

Featured Article

# A phase 1 clinical trial of the sigma-2 receptor complex allosteric antagonist CT1812, a novel therapeutic candidate for Alzheimer's disease

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## Abstract

**Background:** Elayta (CT1812) is a novel allosteric antagonist of the sigma-2 receptor complex that prevents and displaces binding of A $\beta$  oligomers to neurons. By stopping a key initiating event in Alzheimer's disease, this first-in-class drug candidate mitigates downstream synaptotoxicity and restores cognitive function in aged transgenic mouse models of Alzheimer's disease.

**Methods:** A phase 1, two-part single and multiple ascending dose study was conducted in 7 and 4 cohorts of healthy human subjects, respectively. In part A, healthy, young subjects (<65 years old) received CT1812 doses ranging from 10 to 1120 mg (6:2 active to placebo [A:P] per cohort). In part B, subjects were administered 280, 560, and 840 mg once daily for 14 days (8:2 A:P per cohort). An elderly cohort, aged 65-75 years, was dosed at 560 mg once daily for 14 days (7:2 A:P). Serum concentrations of CT1812 in part B were measured on day 3 and 14 and cerebrospinal fluid concentrations on day 7 or 9. Cognitive testing was performed in the healthy elderly cohort at baseline and at day 14 of treatment.

**Results:** Treatment with CT1812 was well tolerated in all cohorts. Adverse events were mild to moderate in severity and included headache and GI tract symptoms. Plasma concentrations of drug were dose proportional across two orders of magnitude with minimal accumulation over 14 days. Cognitive scores in the healthy elderly cohort were similar before and after treatment.

**Conclusions:** CT1812 was well tolerated with single dose administration up to 1120 mg and with multiple dose administration up to 840 mg and 560 mg in healthy young and healthy elderly subjects, respectively. CT1812 is currently being studied in early phase 2 trials in patients with Alzheimer's disease.

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## Keywords:

CT1812; Alzheimer's disease (AD); Amyloid beta (A $\beta$ ); Safety; Pharmacokinetics; Clinical trial; Therapy; Single ascending dose (SAD); Multiple ascending dose (MAD); Cerebrospinal fluid (CSF)

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## 1. Introduction

Alzheimer's disease (AD) afflicts approximately 6 million people in the United States [1], a number that is expected to more than double by 2050 [2]. As the sixth leading cause of death in the United States [3], disease-modifying therapies for AD continue to be a huge unmet medical need. Such therapeutics have potential to substantially reduce morbidity, mortality, and health care expenditures for patients with AD (total 2018 payments estimated at \$277B) [1] as well as lessen disease burden for families and caregivers.

Cognition Therapeutics Inc. (CogRx) has discovered a highly brain penetrant, first-in-class drug, Elayta (CT1812), that displaces A $\beta$  oligomers (A $\beta$ Os) bound to neuronal receptors at synapses. CT1812, a lipophilic isoindoline formulated as a fumarate salt, works similarly to a related class of compounds which have high affinity and specificity for the sigma-2 receptor complex, a key regulator of oligomer receptors [4,5]. Binding allosterically to the sigma-2 receptor complex, this family of molecules destabilizes the A $\beta$ O binding site, increasing the off-rate of A $\beta$ Os, which are cleared into the cerebrospinal fluid (CSF). In preclinical models, CT-family compound receptor occupancy at or exceeding 80% prevents downstream synaptotoxicity and restores memory in aged transgenic mouse models of AD [4,5].

There are no approved AD therapeutics specifically targeting A $\beta$ Os, although they are often regarded the most neurotoxic structural form of the A $\beta$  protein [6,7]. Symptomatic treatments that are available for AD only transiently slow cognitive decline [8], and prior clinical investigation of small molecule inhibitors and modulators of the  $\gamma$ -secretase and  $\beta$ -secretase enzymes that cut A $\beta$  from its full-length precursor have not shown significant clinical efficacy [9–11]. Monoclonal antibody approaches targeting A $\beta$  clearance also remain to be proven [12–14].

This article describes a first-in-man, double-blind, placebo-controlled phase 1 clinical study to test the safety, tolerability, and pharmacokinetics of CT1812 in healthy subjects.

## 2. Materials and methods

### 2.1. Study design

A two-part phase 1, randomized, double-blind, placebo-controlled study of CT1812 was conducted in healthy young and elderly subjects: a single ascending dose (SAD)/food-effect study (part A) and a multiple ascending dose (MAD) study (part B). The primary endpoint was safety and tolerability. Secondary objectives included plasma pharmacokinetics (PK) in parts A and B. CSF samples were also collected in the MAD study for analysis of PK and PD biomarkers. Cognitive testing was included in the elderly cohort in part B as part of the safety assessment. Safety was assessed after completion of each cohort before ascending to the next dose level. The SAD/food-effect and MAD studies were conducted at Nucleus Network, Royal Alfred Hospital, Melbourne, Australia.

Part A was a single ascending dose cohort study in which healthy, young subjects (less than 65 years old) received one dose of study drug in the morning after an overnight fast. Cohort dosing started at 10 mg and increased to 30 mg, 90 mg, 180 mg, 450 mg, and 1120 mg in subsequent cohorts. Six drug-treated and two placebo-treated subjects were randomized in each cohort. A seventh cohort of six subjects each received a single 90 mg dose of drug 30 min after a meal. After completion of all safety assessments and blood draws for PK analyses, subjects were discharged on day 3.

In part B, healthy young subjects in each cohort received the same dose once daily for 14 days after overnight fasting. Cohort dosing started at 280 mg, followed by 560 mg and 840 mg in subsequent cohorts. In each cohort, eight subjects received drug and two received placebo. A fourth cohort of healthy elderly subjects ( $\geq 65$  years old) received a 560 mg dose vs. placebo daily for 14 days (seven active, two placebo).

Subjects were dosed in the morning with 240 mL of water after an 8-hour fast, and remained in a semireclined position for 1 hour and fasting for 2 hours after administration, except for the fed cohort in part A. Subjects in each MAD cohort were confined to the clinical facility from check-in on day 0 until the pharmacokinetic sample was collected on day 16, 48 hours after administration of the last dose on day 14. Subjects returned to the clinical facility for follow-up visits on days 24 and 35.

### 2.2. Participants

Healthy male and female subjects (determined by history, examination, and laboratory) were enrolled, with young subjects aged 18 to 64 years and elderly subjects aged  $\geq 65$  and  $\leq 75$  years. Female subjects must have been postmenopausal or surgically sterile. A history of acute/chronic hepatitis B or C and/or serology consistent with being a carrier of hepatitis B or HIV infection was exclusionary. All prescription, over-the-counter, and herbal medications were prohibited within 10 days of study dosing (with the exception of nasal steroids, ocular medications, and paracetamol  $\leq 1000$  mg/day at the discretion of the investigator). Any contraindication to undergoing a lumbar puncture was also exclusionary for subjects undergoing CSF collection in part B.

The study protocol was approved by the Human Research Ethics Committee at the Alfred Hospital, Melbourne, Australia, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent before participating.

### 2.3. Pharmacokinetic assessments

In part A, blood draws for assessment of PK parameters occurred before dose and at 15, 30, 45, 60, and 90 minutes after dose, as well as at 2, 3, 4, 8, 12, 24, 36, and 48 hours after dose. Subjects in cohorts 5 and 6 had an additional sample drawn 72 hours after dosing. In part B, blood samples for plasma PK analysis were taken on day 1 before dose and at

2 hours after dose; on day 3 before dose and at 15, 30, and 45 minutes and 1, 2, 3, 4, 8, 12, and 24 hours after dose; on days 4, 6, 8, and 10 before dose and at 1.5 hours after dose and after the final dose on day 14 before dose and 15, 30, and 45 minutes and 1, 2, 4, 8, 12, 24, 36, and 48 hours after dose. CT1812 concentrations in plasma samples were quantified using a validated liquid chromatography method with tandem mass spectrometric detection.

Plasma concentrations for each dose level following single and repeated oral doses of CT1812 were used to determine PK parameters using noncompartmental methods, including:  $C_{max}$ —maximum concentration,  $T_{max}$ —time to maximum observed plasma drug concentration,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $AUC_{0-24}$  (after multiple dosing)—area under the curve,  $CL/F$ —apparent drug clearance after a single oral dose,  $CL_{ss}/F$ —apparent drug clearance after an oral dose at steady-state,  $\lambda_z$ —terminal phase rate constant,  $t_{1/2}$ —terminal half-life, and time to reach steady state.

In part B, CSF samples (approximately 10 mL) were drawn from the 560 mg and 840 mg healthy young cohorts with a single lumbar puncture on day 7 or 9 of treatment at 1.5 hr after the morning dose (approximate plasma  $T_{max}$ ).

#### 2.4. Cognitive testing

The Alzheimer's Disease Assessment Scale–Cognition Subscale and a cognitive battery (including the category fluency test, controlled word association test, WMS-R digit span, digit symbol substitution test, and Rey Auditory Verbal Learning Test) were administered to subjects in the elderly cohort at the baseline and on day 14.

#### 2.5. Safety assessments

Safety variables, including incidence of adverse events (AEs), vital signs, clinical laboratory findings, 12-lead electrocardiographs, physical examination, and affective and cognitive measures (part B only), were summarized for all subjects who received study drug.

#### 2.6. Statistical analysis

No formal statistical determination of cohort size was conducted; however, the number of subjects used is considered sufficient to explore safety in an early clinical study. Pharmacokinetic parameters of plasma CT1812 were summarized by treatment, using descriptive statistics.

The analysis included the effect of food on bioavailability (part A, cohort 7 fed dose compared with cohort 3 subjects administered the same dose in the fasted state) and the effect of age on CT1812 PK (part B, cohort 5 subjects aged at least 65 years [elderly] compared with cohort 2 subjects aged up to 64 years [young]). These were assessed by analysis of variance of log-transformed  $C_{max}$ ,  $AUC_{0-24}$ ,  $AUC_{0-48}$ , and/or  $AUC_{0-inf}$ , using a model with factors for treatment (fed status or age [young vs. elderly] status) and subject within sequence. Treatment mean differences and 90% confidence intervals of

the log-transformed PK parameters were back-transformed to present the geometric least-squares means ratios and 90% confidence limits. Determination of time to steady state for CT1812 in part B was performed using Helmert contrasts in analysis of variance of predose trough concentrations on days 3, 4, 6, 7, 8, 9, 10, and 14, and the concentration at 24 hours after dose on day 15. Dose proportionality was investigated using the power model, determined by regression of log-transformed parameters and dose level, parameter =  $\alpha * dose^{\beta}$ .

### 3. Results

#### 3.1. Demographics and disposition of subjects

A total of 93 subjects participated in the study. In the SAD phase, a total of 54 subjects were enrolled and randomized to treatment. Subjects were predominantly male (70%) and Caucasian (85%), with a median age of 26 years (range 19-55 years) (Supplementary Table 1). In the MAD phase, a total of 39 subjects were enrolled and randomized to treatment. In the 3 young cohorts, subjects were predominantly male (77%) and Caucasian (87%), with a median age of 28.5 years (range 19-60 years). In the elderly cohort, 9 subjects were treated (7 CT1812, 2 placebo), as one subject withdrew before dosing. The elderly subjects were all Caucasian and 55% male, with a median age of 69 (range 64 to 73) years (Supplementary Table 2).

#### 3.2. Pharmacokinetic results

In part A (SAD), median CT1812  $T_{max}$  values in plasma peaked at 0.88 to 1.5 hours (Fig. 1, Table 1).  $C_{max}$  and AUC increased slightly greater than dose proportionally after single dose administration from 10 mg to 1120 mg. Consistent with this, the clearance value  $CL/F$  showed a slight but steady downhill trend with increasing dose (Table 1). The apparent mean half-life ranged from 11.1 to 14.0 hours. After administration of a single 90 mg oral dose, the geometric least-squares mean for  $C_{max}$ ,  $AUC_{0-48h}$ , and  $AUC_{0-inf}$  were approximately 40%, 20%, and 20% lower, respectively, at a dose of 90 mg under fed conditions compared with those observed in the fasted state. These differences were not considered clinically significant.

In part B (MAD), CT1812  $T_{max}$  values in plasma peaked at 0.88 to 2.0 hours (Fig. 1, Table 1). The PK parameters that reflect systemic exposure ( $C_{max}$  and AUC) increased slightly greater than dose proportionally from 280 to 840 mg, which was reflected by a slight but steady downhill trend in  $CL_{ss}/F$  with increasing dose (Table 1). Steady state was reached by approximately day 3 or day 4 of once daily dosing. Average terminal half-life was approximately 12 hours at steady state, which is consistent with that observed after a single dose in part A.

On day 3 of part B, geometric least-squares mean  $C_{max}$  and  $AUC_{0-24h}$  values in the aged cohort (>65 years old) that received a daily dose level of 560 mg CT1812 were approximately 1.7- and 1.34-times higher compared with

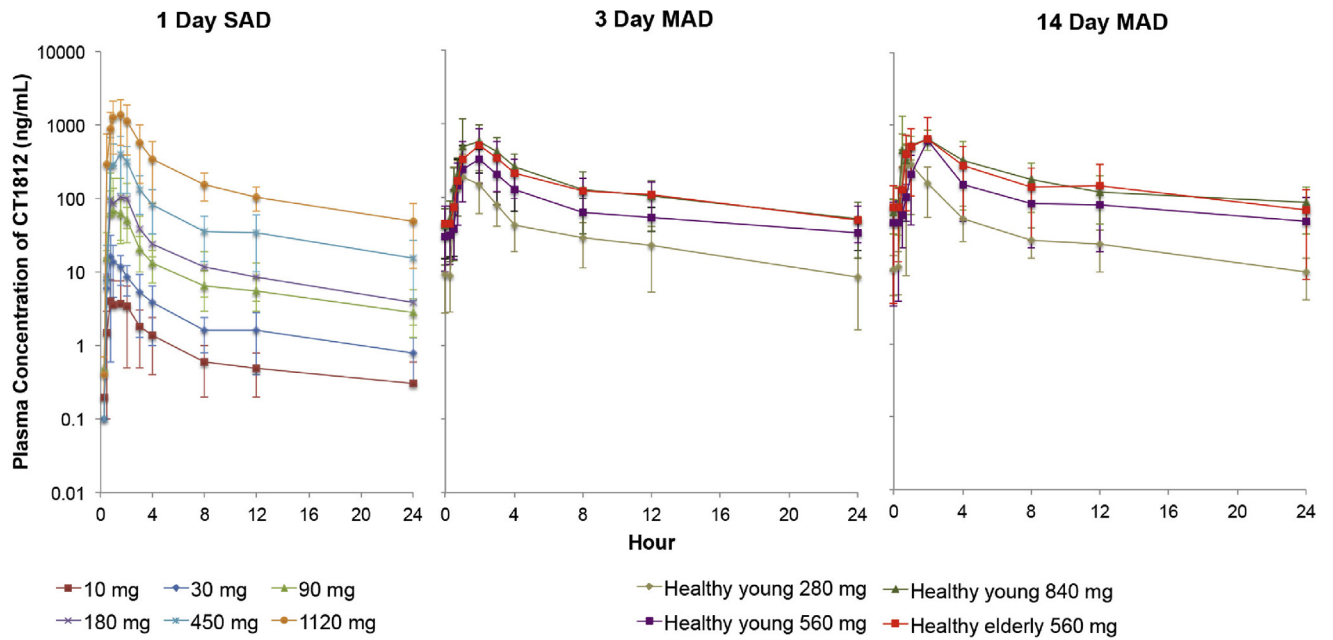


Fig. 1. Plasma concentrations of CT1812 following a single oral dose (SAD) or after Q.D. dosing for 3 or 14 days (MAD) in healthy young and elderly subjects. Plasma concentration increases were slightly greater than proportional with dose and exhibited minimal accumulation with repeat dosing. Abbreviations: SAD, single ascending dose; MAD, multiple ascending dose.

Table 1  
Mean plasma pharmacokinetic parameters

SAD CT1812 dose (mg)	Dose day	C <sub>max</sub> ng/mL (CV%)*	T <sub>max</sub> <sup>†</sup> hr (range)	AUC <sub>0-inf</sub> hr•ng/mL (CV%)	t <sub>1/2</sub> hr <sup>‡‡</sup> (CV%)	CL/F (CV%)
Fasted						
10 mg (n = 6)	Day 1	5.07 (82%)	1.50 (0.50–2.00)	30.6 <sup>‡</sup> (67%)	12.0 <sup>‡</sup> (39%)	662 <sup>#</sup> (118%)
30 mg (n = 6)		19.5 (68%)	0.88 (0.75–1.50)	77.2 (49%)	14.0 (29%)	505 (59%)
90 mg (n = 6)		109 (46%)	1.25 (0.75–2.00)	305 (43%)	12.1 (25%)	340 (38%)
180 mg (n = 6)		161 (59%)	1.25 (0.75–2.00)	478 (45%)	11.1 (31%)	460 (50%)
450 mg (n = 6)		504 (69%)	1.50 (0.75–2.00)	1752 (65%)	12.2 (14%)	443 (87%)
1120 mg (n = 6)		1462 (54%)	1.50 (1.05–2.00)	6316 (50%)	11.8 (29%)	228 (59%)
Fed						
90 mg (n = 6)		81.7 (94%)	1.50 (0.50–3.07)	261 (58%)	11.6 (37%)	445 (55%)
MAD CT1812 dose (mg)	Dose day	C <sub>max</sub> ng/mL (CV%)	T <sub>max</sub> <sup>†</sup> hr (range)	AUC <sub>0-24h</sub> hr•ng/mL (CV%)	t <sub>1/2</sub> hr <sup>‡‡</sup> (CV%)	CL <sub>ss</sub> /F (CV%)
Age up to 64 years						
280 mg (n = 8)	Day 3	238 (77%)	1.50 (1.00–2.00)	851 (62%)	8.97 <sup>§</sup> (19%)	
	Day 14	431 (95%)	0.88 (0.50–2.00)	1063 (59%)	12.0 (35%)	387 (75%)
560 mg (n = 8)	Day 3	407 (48%)	2.00 (0.75–3.03)	1943 (41%)	8.56 <sup>¶</sup> (4.0%)	
	Day 14	651 (102%)	2.00 (1.00–2.00)	2811 (88%)	12.3 (20%)	296 (56%)
840 mg (n = 7)	Day 3	813 (79%)	2.00 (1.00–4.00)	3612 (68%)	9.39 <sup>#</sup> (13%)	
	Day 14	991 (84%)	2.00 (0.75–4.00)	4989 (53%)	8.93 <sup>§</sup> (25%)	212 <sup>††</sup> (48%)
Age at least 65 years						
560 mg (n = 7)	Day 3	567 (57%)	2.00 (1.00–4.00)	3330 (49%)	8.83 <sup>**</sup> (27%)	
	Day 14	853 (64%)	1.00 (0.75–4.00)	4447 (82%)	12.8 (20%)	169 <sup>††</sup> (40%)

Abbreviations: SAD, single ascending dose; MAD, multiple ascending dose.

\*CV, Coefficient of variation.

<sup>†</sup>Median.

<sup>‡</sup>n = 5.

<sup>§</sup>n = 6.

<sup>¶</sup>n = 2.

<sup>#</sup>n = 5.

<sup>\*\*</sup>n = 4.

<sup>††</sup>n = 7.

<sup>‡‡</sup>t<sub>1/2</sub> values on day 3 were determined over a maximum timeframe of 24 hours after dose.

subjects under 65 years of age, respectively. The trend continued to day 14 (steady state), with the  $C_{max}$  and  $AUC_{0-24h}$  in the aged cohort ( $\geq 65$  years old) exceeding that of younger subjects ( $\leq 64$  years) by 1.6- and 1.5-times, respectively. CT1812 was measurable in CSF at 1.5 hr after dose on day 7 to day 9 in all subjects who received CT1812 daily at dose levels of 560 mg and 840 mg. Mean ( $\pm$ SD) levels of CT1812 in CSF were 8.0 ( $\pm 4.3$ ) and 23.3 ( $\pm 15.6$ ) ng/mL for 560 mg and 840 mg, respectively (Fig. 2).

### 3.3. Safety results

#### 3.3.1. Safety summary for SAD phase

Treatment-emergent AEs were reported for 18 of 42 subjects (43%) after single dose administration of CT1812 and 2 of 12 subjects (17%) after administration of placebo (Table 2). There were no deaths or other serious AEs.

Most AEs (23 of 30, 77% of all AEs) were classified as mild in severity, with 7 AEs (23%) classified as moderate in severity (catheter site swelling, vomiting, nausea, vaccination site reaction, dysmenorrhea, and headache [2 AEs]). No AEs were classified as severe.

There were no subjects with clinically significant laboratory results in the SAD part of the study. All clinical laboratory results outside of the normal range were deemed not clinically significant. There were no marked differences by treatment (CT1812 vs placebo) or apparent dose-dependent trends in clinical laboratory results. No electrocardiograph parameters or changes were assessed as clinically significant.

#### 3.3.2. Safety summary for MAD phase

Treatment-emergent AEs were reported for 25 of 31 subjects (81%) after multiple dose administration with CT1812

and 6 of 8 subjects (75%) after multiple dose administration of placebo (Table 3). One serious AE was recorded in part B (MAD); a subject receiving 840 mg CT1812 was hospitalized for a respiratory picornavirus infection deemed unrelated to study treatment. There were no deaths.

A total of 82 AEs were reported, with most (67 of 82, 82% of all AEs) classified as mild in severity, 14 AEs (17%) as moderate in severity, and one (1%) as severe. Qualitatively, there was no trend of increasing AE frequency with dose, with the exception of vomiting, where the two instances with active drug occurred at the 840 mg dose for an incidence of 25%. One subject in the placebo group experienced vomiting (17%).

Four subjects in the MAD study showed an increase in liver function tests below  $3\times$  the upper limit of normal (including one subject on placebo). One subject developed a rash while on study drug, which showed improvement after discontinuing CT1812. There were no marked differences by treatment (CT1812 vs placebo) or apparent dose-dependent trends in clinical laboratory results. No electrocardiograph parameters or changes were assessed as clinically significant.

### 3.4. Cognitive testing

To ensure there were no deleterious effects on cognitive function in subjects given CT1812, cognitive testing was performed on the healthy elderly cohort receiving 560 mg of CT1812 per day before initiation of dosing and at the end of the study. Alzheimer's Disease Assessment Scale–Cognition Subscale scores at day zero were  $10.23 \pm 2.57$  (SD) and were similar after day 14 of dosing ( $10.03 \pm 4.24$ ). Results were also similar between day zero and day 14 on the other cognitive tests (Supplementary Table 3).

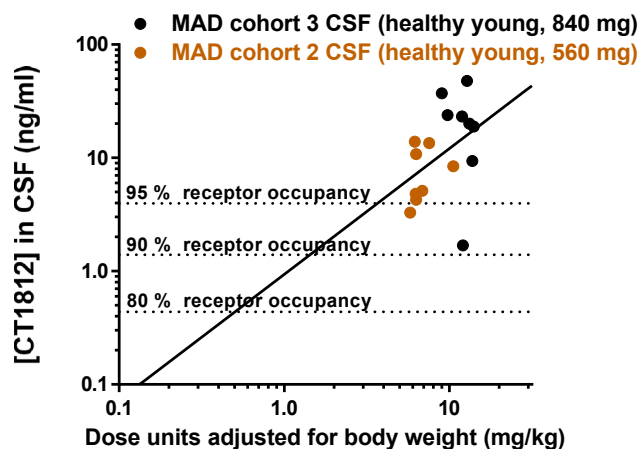


Fig. 2. CT1812 concentrations in cerebrospinal fluid (CSF) increased in a dose-dependent manner. In the 560 mg–840 mg dose range, average CSF concentrations (at the approximate plasma  $T_{max}$ , 1.5 hr after dose) were equivalent to those in mice that have a 97–98% receptor occupancy concentration in the brain. Horizontal lines indicate projected receptor occupancy based on concentration and receptor occupancy determined in preclinical mouse AD models. Abbreviations: AD, Alzheimer's disease; MAD, multiple ascending dose.

## 4. Discussion

CT1812 was safe and well tolerated in healthy subjects over the dose range tested. In both parts (SAD and MAD), AEs were generally mild and included headache and GI disturbances. Plasma concentrations of drug increased slightly greater than dose proportionally across two orders of magnitude in part A, and across a three-fold increase in dose in part B. CT1812 levels assayed in CSF at peak plasma concentrations revealed dose-dependent increases in CT1812.

CT1812 levels in the CSF confirm that CT1812 penetrates the blood-brain barrier in humans, and extrapolations from mouse studies suggest that human doses administered once daily result in target concentrations that exceed the expected minimum concentration required to improve memory in mice (i.e., the concentration associated with  $>80\%$  receptor occupancy). At the 560 mg dose, CSF CT1812 levels reached those associated with 97–98% receptor occupancy in transgenic mouse brain [4,5]. At the 840 mg dose, CSF levels reached those associated with 98% receptor occupancy. Although no differences in CSF CT1812 concentrations are

Table 2  
Summary of treatment-emergent adverse events in the SAD study

Preferred terms reported in more than 2 subjects	Number of subjects (%) with treatment-emergent AE										
	Fasted CT1812						Fed CT1812		Placebo		All subjects (n = 54)
	10 mg (n = 6)	30 mg (n = 6)	90 mg (n = 6)	180 mg (n = 6)	450 mg (n = 6)	1120 mg (n = 6)	90 mg (n = 6)	Total active (n = 42)	pooled (n = 12)		
All TEAEs	2 (33%)	4 (67%)		2 (33%)	4 (67%)	4 (67%)	2 (33%)	18 (43%)	2 (17%)	20 (37%)	
Nervous system disorders											
Headache		3 (50%)			1 (17%)	1 (17%)	1 (17%)	6 (14%)	1 (8%)	7 (13%)	
Gastrointestinal disorders											
Nausea		1 (17%)			2 (33%)	3 (50%)		6 (14%)		6 (11%)	

Abbreviations: SAD, single ascending dose; TEAEs, treatment-emergent adverse events.

expected between patients with AD and age-matched cognitively normal individuals, future confirmatory studies will measure CSF levels of CT1812 in patients with AD. One additional cohort was given 90 mg of CT1812 after a meal to compare PK in the fed vs. fasted state, and there was no significant difference in CT1812 exposure based on AUC.

CT1812 is a novel, brain penetrant small molecule antagonist that prevents binding of A $\beta$ Os to neuronal receptors. This drug candidate was safe and well tolerated in healthy subjects in this phase 1 trial, mitigates downstream synaptotoxicity, and restores memory to normal in aged transgenic mouse models of AD [4,5]. CT1812 prevents and displaces A $\beta$ Os through selective allosteric antagonism of the sigma-2 receptor complex, which, in turn, regulates the affinity of A $\beta$ Os to their receptor protein [4,5]. CT1812 decreases the affinity of bound A $\beta$ Os to their receptor, causing their release and subsequent clearance from the brain. Importantly, this allosteric inhibition of binding by CT1812 is not likely to be overcome by high A $\beta$ O concentrations in

later stages of the disease, as might occur with a competitive antagonist. As A $\beta$ Os are likely neurotoxic throughout the course of AD, CT1812 may be effective in patients with symptomatic AD, whereas other therapeutics may be less effective in treating established disease.

AD is a complex disease that likely will require multitargeted treatment [15]. Some current experimental approaches may eventually prove to be effective. However, these approaches will likely not completely ameliorate the negative effects of increasing concentrations of toxic A $\beta$ Os that likely contribute to ongoing disease progression. CT1812, with its unique ability to decrease the affinity of bound A $\beta$ Os to their receptors and clear them from the brain, may have potential to address this therapeutic gap. Because of its unique mechanism of action (by displacing oligomers and preventing their rebinding), CT1812 could shield synapses, allowing fibril-clearing therapeutics to operate more effectively, potentially at lower doses with fewer side effects and be effective alone and throughout the disease course, from early

Table 3  
Summary of treatment-emergent adverse events in the MAD study

Preferred terms reported in more than 2 subjects	Number of subjects (%) with at least one treatment-emergent AE								
	Age $\leq$ 64 years				Age $\geq$ 65 years		Total		
	280 mg (n = 8)	560 mg (n = 8)	840 mg (n = 8)	Placebo (n = 6)	560 mg (n = 7)	Placebo (n = 2)	Total Active (n = 31)	Total Placebo (n = 8)	Grand Total (n = 39)
All TEAEs	7 (88%)	7 (88%)	6 (75%)	5 (83%)	5 (71%)	1 (50%)	25 (81%)	6 (75%)	31 (79%)
Infections and infestations									
Upper respiratory tract infection	5 (63%)	1 (13%)	2 (25%)	2 (33%)			8 (26%)	2 (25%)	10 (26%)
Nervous system disorders									
Dizziness	1 (13%)		1 (13%)		1 (14%)		3 (10%)		3 (8%)
Headache	2 (25%)	1 (13%)	4 (50%)	1 (17%)	3 (43%)		10 (32%)	1 (13%)	11 (28%)
Gastrointestinal disorders									
Dyspepsia	1 (13%)	1 (13%)	1 (13%)				3 (10%)		3 (8%)
Nausea	1 (13%)		1 (13%)	1 (17%)			2 (6%)	1 (13%)	3 (8%)
Vomiting			2 (25%)	1 (17%)			2 (6%)	1 (13%)	3 (8%)
Musculoskeletal and connective tissue disorders									
Back pain			1 (13%)	1 (17%)	1 (14%)		2 (6%)	1 (13%)	3 (8%)
General disorders and administration site conditions									
Catheter site phlebitis		1 (13%)	1 (13%)	1 (17%)			2 (6%)	1 (13%)	3 (8%)
Injury, poisoning and procedural complications									
Procedural pain		4 (50%)	2 (25%)	2 (33%)			6 (19%)	2 (25%)	8 (21%)

Abbreviations: MAD, multiple ascending dose; TEAEs, treatment-emergent adverse events.

to more advanced stages of illness involving substantial synaptic/neuronal impairment. We are currently conducting phase 2 clinical trials to test this.

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### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.trci.2018.11.001>.

### RESEARCH IN CONTEXT

1. Systematic review: Comprehensive searches of PubMed and the clinical trials database [clinicaltrials.gov](https://clinicaltrials.gov) were performed for all relevant key words, individually and in combination. To our knowledge CT1812 is the first selective sigma-2 receptor complex allosteric antagonist to reach clinical testing in humans.
2. Interpretation: The results presented in this article indicate that CT1812 was safe and well tolerated in healthy young and elderly cohorts, drug concentrations and exposure increased in an approximately dose proportional manner, in the fed and fasted state, and drug was detectable in cerebrospinal fluid at levels exceeding the expected therapeutic concentration based on preclinical models.
3. Future directions: This drug candidate is suitable for advancement to later stages of clinical development. CT1812 is currently being studied in early phase 2 trials of patients with Alzheimer's disease.

### References

- [1] 2018 Alzheimer's disease facts and figures. *Alzheimer's Dement* 2018;14:367–429.
- [2] Hebert LE, Beckett LA, Scherr PA, Evans DA. Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. *Alzheimer Dis Assoc Disord* 2001; 15:169–73.
- [3] Murphy SL, Xu J, Kochanek KD, Curtin SC, Arias E. National Vital Statistics Reports Volume 66, Number 6, November 27, 2017. Available at: [https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66\\_06.pdf](https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_06.pdf). Accessed June 18, 2018.
- [4] Izzo NJN, Staniszewski A, To L, Fa M, Teich AFAF, Saeed F, et al. Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers I: Abeta 42 oligomer binding to specific neuronal receptors is displaced by drug candidates that improve cognitive deficits. *PLoS One* 2014; 9:e111898.
- [5] Izzo NJN, Xu J, Zeng C, Kirk MJ, Mozzoni K, Silky C, et al. Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers II: Sigma-2/PGRMC1 receptors mediate Abeta 42 oligomer binding and synaptotoxicity. *PLoS One* 2014;9:e111899.
- [6] Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* 2016;8:595–608.
- [7] Viola KL, Klein WL. Amyloid beta oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis. *Acta Neuropathol* 2015; 129:183–206.
- [8] Karran E, Mercken M, De Strooper B, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* 2011; 10:698–712.
- [9] De Strooper B, Chávez Gutiérrez L. Learning by failing: ideas and concepts to tackle  $\gamma$ -secretases in Alzheimer's disease and beyond. *Annu Rev Pharmacol Toxicol* 2015;55:419–37.
- [10] Toyn JH, Thompson LA, Lentz KA, Meredith JE, Burton CR, Sankaranarayanan S, et al. Identification and preclinical pharmacology of the  $\gamma$ -secretase modulator BMS-869780. *Int J Alzheimers Dis* 2014;2014:431858.
- [11] Ghidoni R, Albertini V, Squitti R, Paterlini A, Bruno A, Bernardini S, et al. Novel T719P A $\beta$ PP mutation unbalances the relative proportion of amyloid- $\beta$  peptides. *J Alzheimer's Dis* 2009; 18:295–303.
- [12] Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014;370:322–33.
- [13] Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* 2014;370:311–21.
- [14] Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces A $\beta$  plaques in Alzheimer's disease. *Nature* 2016;537:50–6.
- [15] Frautschy SA, Cole GM. Why pleiotropic interventions are needed for Alzheimer's disease. *Mol Neurobiol* 2010;41:392–409.