Full central neurokinin-1 receptor blockade is required for efficacy in depression: evidence from orvepitant clinical studies

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Abstract

Full, persistent blockade of central neurokinin-1 (NK1) receptors may be a potential antidepressant mechanism. The selective NK1 antagonist orvepitant (GW823296) was used to test this hypothesis. A preliminary positron emission tomography study in eight male volunteers drove dose selection for two randomized six week studies in patients with major depressive disorder (MDD). Displacement of central [^{11}C]GR205171 binding indicated that oral orvepitant doses of 30–60 mg/day provided >99% receptor occupancy for ≥24 h. Studies 733 and 833 randomized patients with MDD and 17-item Hamilton Depression Rating Scale (HAM-D)≥22 to double-blind treatment with orvepitant 30 mg/day, orvepitant 60 mg/day or placebo (1:1:1). Primary outcome measure was change from baseline in 17-item HAM-D total score at Week 6 analyzed using mixed models repeated measures. Study 733 (n=328) demonstrated efficacy on the primary endpoint (estimated drug-placebo differences of 30 mg: −2.41, 95% confidence interval (CI) (−4.50 to −0.31) p=0.0245; 60 mg: −2.86, 95% CI (−4.97 to −0.75) p=0.0082). Study 833 (n=345) did not show significance (estimated drug-placebo differences of 30 mg: −1.67, 95% CI (−3.73 to 0.39) p=0.1122; 60 mg: −0.76, 95% CI (−2.85 to 1.32) p=0.4713). The results support the hypothesis that full, long lasting blockade of central NK1 receptors may be an efficacious mechanism for the treatment of MDD.

Keywords

Depression, receptor occupancy, neurokinin, substance P, clinical trials

Introduction

All currently approved pharmacologic treatments for major depressive disorder (MDD) are based on monoaminergic mechanisms, despite decades of exploration of alternative neurobiological pathways (Li et al., 2012). The large number of patients who neither respond to nor tolerate current therapies has led to exploration of novel mechanisms in the belief that these will lead to improvements in onset of action, spectrum of efficacy and/or tolerability (Rush et al., 2006). One such mechanism, antagonism of neurokinin-1 (NK1) receptors has shown efficacy in clinical trials conducted with as many as four different high-affinity, selective NK1 antagonists. In an initial study, aprepitant (MK-869) 300 mg/day (estimated to provide ≥95% NK1 central receptor occupancy (RO) in the human brain) achieved clinically meaningful separation from placebo (Hargreaves, 2002; Kramer et al., 1998). This was followed by trials with two other NK1 antagonists; L-759274 (Kramer et al., 2004) and an unpublished study with CP-122,721 (Chappell, 2002) with both trials reporting positive efficacy findings. However, five further studies with aprepitant, using a revised nano-milled formulation, with doses up to 160 mg/day (estimated to provide ~92% RO) failed to demonstrate efficacy, including two studies in which the positive control, paroxetine, separated from placebo (Keller et al., 2006). As a result of this failure, enthusiasm dissipated for further development of the NK1 antagonist mechanism as a novel antidepressant approach.

However, we propose that full and long lasting saturation of the central NK1 receptor compartment may be a critical requirement for the antidepressant effects of NK1 antagonists to be realized. To test this hypothesis, a novel series of highly potent,

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selective and non-surmountable NK1 receptor antagonists were developed. positron emission tomography (PET) studies with the first of these molecules, casopitant (GW679769), demonstrated it to be highly brain penetrant and to achieve full (>99%) RO at steady-state at doses higher than 30 mg/day (DiFabio et al., 2011; Zamuner et al., 2012). In fact a statistically and clinically significant antidepressant effect on the primary endpoint (17-item HAM-D) was observed in a Phase II study with casopitant at a dose of 80 mg/day (Ratti et al., 2011). In addition, animal studies have supported this concept: in the two Gerbil active locomotory anxiety model, three NK1 antagonists (GR205171, aprepitant and vestipitant) only produced anxiolytic-like activity at doses producing greater than 96% receptor occupancy (Carletti et al., 2005). To further confirm this hypothesis, the second of these novel NK1 antagonists, orvepitant (GW823296) was studied in two six week, placebo-controlled Phase II trials described in this report, the only studies conducted to date with this molecule in MDD. The orvepitant doses were chosen on the basis of a PET study, also described here, to provide full (>99%) and persistent (≥24hr) NK1 RO following once-daily dosing. The objectives of these studies were to evaluate the antidepressant efficacy, safety, and tolerability of orvepitant, and to characterize its pharmacokinetic-pharmacodynamic relationship in depressed subjects. The design of these two multicenter North American studies was identical with respect to number of arms, patient numbers and dose, but differed significantly in the methods used to assess patient eligibility and longitudinal change.

Methods and materials

PET imaging study

Design. The PET imaging study (GSK protocol NKG10002) was a single center, open label, non-randomized, two-session trial in which all subjects underwent two PET scans immediately following the administration of the NK1 selective radioligand [^{11}C] GR205171. One PET scan was conducted under baseline conditions, while the second took place 24 h following a single oral dose of orvepitant. Orvepitant doses ranged from 0.25–60 mg and were selected in an adaptive design, in which occupancy data from preceding subjects was assessed and used to determine the dose for subsequent subjects in an effort to characterize the full plasma concentration – NK1 RO curve.

Patients

Eight healthy male volunteers, 35–65 years of age with body mass index (BMI) within the range 19–30.5 kg/m^2, and weight within the range 55–95 kg were enrolled. All subjects satisfied eligibility criteria and passed a medical screen for fitness to participate in the study.

Assessments

[^{11}C]GR205171 was synthesized as previously described (Bergrsöm et al., 2000) with radiochemical purity >95% and was injected as an intravenous (iv) bolus over 30 s. All PET scans were carried out at the Cyclotron Unit, Hammersmith Imanet Ltd, London, UK, on a Siemens/CTI PET scanner ECAT EXACT3D (Spinks et al., 2000) with an axial field of view of 23.4 cm and 95 reconstructed transaxial image planes. A 5 min transmission scan using a ^{137}Cs point source was performed before each study for subsequent attenuation and scatter corrections. Data were collected in 3D mode over 90 min following iv bolus injection of [^{11}C]GR205171. Arterial blood was sampled continuously from an indwelling radial cannula for the first 15 min of each scan. Discrete arterial blood samples were collected throughout each scan for cross-calibration, assay of total blood and plasma radioactivity and for assay of the plasma parent fraction as previously described (Luthra et al., 1993).

Statistical analysis

Regions of interest outlined on the magnetic resonance (MR) images were co-registered to the PET summated images (integral images from 0–90 min) and applied to the dynamic PET scans. Binding of [^{11}C]GR205171 was evaluated in cortical regions (medial temporal cortex, lateral temporal cortex, frontal cortex, parietal cortex, occipital cortex). Cerebellum was used as the reference region to define levels of free and non-specifically bound [^{11}C]GR205171.

Consensus nomenclature of PET data was used throughout (Innis et al., 2006). Total radioactivity was quantified in arterial blood and plasma samples collected during PET scans, as well as percentage of the total plasma radioactivity attributable to intact [^{11}C]GR205171. These data were used to construct a metabolite corrected arterial plasma input function (AIF) for each PET scan. The AIF was used in conjunction with the regional PET emission data in a two-tissue compartment kinetic model to derive the total volumes of distribution (V_T) for each region. The cerebellum was used as a reference region and the cerebellar V_T was assumed to represent the non-displaceable volume of distribution (V_{ND}). Regional measures of specific binding (binding potential with reference to non-displaceable binding (BP_{ND}) were estimated from regional V_T and the V_{ND} utilizing

$$BP_{ND} = \frac{V_T}{V_{ND}} - 1$$

NK1 RO was estimated from the BP_{ND} in the baseline and post-dose scan for each subject at baseline and post-dose using:

$$Occupancy = \frac{BP_{ND}^{baseline} - BP_{ND}^{post-dose}}{BP_{ND}^{baseline}}$$

Mean cortical occupancy for each subject was used to estimate the relationship between administered dose of orvepitant and NK1 RO in this study. The orvepitant dose leading to 50% occupancy of the NK1 receptor (ED_{50}) was estimated by fitting the data to:

$$Occupancy = \frac{Dose}{Dose + ED_{50}}$$

However, to describe the plasma concentration and RO relationship, a direct link model between the plasma concentration of orvepitant measured 24 hours post-dose (C24h) and BP_{ND} was used:

$$BP_{ND} = BP_{ND}^{baseline} \bullet \left(1 - \frac{C_{24h}}{IC_{50} + C_{24h}}\right)$$

where IC_{50} is the plasma concentration leading to 50% reduction of baseline binding potential. This pharmacokinetic-pharmacodynamic (PK-PD) model was developed using the nonlinear mixed effect modeling approach as implemented in the NONMEM (version VI) software as previously described (Zamuner et al., 2012).

Efficacy studies

Design

The two efficacy studies (Study 733 (GSK protocol NKG111733-NCT00880399) and Study 833 (GSK protocol NKG110833-NCT00880048)) were six-week double-blind, placebo-controlled, parallel-group, fixed-dose, multi-center trials which randomized patients in a 1:1:1 ratio to orvepitant 30 mg/day, 60 mg/day or placebo. Clinical supplies consisted of placebo, orvepitant 30 mg and orvepitant 60 mg tablets that were identical in appearance and packaged in identical bottles with Medication Event Monitoring Systems caps (MEMS, Aardex Ltd, Zug, Switzerland) to compile dosing histories. Subjects were assigned to double blind study treatment via a 1:1:1 randomization schedule generated per site in medication blocks using an automated randomization allocation system. Dose selection was guided by brain RO data calculated from the PET study and doses were chosen to produce complete (>99%) RO in all brain areas in the majority of the population for the full duration of the trial. Patients were required to stop the use of psychotropic medications three weeks before planned randomization (five weeks for fluoxetine) and for the entire duration of the study with the exception of zolpidem, zaleplon and zopiclone which were permitted during the first two weeks of the study but no more than three times per week, and were not permitted the night before an assessment visit. Randomized patients were instructed to take study medication once daily at bedtime. Study 733 was conducted from March 2009–June 2010 at study centers in USA (n=17) and Canada (n=3). Study 833 was conducted from March 2009–June 2010 at study centers in USA (n=27) and Canada (n=4).

Patients

Both studies enrolled male and female outpatients between the ages of 18–64 years inclusive with a primary diagnosis of major depressive episode (MDE) associated with MDD, single episode or recurrent, according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (296.2 or 296.3), diagnosed through a comprehensive psychiatric evaluation in conjunction with the Structured Clinical Interview for DSM-IV Axis Disorders Overview (First et al., 2002), with a duration of the current MDE ≥4 weeks (Study 833) or ≥8 weeks (Study 733) prior to screening. The studies also required a baseline HAM-D 17-item total score of ≥22 (Study 833) or ≥24 (Study 733) using the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D; Williams, 1988). Women of childbearing potential were eligible if they committed to, and could document consistent and correct use of an acceptable method of contraception. Subjects whose mood-related symptoms were better accounted for by a diagnosis other than depression; subjects diagnosed with Alzheimer's Disease or other form of dementia; subjects diagnosed with a current/recent eating disorder such as anorexia nervosa or bulimia; and subjects with a diagnosed history of schizophrenia, schizoaffective disorder, or bipolar disorder were excluded. Secondary diagnoses (with MDD primary) of anxiety disorders were permitted, including generalized anxiety disorder, posttraumatic stress disorder, social anxiety and acute stress disorders. Ineligible patients also included those who were currently receiving or had received, during the 12 weeks prior to screening, regularly scheduled psychotherapy, or if they had previously failed to respond to adequate courses (e.g. maximum-labelled doses for ≥4 weeks) of pharmacotherapy from two different classes of antidepressants. Patients who, in the investigator's judgement, posed a homicidal or serious suicidal risk, or had made a suicide attempt within the six months preceding screening, or who had ever been homicidal, were excluded from the study as were those with clinically significant electrocardiogram or laboratory abnormalities, or any history of seizure, positive urine drug screen for illegal drug use, or history of substance use or dependence within the past six months. All subjects were required to have contact with another adult on a daily basis. For all three studies, approval was obtained from national, regional, or investigational center ethics committees or institutional review boards and written informed consent was obtained from each subject prior to the performance of study-specific procedures.

Assessments

For the efficacy studies, a screening session was carried out 7–21 days before the randomization visit. Post-randomization, patients were required to visit the clinic at the end of weeks 1, 2, 4 and 6 and to return for follow-up visits 14 and 28 days after last dose. Efficacy and safety assessments conducted at each visit included the HAM-D (17-item using the SIGH-D, Williams, 1988), Clinical Global Impressions - Severity of Illness (CGI-S) and Improvement (CGI-I, Guy, 1976) (Guy, 1976), the Clinical Global Impression of Improvement (CGI-I, 18), the Quick Inventory of Depressive Symptomatology (self-reported, QIDS-SR, Rush et al., 2003), the Cognitive and Physical Function Questionnaire (CPFQ, Fava et al., 2009), the Morning Sleep Questionnaire (Roehrs et al., 1984, captured by Clinphone Plc, Nottingham, UK), the Columbia Suicidality Severity Rating Scale (CSSRS, Posner et al., 2011), and the Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ, Fava et al., 1998; Labbate and Lare, 2001). The Discontinuation-Emergent Signs and Symptoms (DESS, Fava, 2006) scale was administered at the end of double-blind treatment and the 14 day follow-up visit.

The efficacy studies differed in the methods of assessing MDD severity. In Study 733 the initial MDD diagnosis was made by the principal investigator at the site while all HAM-D ratings were performed by an independent rater at the site who had no access to all other study assessments. The initial diagnosis and at least one post-baseline HAM-D rating were confirmed via a structured interview (SAFER criteria, Targum et al., 2008) administered by expert clinicians who served as remote raters (MGH Clinical Trials Network and Institute, Boston, Massachusetts, USA) linked in via teleconference. This same rater also confirmed the HAM-D minimum severity criteria utilizing the SIGH-D. In Study 833, the psychiatric diagnosis and the screening, baseline and on-treatment

HAM-D and CGI-S ratings were conducted remotely by an independent centralized rater via live subject interview using a Polycom Videoconferencing unit linked via Virtual Private Network (Medavante, Trenton, New Jersey, USA).

All other efficacy evaluations were administered or facilitated by the investigator (or designee) who had access to the subject's study records: CGI-S at randomization and CGI-S and CGI-I at weeks 1, 2, 4 and 6 (study 733 only); CPFQ and QIDS-SR (randomization and weeks 1, 2, 4 and 6). Safety was evaluated during scheduled clinic visits by monitoring of adverse events (AE), physical examinations and clinical laboratory assessments. AEs were captured by direct questioning and rated with respect to seriousness, severity, duration and drug-relationship by a blinded study physician, on the basis of the patient's reports. An unblinded Independent Data Monitoring Committee (IDMC) was established to examine the accruing safety data to look for any emerging patterns/safety signals with respect to the central nervous system. The IDMC had the authority to take appropriate measures to assure the safety of study subjects.

Blood for pharmacokinetic analysis of orvepitant was obtained using a sparse sampling approach at weeks 1, 2, 4, and 6 at the end of each clinic visit, following completion of the efficacy assessments.

Statistical analysis

The primary population of interest for efficacy analyses was the intent to treat (ITT) population. The ITT population consisted of all subjects who gave informed consent, were randomized, received at least one dose of study medication and for whom at least one post-baseline assessment was available. Safety analyses were performed using the all subjects population which consisted of all subjects who received at least one dose of study medication. The pre-specified protocol-defined primary efficacy variable was the change from baseline in the 17-item HAM-D total score at the week 6 endpoint using mixed models repeated measures (MMRM) analysis. The model included terms for treatment, week, baseline, center (grouped), treatment by week interaction and baseline by week interaction. Analysis of the last observation carried forward (LOCF) HAM-D total score was used to provide supportive evidence.

The enrolment goal of 110 evaluable patients in each treatment arm provided a power of 90% to detect a 3.5 point difference in HAM-D at week 6 between treatment and placebo, assuming a 5% significance level and a standard deviation (SD) of 8. The results of the analyses were presented as point estimate, 95% confidence interval and associated *p*-value for the adjusted mean difference between treatments at every visit. All hypothesis tests of comparison of active treatments with placebo were two-sided at the 5% level of significance. Proportion of responders and remitters was analyzed using logistic regression, adjusting for baseline endpoint score (where appropriate). Because no corrections or adjustments were made for multiple comparisons, the uncorrected *p*-values provided for secondary outcomes should be interpreted with caution.

Results

PET imaging and pharmacokinetic results

All eight subjects studied completed both PET scans and provided technically adequate imaging data. ROs are summarized in Table 1. Administration of a single 60 mg oral dose of orvepitant produced RO of approximately 100% when assessed 24 h post-administration. The pharmacokinetic data for all subjects was consistent with that obtained from phase I studies (Supplementary Material, Tables E1 and E2). For subjects at lower doses (0.25–1 mg), plasma concentrations were below the limits of quantification at time points beyond 4–8 h. The population pharmacokinetics-receptor occupancy model estimated an IC_{50} of approximately 0.07 ng/mL (mean IC_{50} equal to 0.07 ng/mL in parietal cortex and occipital, 0.06 ng/mL in frontal cortex, 0.08 ng/mL in lateral temporal cortex). The PD-RO model indicated that NK1 RO of >99% would be achieved at orvepitant plasma concentrations >7 ng/mL. Mean orvepitant steady-state plasma concentrations in the 733 and 833 studies ITT populations ranged from 112–117 ng/mL and 90–111 ng/mL, respectively, in the 30 mg cohorts, and from 362–389 and 353–460 ng/mL, respectively, in the 60 mg cohorts. Dose-dependent accumulation was observed after repeat dosing at 30 and 60 mg/d with plasma concentrations averaging 3.5 to 4-fold and 4 to 4.5-fold higher respectively than after single dose administration (Supplementary Material, Tables E3 and E4). Steady state was achieved on average after 14 days.

Efficacy results

Patient disposition is summarized in Table 2. Studies 733 and 833 enrolled 328 and 345 patients, respectively, with 328 and 343 entering the all subjects population. There were 320 and 339

Table 1. Receptor occupancy data from imaging study.

Subject	Dose (mg)	Medial temporal	Lateral temporal	Frontal	Parietal	Occipital
6	0.25	52%	68%	75%	45%	62%
7	0.5	25%	57%	49%	44%	42%
8	0.5	51%	41%	69%	37%	68%
3	1	56%	73%	78%	76%	75%
4	1	60%	61%	63%	70%	40%
1	10	93%	92%	96%	94%	94%
2	10	68%	87%	85%	NE[a]	89%
5	60	102%	100%	102%	102%	100%

[a]NE: not estimated due to noise.

Table 2. Summary of patient disposition and demographics.

	Study 733			Study 833		
	Placebo	Orvepitant 30 mg	Orvepitant 60 mg	Placebo	Orvepitant 30 mg	Orvepitant 60 mg
Randomized, *n*	108	113	107	116	116	113
All subjects population, *n* (%)	108 (100)	113 (100)	107 (100)	116 (100)	115 (100)	112 (100)
ITT population, *n* (%)	103 (95)	110 (97)	107 (100)	116 (100)	112 (97)	111 (99)
Completed, *n* (%)	77 (71)	84 (74)	81 (76)	88 (76)	82 (71)	77 (69)
Withdrawals, *n* (%)	31 (29)	29 (26)	26 (24)	28 (24)	33 (29)	35 (31)
Study terminated	3 (3)	7 (6)	4 (4)	9 (8)	7 (6)	6 (5)
Lost to follow-up	8 (7)	5 (4)	3 (3)	6 (5)	6 (5)	5 (4)
Consent withdrawn	6 (6)	3 (3)	3 (3)	5 (4)	8 (7)	5 (4)
Adverse event	4 (4)	6 (5)	5 (5)	2 (2)	3 (3)	5 (4)
Protocol violation	4 (4)	4 (4)	6 (6)	4 (3)	6 (5)	5 (4)
Lack of efficacy	1 (<1)	4 (4)	2 (2)	1 (<1)	2 (2)	2 (2)
Other	5 (5)	0	3 (3)	1 (<1)	1 (<1)	7 (6)
Age-years, mean (SD)	40 (11.7)	41 (11.4)	38 (11.2)	42 (10.6)	40 (11.4)	43 (10.7)
% female	70	60	65	59	65	65
% male	30	40	35	41	35	35
Baseline HAM-D, mean (SD)	26.7 (2.02)	27.3 (2.60)	27.2 (2.84)	26.0 (2.75)	25.6 (2.30)	26.0 (2.42)

ITT: intent to treat; SD: standard deviation; HAM-D: Hamilton Depression Rating Scale (17-item).
Percentages are based on all subjects population.

patients comprising the ITT population for each study. Completion rates were 74% and 72%, respectively, with similar rates for all study arms. Both studies were terminated by the sponsor due to safety reasons (see safety section), but this occurred just prior to completion of all subjects in each case, thereby accounting for only 4% and 6% of subjects' withdrawals in studies 733 and 833, respectively. Therefore, the original analysis plan was adhered to, given that termination of the studies occurred so close to their originally planned completion and because the study blind was maintained in each case. Reasons for early discontinuation were similarly distributed for all treatment groups. The ratio of female to male patients was approximately 2:1. Patient sex, age, race and BMI were similar across all study groups in both studies (Table 2 and Supplementary Material, Tables E5 and E6). Mean baseline HAM-D scores were in the 25–28 range with QIDS-SR scores in the 16–19 range. Mean number of tablets taken was similar across all treatment groups in both studies and ranged from 34–37, with SD 10–13 and range 1–50, and was similar across all treatment groups.

Study 733: The primary endpoint, MMRM analysis in the ITT population showed statistically significant improvement vs placebo in HAM-D from weeks 2–6 in both the 30 mg and 60 mg orvepitant groups (Figure 1(A)). The adjusted mean (SE) change from baseline at week 6 (endpoint) for placebo, orvepitant 30 mg and orvepitant 60 mg were, respectively: −9.08 (0.777), –11.49 (0.735) and –11.93 (0.749) resulting in estimated drug-placebo differences of 30 mg: –2.41 95% CI (–4.50 to −0.31) p=0.0245 and 60 mg: –2.86, 95% CI (–4.97 to –0.75) p=0.0082.

Study 833: MMRM (primary) analysis in the ITT population showed a statistically significant improvement vs placebo in HAM-D from weeks 1–2 in the 30 mg orvepitant group and weeks 1–4, but not at week 6 in the 60 mg orvepitant group (Figure 1(B)). Adjusted mean (SE) of the change from baseline at week 6 for placebo, orvepitant 30 mg and orvepitant 60 mg were, respectively: –8.29 (0.727), –9.95 (0.754) and –9.05 (0.777) resulting in estimated drug-placebo differences of 30 mg: −1.67, 95% CI (–3.73 to 0.39) p=0.1122 and 60 mg: –0.76 to 95% CI (–2.85 to 1.32) p=0.4713. ITT analysis using LOCF and analysis of covariance yielded similar results to MMRM analysis for both studies (Supplementary Material, Tables E7 and E8).

Secondary efficacy measures are summarized in Table 3 and Supplementary Material, Tables E9–E38. In study 733 the proportion of HAM-D responders (≥50% decrease from baseline) was significantly higher for orvepitant 60 mg vs placebo at week 4 (19% vs 33%, p=0.0257) and approached significance (29% vs 42%, p=0.0874) for the 30 mg group at week 6. There were no significant differences vs placebo on this measure for either orvepitant group in study 833 at any assessment. In study 733, the proportion of HAM-D remitters (total score ≤7) did not differ significantly between treatment groups at any time point. In study 833 the proportion of remitters was significantly higher for orvepitant 60 mg vs placebo (16% vs 6%, p=0.0455) at week 4 but not week 6, whereas the proportion of remitters approached significance at week 6 for orvepitant 30 mg vs placebo (23% vs 11%, p=0.0507). The proportion of CGI-I responders (much or very much improved) was significantly higher for orvepitant vs placebo at week 2 in both studies 733 and 833 for the 30 mg dose (22% vs 10%, p=0.0247; 25% vs 10%, p=0.0067) but not at any other time points or dose levels.

On the Bech Subscale statistically significant improvement was observed for both orvepitant groups vs placebo in study 733 at weeks 2, 4 and 6 and in study 833 at week 1 only (Table 3 and Supplementary Material, Tables E15 and E16). Statistically greater improvement relative to placebo on the HAM-D Anxiety/Somatization Factor subscale was observed only at week 6 (orvepitant 60 mg) in study 733 and at weeks 1 and 4 (orvepitant 60 mg) in study 833. A post-hoc analysis of HAM-D item 1

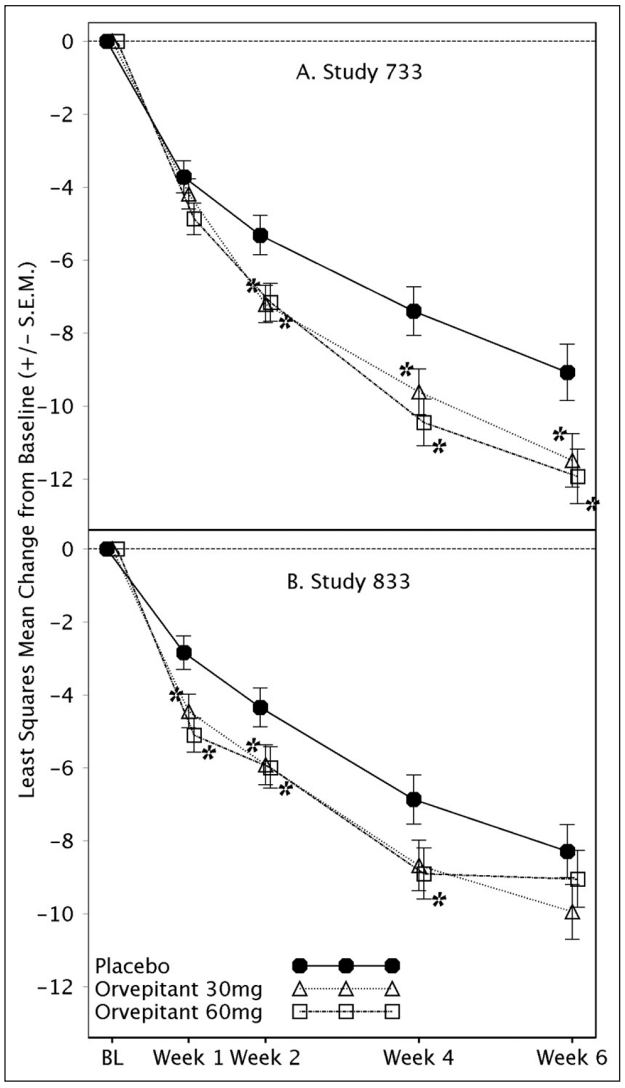

Figure 1. Mixed models repeated measures (MMRM) adjusted mean change from baseline (±standard error of the mean (SEM)) in HAM-D score at each visit by treatment. (A) Study 733, (B) study 833.
*$p<0.05$ vs placebo, BL: baseline.

(depressed mood) showed statistically significant improvement vs placebo for both orvepitant doses at weeks 2, 4 and 6 in study 733, and at week 1 (orvepitant 30 mg) and weeks 1 and 2 (orvepitant 60 mg) in study 833. Similarly, improvements in global illness severity (CGI-S) were significantly greater for both orvepitant doses vs placebo at weeks 2, 4 and 6 in study 733, and at week 6 (orvepitant 30 mg) and week 1 (orvepitant 60 mg) in study 833. On the QIDS-SR statistically significant reductions were observed compared to placebo for orvepitant 30 mg (week 4) and 60 mg (weeks 4 and 6) in study 733, and for orvepitant 30 mg (weeks 2, 4 and 6) and 60 mg (weeks 1, 2 and 4) in study 833. Statistically greater improvement relative to placebo on CPFQ was observed only at week 6 (both orvepitant groups) in study 733 and at week 1 (orvepitant 30 mg) and 2 (orvepitant 60 mg) but not in the later assessments in study 833. Significant drug-placebo differences were observed at multiple time points for the following MSQ domains: Sleep Onset Latency - Study 733 orvepitant 60 mg at weeks 1 and 2, Study 833 both orvepitant 30 and 60 mg at weeks 1 and 6; Total Sleep Time - Study 833 orvepitant 60 mg at weeks 1 and 4; Refreshing Sleep - Study 733 orvepitant 60 mg at weeks 1, 2, 4 and 6, Study 833 orvepitant 60 mg weeks 1, 2 and 6; and Sleep Quality - Study 733 orvepitant 30 mg at weeks 2 and 6, orvepitant 60 mg weeks 1, 2, 4 and 6, Study 833 orvepitant 30 mg weeks 1 and 4 (Table 3 and Supplementary Material, Tables E27–E38).

Safety

Two AEs were reported during the PET imaging study (dry cough, headache − each in one patient). AEs that occurred in at least 5% of patients in any group in either study 733 or 833 are summarized in Table 4, regardless of investigator assessment of causality. AEs that appeared to be consistently increased following orvepitant administration included somnolence (7–10%), fatigue (0–8%), dizziness (2–8%), paresthesia (2–5%) and insomnia (5–8% in the orvepitant 60 mg group). Rates of withdrawal from study for AEs were similar for orvepitant groups (3–5%) and placebo (2–4%) and no AE leading to withdrawal occurred in more than 2% of subjects in any treatment group with the exception of somnolence (Study 733: 3% of orvepitant 30 mg vs 0% for placebo and orvepitant 60 mg). There were no suicide attempts in either study. In study 733, there was one incident of suicidal behavior in which a subject reported taking nine investigational tablets at once (random code was not broken but after study completion was revealed to be orvepitant 30 mg) 33 days after randomization. The investigator considered the event to be unrelated to the investigational product. The subject reported an onset of headache 3 h after the overdose, with resolution 12 h later. In study 733 one patient each in the placebo and orvepitant 30 mg groups, and in study 833 one patient in the orvepitant 30 mg group, were withdrawn from the study due to suicidal ideation. Overall, the incidence of CSSRS events was similar across all treatment groups in both studies (Supplementary Material, Tables E39 and E40).

In study 833, a patient randomized to placebo died following a motor vehicle accident. This patient's psychiatric history included MDD and six years previously the patients was hospitalized following an attempted overdose. The patient's HAM-D score five days prior to death was 15, with a Columbia Suicide assessment 12 days prior to death that was negative for any intent or plan to die, although positive for wish to die.

Non-fatal serious adverse events (SAEs) occurred in two patients in Study 733: one pelvic fracture (placebo) and one report of lower abdominal pain (orvepitant 60 mg) both of which occurred after stopping study drug and neither of which was considered by the investigator to be drug-related. Non-fatal SAEs occurred in four patients in Study 833: one myocardial infarction (leading to withdrawal from the 30 mg orvepitant group but considered to be unrelated to study drug), one spontaneous abortion (45 days after withdrawal from the 60 mg orvepitant group due to pregnancy), and two cases of convulsion (60 mg orvepitant). In one case, a 61 year-old female with a history of recent head trauma and previously undeclared history of similar blackouts was hospitalized for a seizure involving loss of consciousness without generalization the day after receiving the first dose of study medication. Hospital records remarked that it was uncertain if this event was due to sleep deprivation or the experimental medication the patient was taking. No PK samples were available for this patient. In the

Table 3. Secondary efficacy endpoints (intent to treat (ITT) population).

Measure	Timepoint	Study 733			Study 833		
		Placebo (*n*=103)	Orvepitant 30 mg (*n*=110)	Orvepitant 60 mg (*n*=107)	Placebo (*n*=116)	Orvepitant 30 mg (*n*=112)	Orvepitant 60 mg (*n*=111)
HAM-D responders[a]	Week 6	29%	42%	39%	27%	37%	30%
HAM-D remitters[b]	Week 6	10%	19%	18%	11%	23%	14%
CGI-I responders[c]	Week 6	31%	44%	40%	35%	44%	42%
Bech Mean (SD)	Baseline	13.6 (1.35)	13.8 (1.32)	13.7 (1.48)	12.2 (1.54)	11.9 (1.17)	12.3 (1.29)
LS mean (SE)	Δ at Week 6	−4.30 (0.424)	−5.53[d] (0.402)	−5.84[d] (0.409)	−3.69 (0.394)	−4.78 (0.409)	−4.21 (0.421)
HAMD Anx. Subscale							
Mean (SD)	Baseline	8.1 (1.50)	8.1 (1.57)	8.5 (1.42)	7.7 (1.58)	7.7 (1.37)	7.9 (1.47)
LS mean (SE)	Δ at Week 6	−2.60 (0.256)	−3.06 (0.242)	−3.30[d] (0.248)	−2.37 (0.235)	−2.70 (0.244)	−2.56 (0.254)
HAMD mood							
LS mean (SE)	Δ at Week 6	−0.98 (0.112)	−1.35[d] (0.107)	−1.35[d] (0.108)	−1.00 (0.115)	−1.28 (0.119)	−1.00 (0.123)
CGI-S Mean (SD)	Baseline	4.7 (0.52)	4.7 (0.53)	4.7 (0.55)	4.9 (0.62)	4.9 (0.61)	5.0 (0.55)
LS mean (SE)	Δ at Week 6	−1.07 (0.127)	−1.52[d] (0.120)	−1.56[d] (0.122)	−1.07 (0.123)	−1.45[d] (0.127)	−1.27 (0.132)
QIDS-SR Mean (SD)	Baseline	17.0 (4.05)	16.6 (3.23)	16.8 (3.59)	17.8 (3.63)	18.0 (3.53)	18.8 (3.34)
LS mean (SE)	Δ at Week 6	−5.05 (0.551)	−6.34 (0.523)	−6.73[d] (0.532)	−6.17 (0.543)	−7.70[d] (0.562)	−7.58 (0.588)
CPFQ Mean (SD)	Baseline	30.4 (4.45)	30.3 (5.09)	30.3 (4.62)	31.0 (4.53)	31.3 (4.28)	31.7 (3.80)
LS mean (SE)	Δ at Week 6	−5.51 (0.729)	−7.67[d] (0.693)	−7.85[d] (0.704)	−6.34 (0.688)	−7.28 (0.717)	−7.53 (0.746)
MSQ TST (min)							
Mean (SD)	Baseline	335.2 (109.56)	332.6 (109.95)	327.6 (113.06)	325.3 (116.25)	306.1 (105.02)	301.4 (120.00)
LS mean (SE)	Δ at Week 6	39.79 (9.930)	44.26 (9.443)	51.26 (9.523)	52.03 (9.986)	54.21 (10.394)	80.43 (10.956)
MSQ SOL (min)	Baseline	85.2 (70.08)	74.6 (75.16)	81.5 (70.20)	103.8 (132.42)	96.5 (78.19)	90.8 (81.41)
Mean (SD)	Δ at Week 6	−34.50 (5.212)	−27.66 (4.940)	−37.75 (4.998)	−18.93 (8.284)	−47.51[d] (8.684)	−48.99[d] (9.163)
LS mean (SE)							
MSQ WASO (min)							
Mean (SD)	Baseline	58.5 (133.93)	48.7 (52.46)	73.5 (136.68)	56.7 (58.36)	52.6 (67.05)	62.7 (94.83)
LS mean (SE)	Δ at Week 6	−16.99 (10.713)	−21.08 (10.428)	−14.08 (11.198)	1.34 (6.926)	−13.17 (7.479)	−15.76 (7.932)
MSQ NA Mean (SD)	Baseline	2.6 (1.64)	2.6 (1.06)	2.2 (1.25)	2.6 (1.53)	2.6 (1.48)	2.4 (1.45)
LS mean (SE)	Δ at Week 6	−0.36 (0.152)	−0.67 (0.147)	−0.84[d] (0.157)	−0.63 (0.152)	−0.42 (0.165)	−0.87 (0.175)
MSQ RS Mean (SD)	Baseline	3.6 (2.07)	3.4 (1.79)	3.3 (1.68)	2.9 (1.58)	3.1 (1.82)	2.9 (1.77)
LS mean (SE)	Δ at Week 6	1.67 (0.246)	2.31 (0.234)	2.41[d] (0.236)	1.86 (0.242)	2.23 (0.252)	2.57 (0.264)
MSQ SQ Mean (SD)	Baseline	4.0 (2.09)	3.8 (2.03)	3.8 (1.99)	3.5 (1.79)	3.4 (1.76)	3.4 (1.94)
LS mean (SE)	Δ at Week 6	1.53 (0.238)	2.19[d] (0.226)	2.30[d] (0.228)	1.77 (0.234)	2.34 (0.243)	2.09 (0.254)

[a]≥50% reduction from baseline, [b]Total score of ≤7, [c]CGI-I: 1 or 2, [d]$p<0.05$ vs PBO.

Δ: change from baseline; Bech: Bech Melancholia Scale; CGI-I: Clinical Global Impressions-Improvement; CGI-S: Clinical Global Impressions-Severity of Illness; CPFQ: Cognitive and Physical Function Questionnaire; HAM-D: Hamilton Depression Rating Scale; HAMD Anx Subscale: Hamilton Depression Anxiety Factor; MSQ-NA: Morning Sleep Questionnaire-Number of Awakenings; MSQ-RS: Morning Sleep Questionnaire-Refreshing Sleep; MSQ-SOL: Morning Sleep Questionnaire-Sleep Onset Latency; MSQ-SQ: Morning Sleep Questionnaire-Sleep Quality; MSQ-TST: Morning Sleep Questionnaire-Total Sleep Time; MSQ-WASO: Morning Sleep Questionnaire-Wake Time After Sleep Onset; QIDS-SR: Quick Inventory of Depressive Symptoms-Self-Rated Version; SD: standard deviation; SE: standard error.

second case, a 45 year-old male experienced an apparent grand mal seizure 40 days after starting study medication - he subsequently reported five seizures in the past two weeks accompanied by symptoms of confusion, headache, diffuse myalgia and tongue biting. The investigator considered that there was no reasonable possibility that the seizure was caused by the investigational drug and indicated a possible alternative cause of alcohol consumption to which the patient had admitted. Orvepitant levels were below the limit of quantification for this patient's PK sample. No seizures were observed in the 30 mg orvepitant group or in any treatment group in study 733. However, seizure also occurred in one subject following administration of the 60 mg dose in another study:[1] therefore, the IDMC recommended the discontinuation of the orvepitant 60 mg group only. In response, the study sponsor decided to discontinue treatment in all orvepitant arms and as a result, both studies were terminated prior to completion, but still preserving the blind to allow unbiased analysis.

There were no significant changes in hematology or urinalysis parameters in either study. Other laboratory parameters were unremarkable (Supplementary Material, Tables E41–E44). However, in study 733 mean creatinine kinase (CK) levels were increased from baseline at week 6 for both the orvepitant 60 mg (change=8.4 IU/L) and placebo (9.6) groups, but not for orvepitant 30 mg (–0.7). In study 833 CK levels also increased from baseline at week 6 for both the orvepitant 60 mg (23.5 IU/L) and 30 mg group (13.6) compared with placebo (1.9). All CK increases were asymptomatic and there were no differences in the distribution of five-fold or greater increases in CK levels from baseline between

Table 4. Most frequent (≥5% in any treatment group) adverse events (all subjects population).

Adverse event, *n* (%)	Study 733			Study 833		
	Placebo (*n*=108)	Orvepitant 30 mg (*n*=113)	Orvepitant 60 mg (*n*=107)	Placebo (*n*=116)	Orvepitant 60 mg (*n*=115)	Orvepitant 60 mg (*n*=112)
Any adverse event	61 (56)	72 (64)	66 (62)	80 (69)	84 (73)	84 (75)
Headache	10 (9)	11 (10)	5 (5)	19 (16)	19 (17)	25 (22)
Diarrhea	7 (6)	9 (8)	7 (7)	8 (7)	12 (10)	11 (10)
Somnolence	2 (2)	9 (8)	9 (8)	6 (5)	12 (10)	8 (7)
Dry mouth	6 (6)	8 (7)	4 (4)	14 (12)	11 (10)	12 (11)
Nausea	6 (6)	9 (8)	5 (5)	16 (14)	8 (7)	10 (9)
Dizziness	3 (3)	7 (6)	2 (2)	4 (3)	9 (8)	8 (7)
Fatigue	2 (2)	0	9 (8)	2 (2)	9 (8)	7 (6)
Upper respiratory tract infection	6 (6)	3 (3)	5 (5)	4 (3)	7 (6)	7 (6)
Insomnia	2 (2)	3 (3)	5 (5)	2 (2)	4 (3)	9 (8)
Anxiety	4 (4)	2 (2)	2 (2)	2 (2)	6 (5)	5 (4)
Upper abdominal pain	2 (2)	1 (<1)	1 (<1)	3 (3)	4 (3)	8 (7)
Paresthesia	0	3 (3)	3 (3)	2 (2)	2 (2)	6 (5)
Dyspepsia	4 (4)	0	1 (<1)	5 (4)	3 (3)	6 (5)
Flatulence	2 (2)	0	1 (<1)	6 (5)	4 (3)	4 (4)

active treatment and placebo in either study. All CK increased resolved uneventfully, although one case was lost to follow-up. Clinically significant changes in vital signs or body weight were infrequent and not clearly associated with orvepitant treatment (Supplementary Material, Tables E45–E50).

The mean number of discontinuation emergent signs or symptoms was comparable across treatment groups in both studies (Supplementary Material, Tables E51 and E52). Significant changes in sexual functioning as assessed by the MSFQ total score were limited to significant improvement for females in the orvepitant 60 mg group in Study 733 only (–2.26 difference from placebo, 95% CI –4.22 to –0.31, p=0.0234, see also Supplementary Material, Tables E53–E56).

Discussion

The studies reported here and elsewhere (Hargreaves, 2002; Kramer et al., 1998; Ratti et al., 2011) support the hypothesis that NK1 antagonists that provide prolonged and full blockade of NK1 receptors may have significant antidepressant effects in patients with MDD. Based on the PET results, 30 and 60 mg/day doses of orvepitant appear to yield >99% NK1 RO for 24 h in most patients. We suggest that NK1 receptors in pathways that control mood may have a very high receptor reserve for the physiological agonist with a consequence that antagonism at these receptors need to be nearly complete to exert the intended physiological actions. These actions have been postulated to be mediated by increased firing of serotonergic neurons in the dorsal raphe nucleus and noraderenergic neurons in the locus coeruleus (Gobbi and Blier, 2005). Overall, the results of the MDD studies support efficacy and suggest relevant effects on specific symptom domains.

Study 733 demonstrated a statistically significant difference from placebo on the primary endpoint (week 6 change in HAM-D total score) both via the prespecified (MMRM) analysis, as well as sensitivity analyses including LOCF and observed cases. Both dose levels appeared to be equally effective. Differences in HAM-D change in Study 833, although numerically favoring orvepitant vs placebo, did not achieve statistical significance. The primary endpoint result in Study 733 was further corroborated by significant differences from placebo at week 6 on CGI-S (30 and 60 mg), Bech subscale (30 and 60 mg), HAM-D item 1(30 and 60 mg) and QIDS-SR (60 mg). Significant drug vs placebo differences were observed at some time points in Study 833, including CGI-S (30 mg at week 6) and QIDS-SR (30 mg at weeks 2–6, 60 mg at weeks 1–4) providing further supportive evidence for efficacy.

The HAM-D difference from placebo in Study 733 study was ~2.9 points at endpoint, consistent with drug-placebo differences previously observed with the NK1 antagonists aprepitant (Kramer et al., 1998), L-759274 (Kramer et al., 2004) and casopitant (Ratti et al., 2011). This is at the upper end of the range for drug-placebo differences observed in recent depression studies as reported in a 2011 FDA meta-analysis of antidepressant trials (Khin et al., 2011), and somewhat larger than the 1.6–1.8 point HAM-D difference observed for the pivotal studies for the most recently FDA-approved antidepressant, vilazodone (Khan et al., 2011; Rickels et al., 2009).

Sleep disturbance is relatively common in MDD and insomnia has been shown to be both a prodromal and residual symptom of prognostic importance (Fava, 2004). Orvepitant, especially the 60 mg group, showed improvements in total sleep time, sleep onset latency and sleep quality in both studies. The beneficial impact on sleep outcomes reported here is consistent with previous findings with NK1 antagonists showing significant beneficial effects on sleep in both depressed (Kramer et al., 1998, 2004; Ratti et al., 2011) and primary insomnia patients (GSK Clinical Study Register, 2009). Considering the high (~50%) frequency of comorbid insomnia in patients with MDD, as well as the importance of sleep

disturbance as both a prodromal symptom and as a residual symptom predicting remission (Fava, 2004), the beneficial effects of NK1 antagonists on sleep, if further replicated could be clinically meaningful. Conversely, the significant improvements observed in Study 733 on HAM-D item 1 as well as the Bech subscale (which does not include sleep items) provide reassurance that the antidepressant effects of orvepitant are not restricted to sleep domains, but also include other core symptoms of depression.

As with other NK1 antagonists, orvepitant was generally well tolerated and there was no evidence in these studies of sexual dysfunction, gastrointestinal side effects or impact on weight, these being issues that affect compliance with current antidepressants (Li et al., 2012). Similarly, there was no evidence of imbalance between placebo and orvepitant on suicidality or treatment discontinuation emergent events. However there were two cases of seizure in patients randomized to the 60 mg dose in Study 833. Prior clinical experience with NK1 antagonists does not support that this is a mechanism-based toxicity and preclinical data with orvepitant and other NK1 antagonists does not suggest pro-convulsant properties. Thus, NK1 receptor (TACR1) knockout mice do not exhibit a seizure-prone phenotype (De Felipe et al., 1998; Santarelli et al., 2001) and mice that lack a Tac1 gene are resistant to kainate-induced seizures and neurotoxicity (Liu et al., 1999a). Indeed rodent data indicate that NK-1 receptor antagonists are actually anticonvulsant, since they can block seizure activity induced by either substance P (Liu et al., 1999b; Robinson et al., 2012) or kainite (Zachrisson et al., 1998). These findings are further supported by the observation that an NK-1 antagonist potentiated the anticonvulsant efficacy of sodium channel inhibitors in a rat model (Kalinichev et al., 2010). Seizures have not been observed in previous Phase I clinical studies with orvepitant (up to 240 mg) although a single seizure was observed at 60 mg in a study in post traumatic stress disorder (PTSD) for which confounding issues (positive urine drug screen for methadone) were also identified (GSK Clinical Study Register, 2010). The confounding issues, the previous safety profile of other NK1 antagonists, the lack of any preclinical signal of proconvulsant activity, as well as epidemiological studies suggesting that depressed populations have a seizure risk several times that in the normal population (Alper et al., 2007; Hesdorffer et al., 2006), all suggest that a causal role for orvepitant appears to be unlikely, though this risk cannot yet be discounted.

Clinical development of antidepressants has been plagued by a high failure risk. Placebo effect is high in this disorder and several approaches have been recently proposed to reduce it and to improve the probability of trial success. Most of these approaches concentrate on patient selection and on independence of efficacy evaluations. We applied two different approaches in the two otherwise nearly identical clinical studies, which may have contributed to the difference in efficacy results observed between the two studies. In Study 733 patients proposed for randomization by each site were then interviewed remotely by a clinical expert using the SAFER criteria (Targum et al., 2008) for diagnostic reassessment, confirming the eligibility or excluding the patient according to the study's psychiatric inclusion and exclusion criteria. HAM-D and CGI-S were then administered by an independent rater at the site. In contrast, for Study 833 psychiatric screening and HAM-D and CGI-S were performed remotely via live videoconference interview, without a specific focus on diagnostic reassessment. In Study 733, orvepitant separated significantly from placebo on the primary endpoint and on many of the secondary endpoints. Results were in the same direction in Study 833, but a significant separation was not observed on the primary endpoint. It is noteworthy that orvepitant was efficacious in both studies based on the sole self-rated assessment of efficacy (QIDS-SR). Although other differences between the two studies (slightly stricter HAM-D entry criteria in 733 (≥24) vs 833 (≥22); duration of current depressive episode ≥8 vs ≥4 weeks; differences in number of centers participating (31 vs 20)) may have contributed to differences in the primary outcome, we suggest that proper subject selection may be more critical to enhancing signal detection than efforts aimed at maintaining full independence of assessments.

The main limitation of the clinical studies is their premature termination. However, study termination occurred very close to the natural end of the two studies. Indeed, only a small percentage of patients were withdrawn due to study termination and the percentage of study drop-outs observed in the two studies is similar to those previously reported for similar clinical studies. Moreover, study termination procedures were all done preserving study blindness. These studies were limited in duration to six weeks. Further studies are required to establish longer term efficacy and efficacy in the prevention of relapse.

In conclusion, these data provide further support for the concept of NK1 receptor blockade as a viable mechanism for the treatment of MDD. These data provide a reason why initial optimism that surrounded the first trials in MDD with this mechanism may not have been misplaced. Overall the data strongly support the hypothesis that high brain penetration together with full and long-lasting NK1 receptor occupancy is required to achieve clinical efficacy in MDD.

Conflict of interest

E Ratti, P Bettica, R Alexander, G Archer, D Carpenter, G Evoniuk, Ro Gomeni, E Lawson, M Lopez, H Millns, EA Rabiner, D Trist, M Trower, and S Zamuner were employees and shareholders of GlaxoSmithKline at the time that these studies were conducted.

R Krishnan and M Fava acted as paid consultants to GlaxoSmithKline in the design and conduct of these clinical trials.

R Krishnan has also acted as a paid consultant to, and/or holds stock directly or indirectly in Cenerx, Orexigen, Cypress Bioscience, Sonexa, Atentiv, Alta and Roche.

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Note

1. A 44 year-old female with no previous history of seizure or head injury developed a grade 3 (severe) seizure six days after beginning treatment with orvepitant 60 mg/day. At the time, the subject's boyfriend noted tonic-clonic movements in all four extremities that lasted approximated 1.5 min with no buccal lesions or urinary or fecal incontinence. This was followed by a post-ictal phase of confusion and inability to speak lasting approximately one hour. In the emergency room, an electrocardiogram, head computed tomography scan, and laboratory testing were all normal. The subject was treated with medications including phenytoin, lorazepam, fosphenytoin sodium and levetiracetam and discharged from the ER. Urine drug screen results were subsequently positive for methadone which the patient had been prescribed to treat abdominal pain due to fecal impaction. The event was considered to be resolved within the same day as the incident. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The investigator considered that there was a reasonable possibility that the seizure may have been caused by investigational product.

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