Maximum Tolerated Dose Evaluation of the AMPA Modulator Org 26576 in Healthy Volunteers and Depressed Patients

A Summary and Method Analysis of Bridging Research in Support of Phase II Dose Selection

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Abstract

Background: A key challenge to dose selection in early central nervous system (CNS) clinical drug development is that patient tolerability profiles often differ from those of healthy volunteers (HVs), yet HVs are the modal population for determining doses to be investigated in phase II trials. Without clear tolerability data from the target patient population, first efficacy trials may include doses that are either too high or too low, creating undue risk for study participants and the development program overall. Bridging trials address this challenge by carefully investigating safety and tolerability in the target population prior to full-scale proof-of-concept trials.

Objective: Org 26576 is an alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor positive allosteric modulator that acts by modulating ionotropic AMPA-type glutamate receptors to enhance glutamatergic neurotransmission. In preparation for phase II efficacy trials in major depressive disorder (MDD), two separate phase I trials were conducted to evaluate safety, tolerability, and pharmacokinetics in HVs and in the target patient population.

Methods: Both trials were randomized and placebo controlled, and included multiple rising-dose cohorts (HV range 100–400 mg bid; MDD range 100–600 mg bid). HVs (n = 36) and patients with MDD (n = 54) were dosed under similarly controlled conditions in an inpatient facility, HVs for up to 14 days and MDD patients for up to 28 days. Safety, tolerability, and pharmacokinetics were assessed frequently.

Results: Despite comparable pharmacokinetic profiles, the maximum tolerated dose (MTD) in depressed patients was 450 mg bid, twice the MTD established in HVs. No clinically relevant safety issues associated with Org 26576 were noted.

Conclusion: This article presents safety, tolerability, and pharmacokinetic data from two different populations examined under similar dosing conditions. The important implications of such bridging work in phase II dose selection are discussed, as are study design and data interpretation challenges.

Introduction

One of the critical challenges in early-stage clinical drug development is the selection of appropriate doses for initial efficacy trials. The lack of validated biomarkers in most central nervous system (CNS) indications leads to phase II dose and regimen selection that is often based on a best guess for efficacy and on safety/tolerability established in preclinical and early phase I work. Although human tolerability is most often determined via early studies in healthy volunteers (HVs), there is good evidence that tolerability profiles in healthy subjects do not necessarily predict tolerability in target patient populations, particularly in CNS disorders.[1] Bridging studies, sometimes known as phase Ib studies, offer a unique opportunity to examine tolerability in target populations in support of dose selection for phase II efficacy trials. Establishing the patient maximum tolerated dose (MTD) as early as possible not only reduces the risk that patients in proof-of-concept trials will be over- or under-exposed to study medication, but also can result in acceleration of the drug development timeline.[2] These trials also provide the opportunity to assess preliminary dose and/or pharmacokinetic relationships with pharmacodynamic measures, including electrophysiologic or neurochemical biomarkers, as well as cognitive or behavioral endpoints.[3,4]

Much of the published bridging work to date has been conducted in Alzheimer's disease and schizophrenia, where small numbers of otherwise healthy patients are exposed to escalating doses of the study drug under controlled conditions.[5] Although there is variability between trials, the MTD is generally defined as the dose one level (or 'step') below the dose that causes an unacceptable number of discontinuations or dose-limiting adverse events (AEs).[6] Doses included in these bridging trials are often selected on the basis of HV data, with an expanded range to allow for the possibility that patient and HV tolerability may differ. Indeed, bridging trials have often led to conclusions that were disparate from those that might have been drawn on the basis of HV data alone.[7-15] Despite relatively comparable pharmacokinetic profiles in most cases, the resulting MTD in these trials was determined to be higher than – and in some cases a multiple of – the MTD in HVs. Importantly, there is no evidence from these trials that safety profiles (i.e. findings on objective safety measures) differ between HVs and patients; the differences appear to be limited to tolerability (i.e. AEs).

The reason for this population-dependent tolerability phenomenon is largely unknown, but it has been suggested that it is due to alteration of receptor activity by prior treatments or by the disease itself.[16] Still, one must exercise caution when drawing generalized conclusions. Although the majority of studies indicate that patients are able to tolerate higher doses than HVs, there are examples where there is no difference or even the opposite is true.[2,17] Furthermore, conflicting outcomes within the same drug class (e.g. acetylcholinesterase inhibitors)[12,17] suggest that specific molecule differences may play a contributory role. Such divergent findings underscore the importance of carefully evaluating tolerability in the target population prior to embarking on phase II efficacy trials of any new investigational drug. While the cumulative MTD literature in schizophrenia and Alzheimer's disease can lend some guidance to drug developers in the CNS arena, published data are comparatively sparse for other
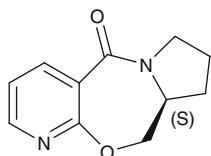
Fig. 1. Chemical structure of Org 26576.

indications, including major depressive disorder (MDD).

The current paper summarizes the bridging data for Org 26576 (chemical name: [9aS]-8,9,9a,10-tetrahydro-5H,7H-pyrido[3,2-f]pyrrolo[2,1-c][1,4]oxazepin-5-one; see figure 1). Org 26576 belongs to a novel class of compounds referred to as alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor positive allosteric modulators (AMPA PAMs), which act by modulating ionotropic AMPA-type glutamate receptors to enhance glutamatergic neurotransmission.[18,19] Dysregulation of the glutamatergic system has been implicated in the pathology of psychiatric diseases such as schizophrenia[20,21] and mood disorders.[22-24] AMPA receptors mediate fast excitatory neurotransmission in the brain, and their activation has been reported to exert a variety of cellular effects, including enhancement of neurotrophic factor activity (particularly brain-derived neurotrophic factor [BDNF]),[25] synaptic plasticity,[26] and neurogenesis.[27] It has been suggested that modulation of these cellular activities may, in part, play a role in the mode of action of current antidepressant agents.[28,29] If so, AMPA PAMs represent a promising novel approach in MDD.

The two trials presented here were undertaken by employing very similar designs and dosing approaches in order to characterize the tolerability, safety, and pharmacokinetic profiles of Org 26576 both in HVs and in patients diagnosed with MDD. The overarching program objective of these trials was to facilitate dose selection for the first proof-of-concept trials with Org 26576 in MDD. HV and patient safety/tolerability and pharmacokinetic data that contributed to dosing decisions are presented here. Secondary, exploratory pharmacodynamic endpoints from the patient trial are presented elsewhere.[30]

Methods

Study Design and Subjects

The studies described herein were conducted in accordance with the principles of Good Clinical Practice and were approved by each center's institutional review board and the appropriate regulatory agency prior to commencement of study activities. All study participants signed an informed consent form before any screening evaluations were performed. Study objectives of both trials were to assess the safety and tolerability, MTD, pharmacokinetics, and pharmacodynamics of Org 26576.

Study 1: A Combined Single- and Multiple-Oral-Dose Tolerability and Pharmacokinetic Study of Org 26576 in Healthy Male Subjects (Organon Protocol 21301)

This study was conducted at Guy's Drug Research Unit, Quintiles Ltd, London, UK, between June and November 2005. This was a randomized, double-blind, crossover, placebo-controlled, single-rising-dose study (part I), and a randomized, double-blind, parallel-group, placebo-controlled, multiple-rising-dose study (part II) in healthy male volunteers aged 18 to 45 years. In the single-dose part of the study (part I), two groups of nine subjects each participated in three successive periods during which they received a single dose of Org 26576 (range 5–250 mg) on two separate occasions and a single dose of placebo on one occasion. The washout period between successive dosing occasions was at least 7 days.

The multiple-dose part of the study (part II) included two sequential nine-subject groups, where six in each group received Org 26576 and three received placebo. In part II, group 3 subjects received either a single dose of Org 26576 (100 mg) or placebo on 3 of 9 days and twice-daily (bid) doses at 12-hour intervals on days 3–8. In this group, the effect of food (a high-fat breakfast) on the pharmacokinetics of Org 26576 was investigated on day 5; four subjects received the morning dose after a standardized high-fat breakfast, and five subjects received the morning dose after an overnight fast. Subjects received the opposite food regimen on day 6. Thereafter, no food

was permitted until 4 hours post-dose. In part II, group 4 utilized a multiple-rising-dose design to determine the MTD. Subjects received either Org 26576 or placebo at 12-hour intervals; starting doses were based on tolerability results from previous groups and were carefully escalated in interim steps of 1.25–1.5 times the previous dose as follows: 100 mg bid on days 1 and 2, 150 mg bid on days 3–5, 225 mg bid on days 6–8, 325 mg bid on days 9–11, 400 mg bid on days 12 and 13, and a single 400 mg dose on day 14.

Study 2: Multiple-Oral-Dose Tolerability and Pharmacokinetics of Org 26576 in Patients Diagnosed with Major Depressive Disorder (Organon Protocol 174001)

This study was conducted at California Clinical Trials in Glendale, CA, USA, between September 2007 and December 2008 (clinicaltrials.gov identifier: NCT00610649). Part I was a randomized, double-blind, placebo-controlled, multiple-rising-dose evaluation in 24 patients. Four sequential cohorts of six patients each received either Org 26576 or placebo in a 2:1 ratio (cohort A dose titration: 100 mg bid on days 1–3, 200 mg bid on days 4–6, 300 mg bid on days 7–9, 450 mg bid on days 10–12, 600 mg bid on days 13–16). Within part I, cohorts A, B, and C started at progressively higher doses (100 mg, 200 mg, or 300 mg), all rising to 600 mg bid, in order to explore the optimal titration schedule; cohort D evaluated cerebrospinal fluid (CSF) pharmacokinetics at the lower end of the dosing range (at 100 and 300 mg bid). The treatment duration in part I was between 10 and 16 days, depending on the titration schedule. Part II was a 30-patient, randomized, double-blind, parallel-group, placebo-controlled design, which evaluated two dose levels of Org 26576 for 28 days (10 subjects assigned to 100 mg bid, 10 subjects assigned to 400 mg bid, and 10 subjects assigned to placebo), with objectives to evaluate tolerability, pharmacokinetics, and pharmacodynamics over an extended treatment period. The doses in part II were selected on the basis of the tolerability results from part I.

All selected patients were male or female, aged 18–65 years, and diagnosed with MDD according to the fourth edition of the *Diagnostic and Sta-*tistical Manual of Mental Disorders (DSM-IV-TR). Current depressive episodes were mild to severe without psychotic features, and no more than 2 years in duration, with a total score of at least 9 but not more than 20 on the Quick Inventory of Depression Symptomatology – Clinician Rating (QIDS-C).[31] Patients who had received antidepressant treatment with an adequate dose and duration in the current episode were excluded. Eligible patients were otherwise generally healthy and medically stable; were taking no concurrent psychotropic medications; and had no history of bipolar disorder, psychosis, post-traumatic stress disorder, obsessive-compulsive disorder, or eating disorder. Patients with a 6-month history of substance dependence (not including nicotine), current substance abuse, or a positive screening or admission urine drug/alcohol test were excluded.

Subjects in both trials were admitted to the unit 1–2 days before the first dosing and confined for the full term of the dosing period. Diet and physical activity were controlled, and subjects were closely monitored for safety and tolerability. Safety evaluations included regular AE assessments, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory assessments, and safety electroencephalograms (EEGs) conducted in a resting state with eyes open and closed, with photic stimulation, and with 3 minutes of hyperventilation. In addition, the patient trial included frequent suicidality assessment using the Beck Scale for Suicidal Ideation (BSS).[32]

In study 1, the MTD was not specifically defined *a priori*; however, safety and tolerability were closely monitored by the study investigators and the sponsor in a blinded fashion, and dosing progression was largely dependent on absence of medication discontinuations due to AEs. The MTD in study 2 was defined *a priori* as the dose one step below the minimum intolerated dose (MID), where the MID was the dose at which ≥50% of subjects experienced multiple moderate AEs or a single severe AE, or the dose at which a serious AE occurred in one or more subjects. Safety/tolerability data were reviewed by the study investigators and the sponsor on an interim and blinded basis before progression to the next dosing level/cohort.

Pharmacokinetic Assessments

Pharmacokinetic assessments were performed following a rich pharmacokinetic sampling scheme in both studies. In study 1, pharmacokinetic samples were taken at pre-dose, at 5, 10, 15, 30, and 45 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours post-dose upon single-dose administration during part I and upon the first (no 36-, 48-, or 72-hour samples) and final dose (no 72-hour sample) in group 3 during part II of this study. For group 4 during part II, an identical sampling scheme was applied up to 12 hours post-dose on days 2 (100 mg), 8 (225 mg), 11 (325 mg), and 14 (400 mg), while additional pharmacokinetic samples at 18 and 24 hours post-dose were taken 18 and 24 hours after the final dose. Pharmacokinetic assessments up to 4 hours post-dose were performed under fasted conditions, with the exception of group 3, where on days 5 and 6 the food effect (a high-fat breakfast) on the pharmacokinetics of Org 26576 was specifically investigated. In study 2, plasma pharmacokinetic samples were taken at pre-dose, at 15, 30, and 45 minutes, and at 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose (but before the evening dose) within a multiple-dosing scheme. To examine the extent to which Org 26576 is able to cross the human blood-brain barrier, continuous CSF was collected over intervals of 30 minutes, starting 2 hours prior to the morning dose through 12 hours following the morning dose on day 1 and day 10 in cohort D only (n = 6). In this study, patients were required to eat a light breakfast 30 minutes before the morning dose.

Study Medication

In Study 1, Org 26576 was provided as freeze-dried cake and was reconstituted at the site pharmacy in 10 mL of sterile water and added to a gelatin/mannitol solution in order to obtain a final volume of 50 mL. Placebo was composed of 50 mL of the gelatin/mannitol solution. The required dose was administered as an oral solution. In Study 2, Org 26576 and placebo were prepared as indistinguishable capsules containing placebo, 50 mg, or 100 mg of Org 26576 for oral administration. The change of medication from oral solution to capsule was not expected to lead to significant formulation-dependent differences in the overall disposition of the drug. This assumption was supported by the overall physicochemical characteristics (Biopharmaceutica Classification System [BCS] class I)[33] and the *in vitro* absorption, distribution, metabolism, and excretion (ADME) profile of Org 26576 (Merck Sharp & Dohme Corp., unpublished data).

Bioanalysis

Org 26576 and its internal standard were isolated from ethylene diamine tetra-acetic acid (EDTA) plasma by solid-phase extraction. Liquid chromatography-mass spectrometry using turbo electrospray ionization in multi-reaction monitoring mode was performed in order to quantify the concentration of Org 26576. The assay has been validated over the range of 0.2–200 ng/mL. Both trials utilized the same bioanalytic approach and followed the same standard operating procedures. Laboratory assessments were conducted in full compliance with Good Laboratory Practice.

Statistical Analysis

Safety and Tolerability

All endpoints for both studies were analyzed using the all-subjects-treated population (participants who took at least one dose of the study medication). Descriptive statistics were calculated; however, no statistical testing was performed.

Pharmacokinetics

In study 1, group 3, a one-way analysis of variance (ANOVA) with a 'Food' factor and repeated measures for each subject on food was applied to the parameters pertaining to treatment with and without food (i.e. the maximum plasma drug concentration [C_{max}] during a dosage interval at steady state [$C_{max,ss}$], the time to reach C_{max} [t_{max}] following drug administration at steady state [$t_{max,ss}$], and the area under the plasma concentration-time curve [AUC] from 0 to 12 hours at steady state [$AUC_{12,ss}$]), which were compared by means of a one-way ANOVA with a 'Food' factor and repeated measures for each subject on

food (i.e. a paired t-test). Food-independent pharmacokinetics were to be concluded if the food effect for all parameters analyzed was not significant. An analogous analysis was applied to explore the presence of a regimen effect (100 mg single dose on day 1, versus 100 mg bid on day 9). For this purpose, parameters pertaining to single dosing (i.e. C_{max}, t_{max}, the elimination half-life [$t_{1/2}$], and the AUC from time zero to infinity [AUC_∞]) and to steady state (i.e. $C_{max,ss}$, $t_{max,ss}$, $t_{1/2,ss}$, and $AUC_{\infty,ss}$) were compared. Time-independent pharmacokinetics were to be concluded if the regimen effect for all parameters analyzed was not significant. In group 4, the parameters (i.e. the dose-normalized [dn] $C_{max,ss}$ [dn-$C_{max,ss}$], $t_{max,ss}$, and dn-$AUC_{12,ss}$) pertaining to the escalating multiple dosing (100, 225, 325, and 400 mg) were compared by means of a two-way ANOVA with fixed factors of 'Dose' and 'Subject'. If there was no significant dose effect, then the pharmacokinetics were to be considered as linear within the dose range studied. In study 2, the Org 26576 pharmacokinetic parameters in part II (i.e. dn-C_{max}, $t_{1/2}$, dn-AUC, and t_{max}) were compared by means of an ANOVA with fixed factors of 'Dose' (low dose: Org 26576 100 mg bid group; high dose: Org 26576 400 mg bid group), 'Day' (1, 4, 27), 'Dose*Day' interaction, and repeated measures for each subject (subject nested within dose).

In both studies, $\log_e$-transformed values of the parameters were used in the ANOVAs, except for t_{max}, for which a Wilcoxon signed rank test was performed. Effects were considered as significant if the p-value was ≤0.05 (p: two-sided tail probability). Since these studies were not powered, all p-values were to be interpreted in the perspective of the explorative character of these trials. The plots, parameters, and analysis pertaining to the pharmacokinetic evaluations were generated using SAS release 9.1 under the Windows XP operating system.

Results

Baseline Characteristics

A total of 36 and 54 subjects were randomized in the HV and patient studies, respectively (see table I). All received at least one dose of study medication and therefore qualified for the all-subjects-treated population. All participants in the HV study were male, as were the majority (65%) in the patient study. The patient study sample was more racially diverse and somewhat older than the HV sample. Weight and body mass index (BMI) were comparable between studies. In the patient study, the majority of patients (76%) were diagnosed with recurrent depression, and the number of lifetime episodes was 4.4; the mean QIDS-C total score at baseline was 15.1 (standard deviation [SD] 2.26), reflecting moderately severe depression.[31]

Safety and Tolerability

Study 1

There were no serious or severe AEs in this study. In study part I (single dose), no subjects discontinued because of AEs. Doses of 100 mg and higher were associated with gastrointestinal AEs (nausea, vomiting, once at 200 and 250 mg) and CNS AEs (dizziness, postural dizziness, headache, and paraesthesia). The 100 mg dose was determined to be the single-dose MTD.

In part II of the study (multiple dose), Org 26576 100 mg bid given for 7 days (group 3) was well tolerated by all subjects. The AEs reported most frequently in the active-treatment group included mild dizziness and mild nausea. In group 4, where an up-titration schedule to 400 mg bid was applied, Org 26576 was tolerated up to doses of 225 mg bid. However, at higher doses, three subjects discontinued, two because of nausea and/or vomiting (both at 325 mg bid) and one because of dizziness (at 400 mg bid). The most common treatment-emergent AEs associated with Org 26576 (occurring in ≥25% of subjects in the active-treatment group of any study group, and with at least 2× the incidence in the placebo group) were nausea, dizziness, and somnolence, as well as feeling drunk and postural dizziness. The MTD with titration was determined to be 225 mg bid.

There were no obvious treatment-related changes observed either for individual subjects or in the summary data for clinical laboratory values, vital signs, or ECG measurements. During the dose-

Table I. Demographic and baseline characteristics of randomized subjects

Characteristic	Study 1: Org 26576 in HVs (n = 36)	Study 2: Org 26576 in MDD patients (n = 54)
Treatment assignment (n [%])		
Active	30 [83.3]	36 [66.7]
Placebo	6 [16.7][a]	18 [33.3]
Sex (n [%])		
Male	18 [100]	35 [64.8]
Female	0	19 [35.2]
Race (n [%])		
Asian	1 [2.8]	3 [5.6]
Black	3 [8.3]	14 [25.9]
White	29 [80.6]	33 [61.1]
Other	1 [2.8]	4 [7.4]
Age (y; mean [range])	27.6 [19–41]	35.4 [18–61]
Weight (kg; mean [range])	77.1 [66.5–94.3]	76.9 [44.0–118.1]
Body mass index (kg/m^2; mean [range])	24.4 [22.0–28.0]	25.3 [19.0–31.9]
Baseline QIDS-C score (mean [SD])	NA	15.1 [2.26]
Course of depression		
First episode (n [%])	NA	13 [24]
Recurrent (n [%])	NA	41 [76]
Total number of lifetime episodes (mean [range])	NA	4.4 [1–20]

a   Accounts for those subjects who received placebo only (i.e. subjects who were part of the active/treatment crossover design of part I are not counted in the placebo total).

HV = healthy volunteer; **MDD** = major depressive disorder; **NA** = not applicable; **QIDS-C** = Quick Inventory of Depression Symptomatology – Clinician Rating; **SD** = standard deviation.

titration part of the study, five of six subjects taking Org 26576, but no placebo subjects, had EEG observations that were interpreted as non-specific and indicative of drowsiness.

Study 2

No randomized patients experienced a serious or severe AE. Two subjects discontinued the trial because of AEs: one subject taking Org 26576 in part I discontinued because of akathisia at the highest dose (600 mg bid), and one subject taking placebo in part II discontinued because of tension headache. Most subjects in the active-treatment and placebo groups reported at least one AE during the treatment period (Org 26576: 97%; placebo: 89%). The treatment-emergent AEs reported most frequently in the active-treatment group (≥25% of subjects in either study part and with at least 2× the incidence in the placebo group) were insomnia, dizziness, nausea, muscle twitch-ing, fatigue, and feeling drunk (described by the investigator as a subjective feeling of 'fuzzy headedness' without objective impairment). On the basis of a post-study unblinded data review, it was determined that in cohort C, two of four drug-treated subjects experienced multiple moderate AEs at the 600 mg bid dose level. In addition, the only active-treatment discontinuation – and, re-gardless of titration schedule, the majority of moderate AEs – occurred at the dose of 600 mg bid. Therefore, the MTD for this study was con-sidered to be 450 mg bid. The optimal starting dose was determined to be 200 mg bid on the basis of the finding that the initial dose of 300 mg bid was associated with more treatment-related AEs than the initial dose of 100 or 200 mg bid.

There were no clinically significant drug-related laboratory, vital sign, ECG, or EEG findings in the study. Orthostatic tachycardia and orthosta-tic hypotension occurred at higher rates in the

Table II. Pharmacokinetic parameters in group 3 healthy volunteers in study 1[a]

Parameter	100 mg single dose	100 mg bid		
	Day 1 fasted (n = 6)	Day 9 fasted (n = 6)	Days 5–6 fasted (n = 6)	Days 5–6 fed (n = 6)
dn-C_{max} (ng/mL/mg)	16.3 [22.8]	15.7 [34.8]	14.2 [20.9]	7.01 [19.4]
t_{max} (h; median [range])	0.50 [0.25–0.75]	0.50 [0.50–1.03]	0.75 [0.50–1.00]	1.25 [0.25–4.00]
$t_{1/2}$ (h)	2.94 [14.5]	2.8 [24.8]	NA	NA
dn-AUC_{∞} (ng • h/mL/mg)	52.0 [40.2]	58.0 [47.7]	NA	NA
dn-AUC_{12} (ng • h/mL/mg)	NA	NA	49.0 [38.4]	43.0 [37.1]
CL/F (L/h)	21.2 [28.8]	19.7 [32.2]	22.3 [27.6]	25.4 [28.3]
V_z/F (L)	87.2 [21.7]	75.6 [21.1]	NA	NA

a The values are expressed as arithmetic mean [CV%] unless specified otherwise.

AUC = area under the plasma concentration-time curve; **AUC_{12}** = AUC from 0 to 12 hours; **AUC_{∞}** = AUC from time zero to infinity; **bid** = twice daily; **CL/F** = apparent total drug clearance after oral administration; **C_{max}** = maximum observed plasma drug concentration; **CV** = coefficient of variation; **dn** = dose-normalized; **NA** = not applicable; **$t_{1/2}$** = elimination half-life; **t_{max}** = time to C_{max}; **V_z/F** = apparent volume of distribution during the terminal phase after oral administration.

drug-treated groups than in the placebo group, though the findings were not considered clinically significant by the investigator and were not associated with any clinical signs. Nine subjects taking active medication (in contrast with zero placebo-treated subjects) had abnormal in-treatment EEG observations, which were felt by the investigator to be not clinically significant, primarily associated with drowsiness, and not indicative of pro-epileptic properties of the drug. No notable differences were observed between treatment groups in the baseline-to-endpoint suicidality mean scores (as measured by the BSS).

Pharmacokinetics

As one aim of the current paper is to compare the pharmacokinetic properties of Org 26576 in two different populations, the pharmacokinetic results reported here focus on the results obtained from both studies for identical doses administered in comparable multiple-dose regimens. Food and regimen analysis results for HVs, as well as dose and regimen results for MDD patients, are presented to further elucidate the overall pharmacokinetic profile of Org 26576.

Study 1: Food, Regimen, and Dose Effects

After oral administration, Org 26576 was rapidly absorbed as well as eliminated (see table II). Plasma concentrations reached C_{max} values about half an hour post-dose and quickly decayed, with a $t_{1/2}$ of about 3 hours. These pharmacokinetic characteristics were consistently observed upon single-dose and multiple-dose administration of Org 26576 100 mg as long as the volunteers were fasted. Intake of a high-fat breakfast prior to dosing affected the pharmacokinetic characteristics of Org 26576 by increasing t_{max} by about 40% and by reducing C_{max} by approximately 50%. AUC was reduced by only 12% with food, which is within the estimated variability of the parameter.[34] This fed-state reduction in the absorption rate translated into lower and smoothed plasma concentrations around the C_{max} values observed in fasted conditions. Regimen effect testing on the log_e-transformed pharmacokinetic parameters of Org 26576 showed that no significant regimen effects on C_{max}, total exposure, or $t_{1/2}$ were found. Analogously, the Wilcoxon signed rank test indicated no regimen effect on t_{max}.

The dose-normalized mean curves for all escalating doses in group 4 are displayed in figure 2, and the descriptive statistics for key pharmacokinetic parameters of the 100 mg and 400 mg bid escalating doses in group 4 are shown in table III. C_{max} values increased subproportionally with dose, while t_{max} and AUC values showed the opposite trend. When compared with the results in group 3, the $t_{1/2}$ was not clearly affected by the dose.
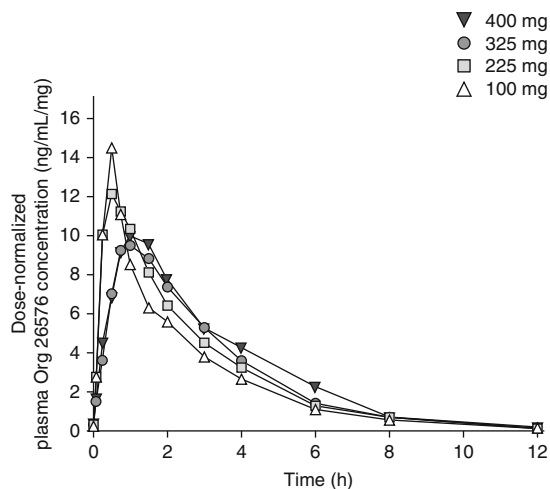
Fig. 2. Mean dose-normalized plasma concentrations of escalating doses of Org 26576 in healthy volunteers.

An overall trend for the dose effect was found for dn-$C_{max,ss}$ (p = 0.09) and was significant for dn-$AUC_{12,ss}$ (p = 0.03). The ANOVA on ranks of t_{max} resulted in a significant dose effect, showing larger t_{max} values for the highest doses (325 and 400 mg) than for the lower doses (100 and 225 mg).

Study 2: Dose and Day Effects

The mean dose-normalized plasma concentrations observed in part II of this study at days 1, 4, and 27 for the 100 mg and 400 mg bid treat-ment groups are displayed in figure 3a and 3b, respectively. The mean dn-C_{max} and dn-AUC values for days 4 and 27 in the 100 mg bid treatment group (see table III) were approximately 30% higher than for day 1 (data not shown). For the 400 mg bid treatment group, similar mean dn-C_{max} and dn-AUC values were found for all days. The mean dose-normalized exposure values for the 400 mg bid group tended to be somewhat higher than those for the 100 mg bid group (see table III). An explorative ANOVA on all subjects in part II showed no statistically significant over-all 'Dose', 'Day', or 'Dose*Day' effects on dn-C_{max}, t_{max}, dn-AUC, and $t_{1/2}$. No major deviations from the dose proportionality and time independence of the kinetics of Org 26576 were observed in this study in the titration schemes and dose range tested. For cohort D of part I, the mean Org 26576 exposure and concentration values in plasma and CSF were similar, both on day 1 (100 mg single dose) and on day 10 (300 mg steady state). The CSF t_{max} followed the plasma t_{max} by approximately 15 minutes with single doses and by approximately 1.5 hours with multiple doses.

Discussion and Conclusion

The studies presented herein describe bridg-ing data for the AMPA PAM Org 26576. On the basis of evidence suggesting that neuropsy-chiatric patients often tolerate higher medication

Table III. Pharmacokinetic parameters in healthy volunteers in study 1 and in patients with major depressive disorder in study 2[a]

Parameter	Study 1 in HVs		Study 2 in MDD patients			
	100 mg bid	400 mg bid	100 mg bid		400 mg bid	
	Day 2	Day 14	Day 4	Day 27	Day 4	Day 27
	(n = 6)	(n = 3)	(n = 10)	(n = 10)	(n = 10)	(n = 9)
dn-C_{max} (ng/mL/mg)	16.3 [38.3]	11.2 [25.8]	11.4 [46.3]	11.2 [34.1]	11.3 [30.8]	12.3 [57.4]
t_{max} (h; median [range])	0.5 [0.25–0.50]	1.00 [0.75–1.50]	1.75 [0.75–2.13]	1.50 [0.75–2.00]	1.75 [0.75–4.0]	2.00 [0.75–4.00]
$t_{1/2}$ (h)	NA	2.40 [20.4]	2.1 [31.4]	2.3 [29.9]	2.49 [33.0]	2.47 [37.6]
dn-AUC_{12} (ng • h/mL/mg)	34.5 [44.1]	38.9 [25.4]	49.1 [59.1]	48.4 [56.7]	56.6 [48.9]	61.7 [64.3]
CL/F (L/h)	33.6 [40.4]	27.0 [28.9]	NA	27.2 [53.1]	NA	35.5 [129]
V_z/F (L)	NA	93.6 [34.1]	NA	79.0 [34.1]	NA	112 [105]

a   The values are expressed as arithmetic mean [CV%] unless specified otherwise.

AUC_{12} = area under the plasma concentration-time curve from 0 to 12 hours; **bid** = twice daily; **CL/F** = apparent total drug clearance after oral administration; C_{max} = maximum observed plasma drug concentration; **CV** = coefficient of variation; **dn** = dose-normalized; **HV** = healthy volunteer; **MDD** = major depressive disorder; **NA** = not applicable; $t_{1/2}$ = elimination half-life; t_{max} = time to C_{max}; V_z/F = apparent volume of distribution during the terminal phase after oral administration.
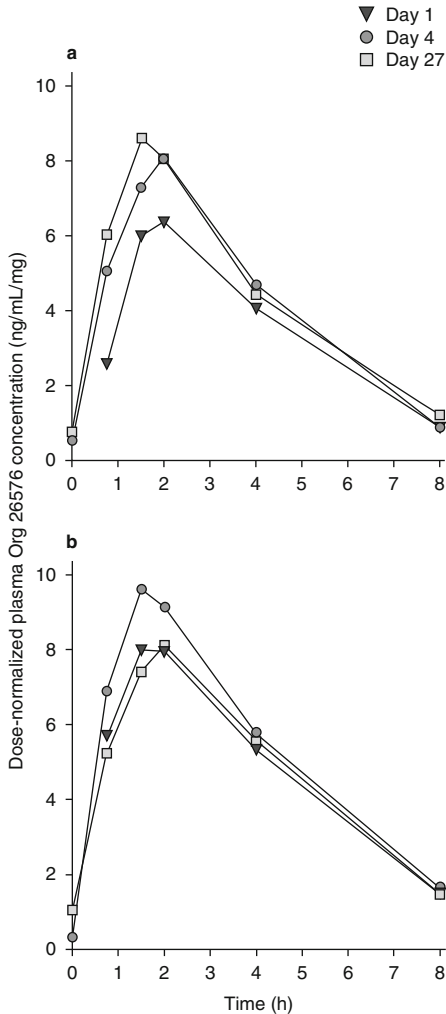
Fig. 3. Mean dose-normalized plasma concentrations of Org 26576 on days 1, 4, and 27 for (**a**) the 100 mg twice-daily dose and (**b**) the 400 mg twice-daily dose in MDD patients.

are based on trial cohorts that included the same multiple-rising-dose approach, starting dose, and regimen; nearly identical titration steps; similar housing conditions; and a similar safety assessment strategy.

In the HV trial, Org 26576 was well tolerated at doses of up to 225 mg bid, while in depressed patients, the MTD was 450 mg bid – twice the maximum dose established in HVs. The patient trial also established that slightly faster titration could be achieved without increasing the number of dose-limiting AEs. The most common AEs associated with the study drug in both populations included dizziness, nausea, and feeling drunk. There were no clinically relevant safety issues associated with Org 26576 at any dose in either population.

In an attempt to learn whether better tolerability in patients could be explained by pharmacokinetic differences between populations, we examined pharmacokinetic parameters for both HVs and patients under highly comparable dosing conditions. Multiple-dose administration of Org 26576 at the same dose level in HVs and MDD patients resulted in pharmacokinetic profiles that were similar overall, though not identical. In both populations, Org 26576 was rapidly absorbed and disposed, with a $t_{\frac{1}{2}}$ not longer than 3 hours. C_{max} and t_{max} values increased subproportionally and underwent a time delay, suggesting a dose-dependent, partially saturated absorption process, although not statistically significant. Further, no regimen effects were observed, indicating linear kinetics over time. The overall exposure of the drug, however, seemed to be somewhat higher and t_{max} values seemed to be greater in patients than in HVs. While the origin of the exposure difference is unclear, food and formulation effects cannot be entirely excluded as underlying causes of the t_{max} difference.

Indeed, one of the principal limitations in this population comparison is the difference between studies under fed/fasted conditions. As is generally the case with early clinical drug development, the phase I and Ib studies were conducted in succession and were designed to build on accumulating animal and human data and other program advancements. The HV study finding of

doses than do HVs, the clinical development plan for the Org 26576 program included both phase I (HVs) and phase Ib (patients diagnosed with MDD) multiple-rising-dose studies. The primary objectives were to establish the MTD and to fully characterize the safety, tolerability, and pharmacokinetics in both populations. Although the trials differed in several design elements, we believe that the data presented here are both comparable and interpretable, given that they

a food effect indicated that C_{max} values were higher in the fasted state than in the fed state, suggesting that the C_{max} 'smoothing' effect of food intake prior to dosing could reduce the risk and/or the frequency of peak-related AEs. Under this assumption, the patient study protocol required all doses to be administered 30 minutes after a meal. However, we do not believe that the food effect on pharmacokinetics fully explains the higher MTD in depressed patients. C_{max} values were comparable between populations at the higher doses, which were the points at which dose-limiting AEs occurred, and the events that drove MTD determination in both studies were not often associated with t_{max}.

Another evolutionary program change was the inclusion of females midway through the patient trial following the finalization of animal reprotoxicity studies. While the HV study included only males, 36% of treated participants in the patient study were female. Although this change was necessary in order to examine safety and tolerability in the broader target population, it raises the question as to whether tolerability differences between the trials can be attributed to sex. However, *post hoc* evaluation showed that exclusion of female subjects from the patient sample did not change the MTD determination at all.

An important difference between trials is how the MTD was defined. In the HV study, the MTD was driven by discontinuations due to AEs. In the patient study, the MTD was defined *a priori* as the dose one step below the MID, where the MID was the dose at which ≥50% of subjects experienced multiple moderate AEs or a single severe AE, or the dose at which a serious AE occurred in one or more subjects. If we applied the HV approach to the patient study, the MTD result would not change. In contrast, if we applied the patient definition to the HV study, an MTD would not be defined, because only one patient experienced multiple moderate AEs. However, we note that patients were much more likely than HVs to continue dosing despite moderate-intensity events. In the HV trial, every subject who reported a moderate AE ultimately discontinued treatment because of the event. In contrast, only one par-

ticipant of nine who experienced moderate AEs in the patient trial discontinued. Whether this is due to better tolerability in general, greater motivation to stay in the treatment unit for lifestyle reasons, the possibility of a treatment effect, differences in the clinical approaches used by different sites and investigators, or some other factor, is difficult to determine. Regardless, the MTD determinations reflect the experience of the participants and the clinical impressions of the investigators, suggesting that the underlying definitions were appropriate for the populations under study.

Although we certainly acknowledge the scientific value of clearly defining the MTD in advance of study implementation, we believe, on the basis of this experience, that clinical judgment has an equally important role. Given the very small sample size included in most tolerability studies, under strict *a priori* criteria small numbers of AEs can drive the MTD determination. When AEs are of questionable relationship to the study drug or are reported by unreliable patients – or, conversely, when safety issues are seen that do not easily fit the MTD criteria – rigid adherence to an *a priori* definition could result in inappropriate dose selection for phase II trials. For this reason, the current phase Ib protocol included provisions for independent unblinded data review if needed to elucidate the tolerability profile, as well as flexibility to allow clinical judgment in the final determination of the MTD.

Whether better patient tolerability can be attributed in this case to alteration of receptor activity by previous antidepressant treatment is an open question. Currently marketed antidepressants are thought to have eventual downstream effects on the glutamate system[35] and on AMPA receptors themselves,[36] suggesting that a prior treatment history could influence tolerability even with this novel compound. However, we note that in the current trial, patients presenting with their first episode of depression (with no prior antidepressant taken in that episode) and those presenting with recurrent depression (and presumably a more robust treatment history) demonstrated very comparable tolerability profiles. Alternative explanations include the possibility

that alteration of receptor activity by depression itself drives better tolerability in patients. Indeed, there is a growing body of evidence suggesting that both glutamate activity[22-24] and AMPA receptor expression[36] are altered in depressed patients. However, the mechanism by which these findings translate into decreased glutamate drug sensitivity remains to be explored.

As a result of this detailed bridging work and further information from animal and human pharmacokinetic/pharmacodynamics modeling, which predicted target levels of AMPA receptor engagement at doses ranging from 100 to 400 mg bid,[37] the upper end of the dose range selected for phase II efficacy trials was significantly higher than the HV MTD. Final dose selection also took into consideration the likelihood that patient tolerability could differ in an outpatient setting, where life demands may mediate the functional impairment associated with drug-related AEs. Here too, patient tolerability data helped to address this question by providing critical information regarding the time of onset, severity, and duration of AEs, and the tendency for specific events to abate over time. The Org 26576 bridging data therefore contributed to confident dose selection for phase II trial planning and, as a result, served the greater purpose of patient and program risk minimization.

Acknowledgments

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