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A Phase 1 Safety Trial of the Aβ Oligomer Receptor Antagonist CT1812

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ABSTRACT

Background: CT1812 is a first in class therapeutic currently in Phase 1/2 testing in AD patients (ClinicalTrials.gov Identifier: NCT02907567) that selectively displaces Aβ oligomers from synaptic receptor sites and clears them from the brain into the cerebrospinal fluid, restoring cognitive performance to normal in aged transgenic mouse models of AD. In prior clinical studies, CT1812 was safe and well tolerated with multiple doses up to 560 mg in healthy elderly volunteers. CSF concentrations observed with multiple dosing of CT1812 indicate that they exceed the expected minimum target concentrations needed to improve memory in AD patients. To further the clinical development of CT1812 a study was conducted to evaluate potential drug-drug interactions of CT1812 involving effects on cytochrome P450 (CYP) isoenzymes.
Methods: A Phase 1, single-center, open-label, single-sequence drug-drug interaction study was performed to evaluate the effect CT1812 on the pharmacokinetics of 4 CYP probe drugs (tolbutamide, midazolam, dextromethorphan and omeprazole) given before and following administration of 6 consecutive daily oral doses of 560 mg CT1812 (steady state).
Results: Small increases (<2 fold) in dextromethorphan and dextrorphan exposure were observed after co-administration of dextromethorphan with steady-state CT1812, consistent with a weak inhibitory interaction of CT1812 on the CYP2D6 enzyme. Small decreases (<50%) in midazolam exposure were observed after co-administration of midazolam with steady-state CT1812, consistent with weak induction of the CYP3A4 enzyme by CT1812. There were no clinically meaningful interactions between CT1812 and omeprazole (CYP2C19) or tolbutamide (CYP2C9).
Conclusions: Based on the weak drug-drug interactions observed in this study between steady-state CT1812 and standard CYP probe drugs, clinically meaningful implications are unlikely. These results permit fewer medication exclusions in AD current and future clinical trials including the planned Phase 2 trial in mild to moderate AD.

METHODS

Study Design
- This was a phase 1, single-center, open-label, single-sequence study
- CT1812 was administered to healthy volunteers before and after administration of sensitive/specific CYP450 enzyme substrates to assess any potential interactions
- A 560 mg dose of CT1812 was selected as it is exceeds (~6-8 fold) the expected minimum target concentrations needed to improve memory in AD patients
- 14 subjects received the same treatment regimen: a single oral dose of each of the probe drugs on Day -2 and Day 6 administered as a "drug cocktail: CYP2C19 (omeprazole), CYP2C9 (tolbutamide), CYP2D6 (dextromethorphan), and CYP3A4/5 (midazolam)
- CT1812 fumarate 712 mg (equivalent to 560 mg CT1812 free base) was administered on 6 consecutive daily doses of between Days 1-6
- A pharmacokinetic profile of all probe drugs was generated pre- and post multiple dosing of CT1812

Inclusion Criteria
- Non-smoking males and females, between the ages of 18 and 55 years
- In good health as determined by medical history, physical exam, laboratory examinations, ECG, and vital signs
- BMI between 18 and 35 kg/m^2 inclusive
- Females either post-menopausal, surgically sterile, or using an acceptable means of birth control

Exclusion Criteria
- Known hypersensitivity to any of the 4 probe drugs
- An absence of one functional allele for CYP2D6, CYP2C9, or CYP2C19 at screening
- Any chronic medical condition
- Clinically significant abnormality in screening laboratory tests
- Use of any prescription, over-the-counter or herbal medications within 14 days prior to study dosing, or 30 days for any medications known to induce/inhibit the studied CYP450 enzymes
- Use of an investigational drug within 30 days or 5 half-lives prior to dosing in this study

RESULTS

- The 15 subjects enrolled into the study included 10 male subjects (66.7%) and 5 female subjects (33.3%) of mean age 36.9 years (range, 25-55 years). Eight subjects were white (53.3%), 7 subjects were black/African American (46.7%), and 1 subject was an American Indian or Alaska native (6.7%). The majority of subjects (86.7%, 13 of 15) were not of Hispanic or Latino ethnicity. Mean BMI was 26.49 kg/m^2. One subject withdrew after a single dose of CT1812, and therefore is not included in PK analysis.
- A weak drug interaction was observed between steady-state CT1812 and midazolam 4 mg (CYP3A4/5 probe). Midazolam AUC_{last} and the AUC_{last} ratio (parent to metabolite) decreased by 24% and 28%, respectively, when midazolam 4 mg was taken with steady-state CT1812 than when midazolam was taken alone
- A weak drug interaction was observed between steady-state CT1812 and dextromethorphan 50 mg (CYP2D6 probe), as indicated by a 1.75-fold and 2-fold increase in dextromethorphan AUC_{last} and C_{max}, respectively, following the combination treatment relative to dextromethorphan alone; however, the dextromethorphan/dextrorphan AUC_{last} ratio was similar between treatments

CONCLUSIONS

- In healthy volunteers, CT1812 has a weak enzyme inductive effect on the CYP3A4/5 enzyme, and a weak inhibitory influence on the CYP2D6 enzyme
- Both are clinically insignificant
- As in previous trials, CT1812 was well tolerated with no notable safety signals

References:
- Guidance for Industry: Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. US Food and Drug Administration, 2012.
- Izzo NJ, 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 10: e0111898, 2014.
- Izzo NJ, 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 10: e0111899, 2014.
- Yuede, et al. Rapid in vivo measurement of β-amyloid reveals biphasic clearance kinetics in an Alzheimer's mouse model. J. Exp. Med. 213: 677–85, 2016.

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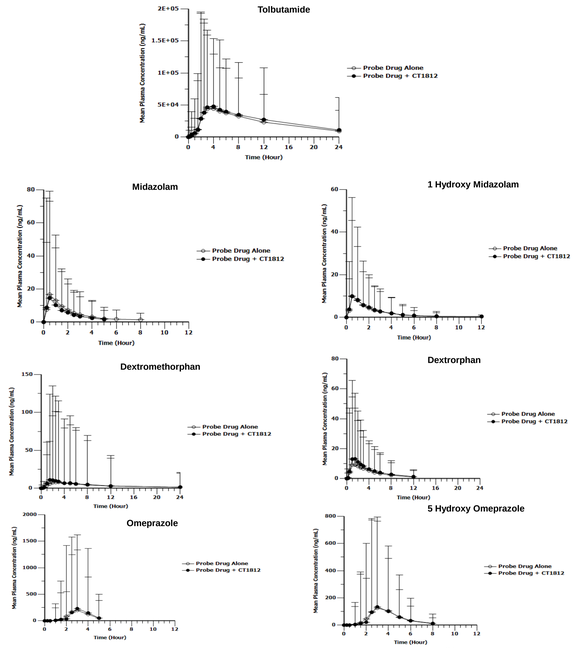
CT1812 exhibits weak influence on CYP probe drug plasma concentrations



Classification of In Vivo Inhibitors of CYP Enzymes[1]

CYP Enzymes	Strong Inhibitors[2]	Moderate inhibitors[3]	Weak inhibitors[4]
	≥ 5-fold increase in AUC or > 80% decrease in CL	≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL

Mean Plasma Concentration vs. Time Curves for CYP Probe Drug Alone and in the Presence of CT1812 at Steady State; Linear Scale (mean + standard deviation)

CT1812 causes weak inhibition of CYP2D6 and weak induction of CYP3A4/5

Pharmacokinetic Parameter	LS Geometric Means: Tolbutamide 500 mg (Reference) N = 15	LS Geometric Means: Tolbutamide 500 mg + Steady-State CT1812[a] (Test) N=14	Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	642036.2[c]	680103.3[d]	105.9	97.6 – 114.9
AUC_{last} (ng·h/mL)	565632.6	612068.8	108.2	102.1 – 114.6
C_{max} (ng/mL)	50640.1	53960.1	106.6	98.5 – 115.3

Pharmacokinetic Parameter	Midazolam: LS Geometric Means: Midazolam 4 mg (Reference) N=15	Midazolam: LS Geometric Means: Midazolam 4 mg + Steady-State CT1812[a] (Test) N=14	Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	39.3	31.3[e]	79.6	70.2 – 90.3
AUC_{last} (ng·h/mL)	35.5	27.0	76.0	67.5 – 85.5
C_{max} (ng/mL)	15.3	13.6	89.3	73.3 – 108.8

Pharmacokinetic Parameter	1-Hydroxy Midazolam: LS Geometric Means: Midazolam 4 mg (Reference) N=15	1-Hydroxy Midazolam: LS Geometric Means: Midazolam 4 mg + Steady-State CT1812[a] (Test) N=14	Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	23.1[d]	25.5[e]	110.2	96.7 – 125.6
AUC_{last} (ng·h/mL)	21.8	24.1	110.5	99.0 – 123.4
C_{max} (ng/mL)	9.6	10.3	107.5	89.2 – 129.6

Pharmacokinetic Parameter	Dextromethorphan: LS Geometric Means: Dextromethorphan 50 mg (Reference) N=15	Dextromethorphan: LS Geometric Means: Dextromethorphan 50 mg + Steady-State CT1812[a] (Test) N=14	Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	37.8[c]	62.1	164.2	132.1 – 204.1
AUC_{last} (ng·h/mL)	31.5	55.1	175.1	144.1 – 212.7
C_{max} (ng/mL)	4.3	8.5	197.9	155.6 – 251.7

Pharmacokinetic Parameter	Dextrorphan: LS Geometric Means: Dextromethorphan 50 mg (Reference) N=15	Dextrorphan: LS Geometric Means: Dextromethorphan 50 mg + Steady-State CT1812[a] (Test) N=14	Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	52.3	68.5	131.0	118.5 – 144.8
AUC_{last} (ng·h/mL)	47.3	63.1	133.4	120.5 – 147.7
C_{max} (ng/mL)	10.0	13.6	136.1	116.3 – 159.2

Pharmacokinetic Parameter	Omeprazole: LS Geometric Means: Omeprazole 20 mg (Reference) N=14	Omeprazole: LS Geometric Means: Omeprazole 20 mg + Steady-State CT1812[a] (Test) N=13	Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	471.0[c]	469.3[d]	0.99.6	84.3 – 117.7
AUC_{last} (ng·h/mL)	416.3	488.8	117.4	101.4 – 135.9
C_{max} (ng/mL)	235.6	298.2	126.5	103.1 – 155.3

Pharmacokinetic Parameter	5-Hydroxy Omeprazole: LS Geometric Means: Omeprazole 20 mg (Reference) N=15	5-Hydroxy Omeprazole: LS Geometric Means: Omeprazole 20 mg + Steady-State CT1812[a] (Test) N=14	Geometric Mean Ratio[b] (Test/Reference)	90% CI[b] for Ratio of LS Means
AUC_{inf} (ng·h/mL)	402.3	409.9[e]	101.9	94.1 – 110.4
AUC_{last} (ng·h/mL)	386.6	374.2	96.8	86.6 – 108.2
C_{max} (ng/mL)	161.2	144.9	89.9	70.3 – 115.1

Classification of In Vivo Inducers of CYP Enzymes[1]

CYP Enzymes	Strong Inducers	Moderate Inducers	Weak Inducers
	≥ 80% decrease in AUC	50-80% decrease in AUC	20-50% decrease in AUC

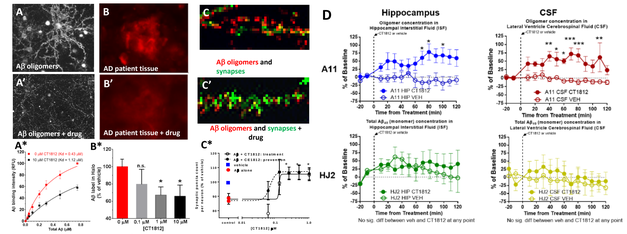
Pharmacokinetic Parameters for CYP Probe Drug Alone and in the Presence of CT1812 at Steady State, CI = confidence interval, LS = least squares, SD = standard deviation
Ratios and confidence intervals are expressed as percentages.

CT1812 is a sigma-2/PGRMC1 antagonist that displaces receptor-bound Aβ oligomers, clears them into CSF and improves memory

sigma-2/PGRMC1 receptor tightly regulates the Aβ oligomer receptor at synapses

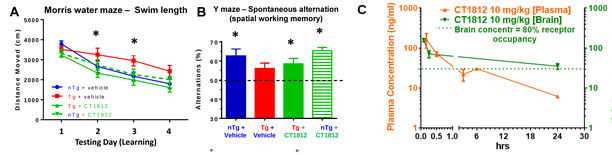
1. **CT1812 displaces oligomers bound to receptors by antagonizing sigma-2/PGRMC1 receptors and improves memory**
   - sigma-2/PGRMC1 receptor binds directly to several receptors and keeps them in the plasma membrane at the surface of neurons: EGFR (Ahmed et al '10), mPRalpha (Thomas et al '14), GLP1R (Zhang et al '14), UNC40/DCC (Runko et al '04), perhaps via its direct binding to vesicle trafficking regulatory proteins
   - sigma-2/PGRMC1 may influence the surface expression of receptors critical for LTP/LTD and memory in the mature brain
   - Aβ oligomer binding to sigma-2/PGRMC1 or an associated receptor complex interferes with sigma-2/PGRMC1 protein association and/or normal function and results in surface receptor downregulation, LTP and synapse loss and memory failure
   - CogRx compounds stop this interference by displacing oligomers from their receptor
2. **sigma-2/PGRMC1 receptors interact with all known pathways implicated in AD pathogenesis by risk loci for late-onset disease**
   - Cholesterol/sterol metabolism: binds to CYP450 proteins and influences the synthesis and metabolism of steroids and cholesterol (Rohe et al '09)
   - Inflammation and the brain's innate immune system: is expressed on glia and expression is upregulated in the presence of Abeta oligomers (Izzo et al '14)
   - Endosomal vesicle recycling: binds directly to vesicle trafficking regulatory proteins NSF, MP1-3CB, UVRAG, ULK2, Atg5, and RB1CC1 and plays a role in autophagy (Behrends et al '10, Mir et al '14)

CT1812 displaces Aβ oligomer bound to synapses on neurons and clears them into CSF



CT1812 displaces Aβ oligomers from binding sites on neurons in vitro (A, A', A*), in human AD patient brain sections (B, B', B*) and in the brains of living transgenic AD mice (D), and as a result restores synapses (C, C', C*) to normal. Aβ oligomer-treated neurons (21DIV) in vitro are shown in the upper row of photomicrographs A and C, Aβ oligomer + CT1812 treated neurons are shown in the middle row A' and C'. Human AD patient brain section treated with saline B or CT1812 B' shows displacement of oligomers from plaques in neocortex. The differences in conditions are quantified in the graphs underneath **A*,B*,C*.** D. Microimmunoelectrodes (Yuede et al 2016) coated with oligomer-specific antibody, A11 (top graphs) or pan-Aβ antibody HJ2 recognizing Aβ monomers (bottom graphs), were placed in the hippocampus (left graphs) or lateral ventricle (right graphs) of 12 month old transgenic hAPP/PS1 mice to detect soluble Aβ in the hippocampal interstitial fluid (ISF) or cerebrospinal fluid (CSF), respectively. Following i.v. injection of 0.3 mg/kg CT1812 (vertical dashed line), soluble Aβ oligomers are significantly elevated in hippocampal ISF in CT1812-treated mice (N=5) compared to vehicle-treated mice (N=6). Aβ oligomers are also significantly elevated in the CSF after drug treatment (N=5) compared to vehicle-treated mice (N=6). CT1812 treatment does not cause a change in Aβ monomer levels in the hippocampus (N=3) or CSF (N=5) compared to vehicle treatment (N=5 hippocampus, N=4). Two-way ANOVA with Holm-Sidak post test for comparing differences between vehicle and CT1812 at each time point in each experimental condition (*p<0.05, **p<0.01, ***p<0.001).

CT1812 improves learning and memory deficits in AD mice



A. Transgenic Thy-1 huAPPSwe/Ldn+ mice treated with CT1812 (Tg + CT1812) learn the Morris water maze task significantly better than transgenic, vehicle-treated mice (Tg + vehicle; p=0.016, two way repeated measures ANOVA, Bonferroni post hoc *p>0.5). CT1812 treatment does not affect non-transgenic animal performance (nTg + CT1812). B. Transgenic mice treated with CT1812 remember previous arms entered in the Y maze task significantly better (p=0.013, Student's t test) than chance (dashed line) but transgenic vehicle-treated animals do not. C. At these efficacious concentrations, CT1812 achieves the target dose of >80% receptor occupancy in the brain for 24 hours.

Safety Summary

- The overall incidence of TEAEs was low, and no clinically relevant difference was observed between treatments in the percentage of subjects who reported a treatment-emergent adverse event or a drug-related TEAE.
- The most commonly reported TEAEs during treatment with CT1812 fumarate alone were nausea and headache (each reported by 2 of 15 subjects). Diarrhea and dizziness (each reported by 2 of 14 subjects) were the most commonly reported TEAEs following treatment with steady-state CT1812 and a single dose of the probe drug cocktail.
- No safety signals were noted in the results of the other safety analyses, including laboratory tests (hematology, chemistry, and urinalysis), vital signs, ECGs, or physical examination findings.