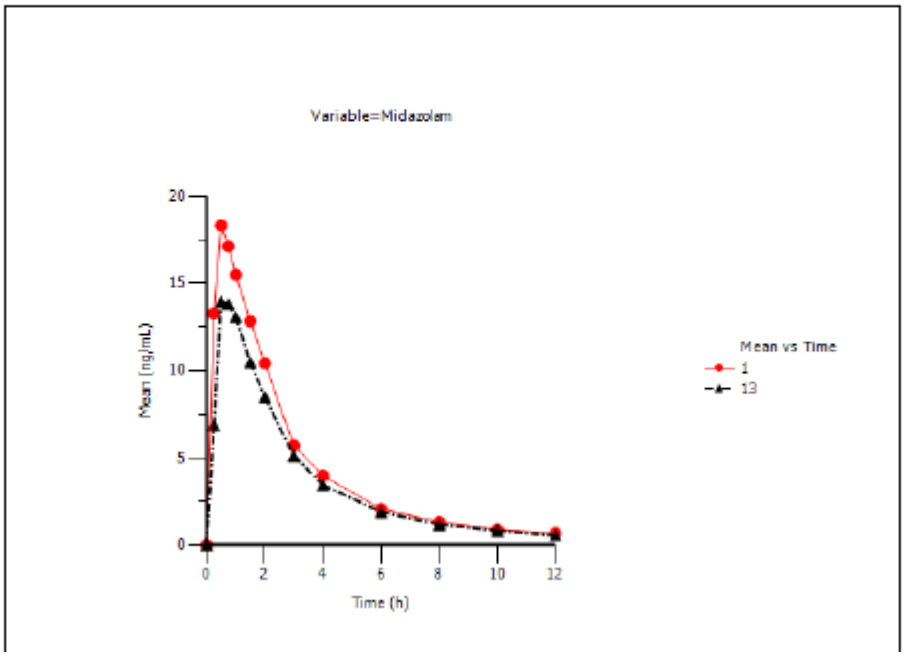


Table 9 **Summary of descriptive and formal statistics of midazolam PK parameters on Day 1 and Day 13**

Day		t_{max}* (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{0-t} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	Metabolite to drug ratio**
1	N	19	19	19	19	19	19
	Mean	0.5	19.8	3.7	53.1	56.7	0.54
	CV%	0.3-1.0	39%	65%	36%	35%	38%
	GM		18.3	3.3	49.7	53.3	0.51
13	N	19	19	19	19	19	19
	Mean	0.8	15.0	3.3	43.8	46.7	0.52
	CV%	0.5-1.0	29%	31%	30%	31%	40%
	GM		14.4	3.1	41.8	44.4	0.49
Point estimate			0.7855		0.8405	0.8330	
90% CI			(0.6837; 0.9025)		(0.7515; 0.9401)	(0.7412; 0.9362)	

* Median, Min-Max; ** $AUC_{0-\infty}$ ratio

Results:

Efficacy / PD:

Not applicable.

PK:

When co-administered with BF2.649, rate and extent ($AUC_{(0-\infty)}$), of absorption of midazolam appeared to be decreased by 21% and 17% respectively and the corresponding 90% CI was slightly out of the BE limits. However, when considering 1-hydroxymidazolam, the primary metabolite of midazolam formed by CYP3A4, no changes were observed between both conditions of administration. Therefore, the impact of BF2.649 on the biotransformation of midazolam into 1-hydroxymidazolam, *i.e.* induction of CYP3A4 activity, appeared negligible and not to be clinically relevant. Hence, BF2.649 is not a CYP3A4 inducer.

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Safety:

A total of 25 TEAEs were reported by 13 subjects, 15 were considered related to at least one of the study treatments (10 to BF2.649, 3 to bupropion, 1 to midazolam, and 1 to BF2.649 and midazolam).

No SAEs were reported. TEAEs intensity was mild (14 cases) or moderate (11 cases). Drug related TEAEs mainly consisted in sleep disorders ascribed to BF2.649.

Mean values of vital signs and ECG parameters remained within the normal ranges from screening to EOS. No significant individual abnormalities were recorded on laboratory parameters, vital signs and ECG parameters.

Overall Sponsor Conslusions

Impact of the co-administration of BF2.649 on midazolam and bupropion pharmacokinetics appeared of limited magnitude and thus, unlikely to be of clinical relevance. Hence, BF2.649 is not a CYP3A4 and a CYP2B6 inducer.

Administration of BF2.649 with midazolam and/or bupropion was considered as well tolerated.

Reviewer Comments and Conclusions

Effect of pitolisant on the PK of midazolam (CYP3A4 substrate) (P15-15): A clinical study was conducted to assess the effect of pitolisant on CYP3A4 using Midazolam as a CYP3A4 model substrate. This study showed that pitolisant (17.8 mg QD for 7 days) reduces exposures of midazolam (2.5 mg single dose) about 20%. Because the commonly used oral contraceptives are substrates of CYP3A4, an effect of pitolisant on the PK of oral contraceptives cannot be ruled out. Therefore, administration of pitolisant concomitantly with oral contraceptives may reduce the systemic exposure and the effectiveness of oral contraceptives, Thus, an alternative or additional reliable contraceptive method should be used when taking pitolisant.

CLINICAL PHARMACOLOGY STUDY REVIEW
Drug Interaction Study—Pitolisant & Itraconazole (CYP3A4 inhibitor)

Study # P11-03; part II	**Study Period:** 8/2/11----10/21/11
NDA 211150 WAKIX	
Title	A three part study to assess the potential impact of concomitant food effect (Study Part I), drug-drug interaction of itraconazole (Study Part II), and paroxetine (Study Part III) on the relative bioavailability of BF2.649 in healthy male subjects (Study Part III)
Objectives :	**Primary objective:** The primary objective of the study was to assess whether single dose BF2.649 (20 mg) oral bioavailability and main PK parameters were modified by concomitant administration of itraconazole leading to an extensive inhibition of CYP3A4. **Secondary objective:** The secondary objective of the study was to assess safety and tolerability of BF2.649 after single oral administration of 20 mg BF2.649 administered alone or after multiple dose of itraconazole in healthy male subjects.

EXECUTIVE SUMMARY:

Effect of itraconazole (CYP3A4 inhibitor) on the PK of pitolisant (P11-03; part II): This study was a cross-over, single sequence, 2-period study with pitolisant alone as well as pitolisant with itraconazole at steady-state. It was conducted in 18 healthy adults aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with itraconazole (200 mg QD for 7 days) had negligible effect on the PK of pitolisant. Therefore, no dosage adjustments are needed for WAKIX when co-administered with moderate or potent CYP3A4 inhibitors.

Study Design:

9.1 OVERALL STUDY DESIGN

The study was a cross-over, single sequence, two-period, open label, single dose (on 2 occasions) study in 18 subjects for each part.

In this study, 18 subjects received 20 mg single dose of BF2.649 on 2 occasions, one alone and one with itraconazole at therapeutic levels leading to extensive inhibition of CYP3A4.

9.2 DISCUSSION OF STUDY DESIGN

The intended dosage form to be marketed was 20 mg tablet, and the optimal therapeutic dose for BF2.649 was 20 mg/ day. In severe case of EDS, mainly in narcolepsy, the dose could be increased to a maximum dose of 40 mg/day.

Considering the mean $t_{1/2}$ of BF2.649 and BP2.951 (about 9 h, the approximate mean $t_{1/2}$, observed in applicable studies), the time between 2 administrations was set to at least 7 days (148 h *i.e.,* more than 16 times the mean $t_{1/2}$) which was considered sufficient to ensure that the previous dose was eliminated and thereby avoided any carryover effects.

Review of the PK profiles of BF2.649 over the 20-120 mg dose range indicated dose proportionality. Upon repeated administrations, the steady state was achieved after 5-6 days of administration with an accumulation leading to an increased serum level around 100%. So 40 mg in single dose led to a comparable systemic exposure than 20 mg at steady-state.

The PK blood sampling time schedule for BF2.649 was determined to allow an accurate determination of C_{max} and t_{max} as well as an appropriate assessment of the AUC extrapolated to infinity *i.e.,* an appropriate evaluation of the elimination phase, and thus an extrapolated AUC lower than 20%.

The single dose of 20 mg BF2.649 (*i.e.,* 1 tablet of 20 mg) was given on both occasions (Day 1 and Day 13). This dose was deemed to allow an appropriate evaluation of the PK parameters of both BF2.649 and its metabolite BP2.951 while preventing as much as possible any systemic overexposure resulting from the change of drug metabolism induced by itraconazole.

Itraconazole dosing schedule comprised 200 mg once daily for 7 days which was a classically well-tolerated dose used for this type of study. Considering the mean $t_{1/2}$ of itraconazole (about 30 h), once daily administration for 7 days of 200 mg of itraconazole (from Day 7 to Day 13) was deemed appropriate to reach therapeutic conditions at the time of second administration of BF2.649 (Day 13) while providing extensive CYP3A4 inhibition.

Number of subjects (planned and analysed):

Planned	:	18	Completed the trial	:	18
Screened/enrolled	:	23	In PK analysis	:	18
Included	:	19	In safety analysis	:	19

Diagnosis and main criteria for inclusion:

The study was carried out in 18 healthy male volunteers, aged 18 to 55 years old and with a body mass index (BMI) between 18 and 30 kg/m^2.

Duration of treatment:

Single dose of BF2.649 on two occasions (Day 1 and Day 13).

Itraconazole *q.d.* (morning administration) from Day 7 to Day 13.

Dosage regimen:

Single dose of 20 mg on 2 occasions for BF2.649 (Day 1 and Day 13)

Multiple dose for itraconazole (200 mg once daily for 7 days). Administration was performed in ambulatory conditions from Day 7 to Day 12

Test product(s), dose and mode of administration, batch number:

Product and Formulation:	BF2.649 / tablet 20 mg
Batch number:	1120011156
Expiry or retest date:	01/12/2011
Mode of administration:	Oral
Dosage/regimen:	Single dose of 20 mg on 2 occasions for BF2.649 (Day 1 and Day 13)

Test product(s), dose and mode of administration, batch number:

Product and Formulation:	Itraconazole / capsule 100mg
Batch number:	LC05549
Expiry or retest date:	05/2012
Mode of administration:	Oral
Dosage/regimen:	Multiple dose (200 mg once daily for 7 days)

Criteria for evaluation:

Efficacy / Pharmacodynamics:

Not applicable

PK:

On Day 1 and Day 13, blood samples for evaluation of BF2.649 (main compound) and BP2.951 concentrations were collected pre-dose and at 0.50, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00, 48.00 and 72.00 h post-dose.

Safety:

Monitoring for the occurrence of AEs. Changes in physical examination, vital signs (blood pressure and pulse rate), ECG, and clinical laboratory tests (biochemistry, hematology, and urinalysis).

Statistical methods:

Efficacy / PD:
Not applicable

PK:
All serum concentrations were summarized by treatment or by day where appropriate. The derived PK parameters were listed by subject and summarized by treatment or by day where appropriate.

The effect of itraconazole on the PK parameters of BF2.649 and BP2.951 was evaluated based on $AUC_{0-\infty}$, AUC_{0-t} and C_{max} by ANOVA using a mixed effect model applied to log transformed PK parameters with treatment as fixed effects and subject as random effect. For each parameter, a point estimate for the ratio of geometric means (BF2.649 (BP2.951) + itraconazole / BF2.649 (BP2.951) alone) were obtained by calculating the difference of least square means on the logarithmic scale and subsequent back transformation with the anti-log function. Likewise, 90% CI for the ratios were obtained and a point estimate for the ratio of geometric means BF2.649 (BP2.951) + itraconazole / BF2.649 (BP2.951) alone were obtained by least square means. The analysis of t_{max} was based on the non-parametric Wilcoxon signed rank test and was carried out.

Safety:
All safety parameters (ECG, vital signs, AEs, etc.) were summarized by day and time point (where appropriate).

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Pitolisant and its metabolites		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Study Population:

A total of 19 male subjects aged between 18 and 54 years old and with a BMI ranging from 18.5 to 29.9 kg/m^2 participated to this study as presented next.

Table 11.2.1 - 1 Summary of demographic data

		All
N		19
Age (Years)	**Mean (SD)**	31.2 (12.2)
	Min - Max	18 – 54
Height (cm)	**Mean (SD)**	178.6 (7.6)
	Min - Max	165 - 193
Weight (kg)	**Mean (SD)**	76.22 (15.21)
	Min - Max	55.0 - 111.2
BMI(kg/m²)	**Mean (SD)**	23.74 (3.43)
	Min - Max	18.5 - 29.9

Inclusion Crietria:

All subjects included in the study had to meet all of the following criteria for inclusion in the study:

- Male healthy volunteers 18 to 55 years of age,
- Light smokers (less than 5 cigarettes per day) or subjects who were non-smokers. No smoking (or use of smoking substitute *e.g.,* nicotine patch) was permitted from screening throughout the study,
- Male subjects with a body weight of at least 50 kg and a body mass index (BMI) calculated as weight in kg/height (in m^2) from 18 to 30 kg/m^2 at screening,
- Able to communicate well with the Investigator and research staff and to comply with the requirements of the entire study,
- Provision of written informed consent to participate as shown by a signature on the volunteer's consent form,
- Normal arterial blood pressure (BP) and pulse rate or, if abnormal, considered not clinically significant by the principal Investigator. These were measured after resting for 5 minutes (min),*
- Registered with the French Social Security in agreement with the French law on biomedical experimentation. [10, 11]

*Normal BP was taken to be [100–150] mmHg systolic and [45–90] mmHg diastolic. Normal pulse rate was taken to be [40–100] bpm.

Exclusion Criteria:

- Had any clinically significant abnormality following review of pre-study laboratory tests (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and alkaline phosphatase (ALP) had to be within normal ranges), vital signs, full physical examination and ECG,
- Were within the exclusion period defined in the National Register for Healthy Volunteers of the French Ministry of Health,
- Forfeited their freedom by administrative or legal award or who were under guardianship,
- Unwilling to give their informed consent,
- Presented a positive laboratory test for Hepatitis B surface antigen (HbsAg), or anti-HIV 1/2 or anti- HCV antibodies
- Had a history of allergy, intolerance or photosensitivity to any drug,
- Had a history of serious allergy, asthma, allergic skin rash or sensitivity to any drug,
- Were known or suspected alcohol or drug abusers (more than 14 units of alcohol per week, one unit = 8 g or about 10 mL of pure alcohol),
- Drank more than 8 cups daily of beverage containing caffeine,
- Presented a positive laboratory test for urine drug screening (opiates, cocaine, amphetamine, cannabis, benzodiazepines),
- Had undergone surgery or had donated blood within 12 weeks prior to the start of the study,
- Had taken any prescribed or over the counter drug (including antacid drug), with the exception of paracetamol (up to 3 g per day) within 2 weeks prior to the first dose administration,
- Presented any clinical condition or prior therapy which, in the opinion of the Investigator, made the subject unsuitable for the study,
- Participated to any clinical trial with an investigational drug in the past 3 months preceding study entry.

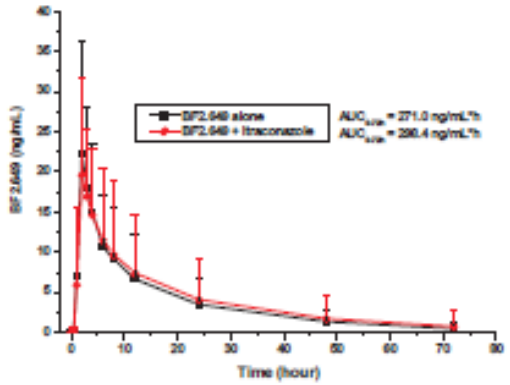
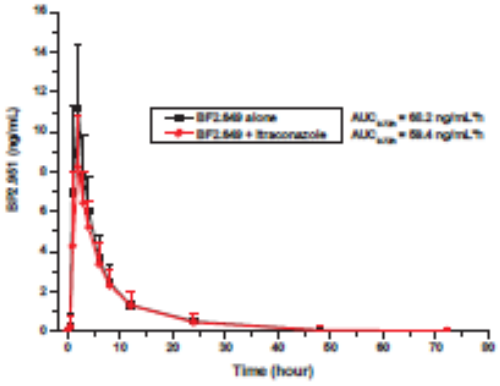
PK Results

A summary of the BF2.649 (parent drug) and BP2.951 (major metabolite) pharmacokinetic results obtained is provided below:

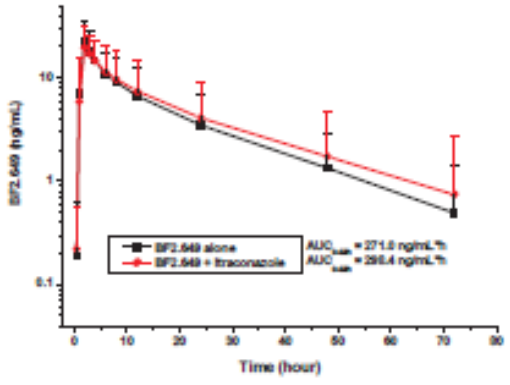
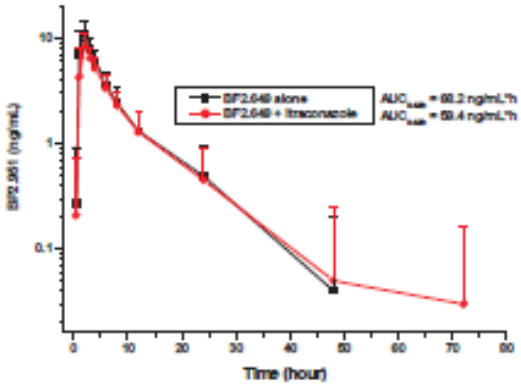
PK parameters	BF2.649		BP2.951	
Day	BF2.649 alone	BF2.649 + intraconazole	BF2.649 alone	BF2.649 + intraconazole
C_{max} (ng/mL) Mean ± SD CV%	23.20 ± 13.41 57.8	21.79 ± 11.83 54.3	11.65 ± 3.52 30.2	8.51 ± 2.46 29.0
T_{max} (h) Mean ± SD CV%	2.2 ± 0.6 29.1	2.2 ± 0.7 32.9	1.9 ± 0.2 12.1	1.9 ± 0.5 27.7
$AUC_{0-\tau}$ (ng/mL.h) Mean ± SD CV%	271 ± 221 81.4	298 ± 321 107.7	68 ± 24 35.8	59 ± 21 35.9
$AUC_{0-\infty}$ (ng/mL.h) Mean ± SD CV%	289 ± 247 85.5	329 ± 400 121.5	68 ± 25 37.1	61 ± 25 41.0
λ_z (1/h) Mean ± SD CV%	0.048 ± 0.013 27.4	0.049 ± 0.014 28.3		
$T_{1/2}$ (h) Mean ± SD CV%	15.7 ± 5.2 33.3	15.5 ± 5.0 32.0		
Clss/F (mL/h) Mean ± SD CV%	2482111 ± 2125773 85.6	2208611 ± 1486627 67.3		
Vdss/F (mL) Mean ± SD CV%	121050 ± 109883 90.8	118950 ± 110079 92.5		

Mean (± standard deviation) BF2.649 or BP2.951 concentrations measured in 18 healthy male volunteers after a single oral administration of BF2.649 dosed at 20 mg alone or with itraconazole

Linear coordinates

BF2.649	BP2.951
	

Semi-logarithmic coordinates

BF2.649	BP2.951
	

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Safety:

Subject No. [redacted], a 20 year-old man without specific medical history, suffered an accidental incision of the right finger on [redacted] corresponding to Day 6 of the study (i.e., on the day just before the first itraconazole administration). He received the planned treatment on Day 7 and Day 8. In the morning of Day 9, a strong inflammation with secondary inflammation was observed around the wounded area without other clinical signs. The subject was withdrawn from the study and consulted the surgical emergency department of [redacted] Diagnosis: septic wound with tenosynovitis, incision of the tendon and septic arthritis. The subject received appropriate treatment consisting in wound cleaning, tendon suture and antibiotic therapy. He was hospitalized from [redacted] No complications were reported post-surgery and the suture was removed on [redacted] The SAE of severe intensity resolved without sequelae on [redacted]. This SAE was completely independent from study conditions, including study drugs.

A total of 5 TEAEs were reported by 4 subjects, none of them was serious. Among these 5 TEAEs, 2 were related to either itraconazole alone or BF2.649 and itraconazole. The intensity of treatment drugs related TEAEs was mild. No subject was discontinued from the study due to AEs.

Neither trends nor relevant changes from baseline were observed in vital signs, ECG parameters, physical examination, and in any laboratory parameters assessed.

Overall Sponsor Conslusions

Safety and tolerability of pitolisant was good with Itraconazole and there was no drug interaction.

Reviewer Comments and Conclusions

Effect of itraconazole (CYP3A4 inhibitor) on the PK of pitolisant (P11-03; part II): This study was a cross-over, single sequence, 2-period study with pitolisant alone as well as pitolisant with itraconazole at steady-state. It was conducted in 18 healthy adults aged 18 to 55 years. Concomitant administration of pitolisant 17.8 mg with itraconazole (200 mg QD for 7 days) had negligible effect on the PK of pitolisant. Therefore, no dosage adjustments are needed for WAKIX when co-administered with moderate or potent CYP3A4 inhibitors.

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/s/

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