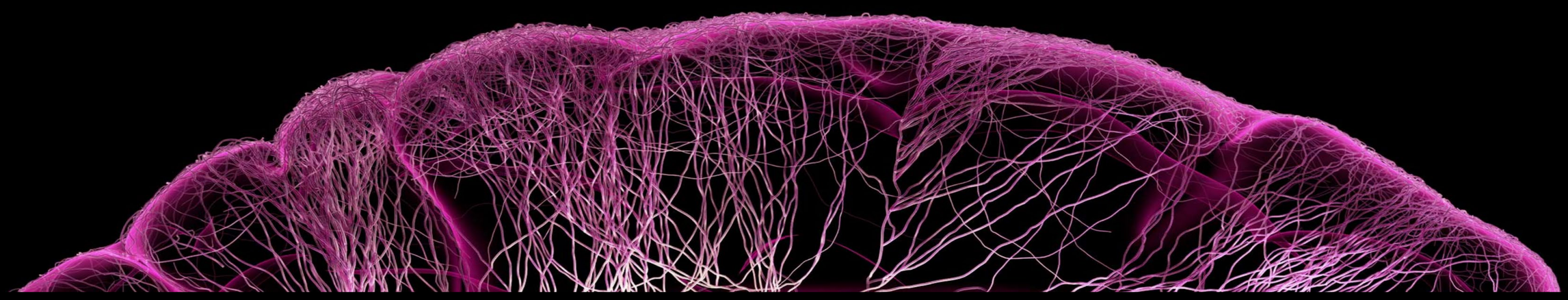

AD101 - the clinical profile of a first-in-class treatment for Alzheimer's Disease

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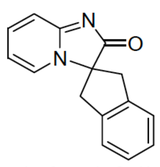
AD101 represents a new therapeutic class that improves global function and cognition when added on to donepezil, the current standard of care for managing the core symptoms of AD.

Background:

- AD101 is a Phase 3-ready small synthetic molecule under development as a treatment to improve the core symptoms of Alzheimer's Disease (AD).
- AD101 is a modulator of low-voltage-gated T-type calcium channels that increases the release of endogenous acetylcholine.

Figure 1: Molecular structure of AD101



Molecular formula $C_{15}H_{12}N_2O$
Molecular weight 236.27

- AD101 is administered orally once daily.

Objectives:

- Characterize the safety, tolerability and pharmacokinetic (PK) properties of AD101 in healthy subjects
- Assess its tolerability and potential for efficacy when administered to AD patients (MMSE 10-26).

Methods:

- Phase 1 Clinical Pharmacology (3 studies) and Phase 2 Proof-of-Concept trials (2 studies) and Open-label long-term extended (OLE) safety (1 study).
- All studies, except OLE, were randomized, double-blind and placebo-controlled.

Outcome Variables:

- Safety and tolerability across all studies.
- PK and detailed cardiac interval analyses in Phase 1.
- Effects on global function (ADCS-CGIC) and cognition (ADAS-cog 11) in controlled Phase 2 trials.

Program Summary:

- A total of 459 subjects have received AD101. Of them, 364 patients with AD have been exposed to AD101 at doses up to 180 mg once daily for up to 6 months.
- Presented herein are data from the Phase 1 multiple-dose safety and tolerability study in healthy subjects and a Phase 2 proof-of-concept study in AD patients who were already receiving a stable 10 mg/day dose of donepezil (Figures 3-6, Tables 2 and 3). Detailed data are provided via the QR code.

Figure 2: Increasing plasma concentrations of AD101 are not associated with increased QTc interval duration.

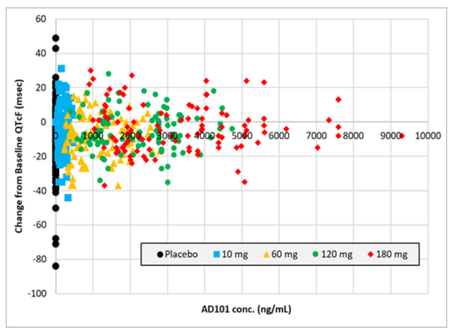


Figure 3: AD101 add-on to stable 10 mg/day donepezil. Study Flow Chart.

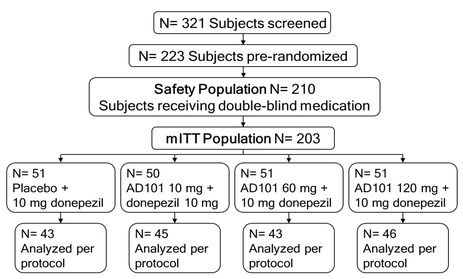


Figure 4: ADAS-cog: LS mean (SE) change from baseline (all AD101 dose groups combined compared to placebo).

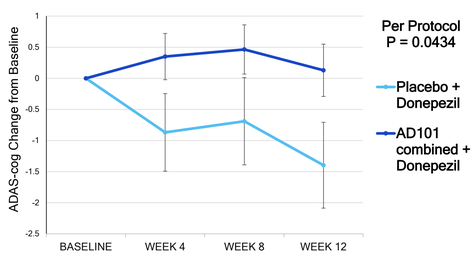


Figure 5: Percentage of patients per ADCS-CGIC outcome distribution after 12 weeks of treatment (CMH analysis, mITT p = 0.0477).

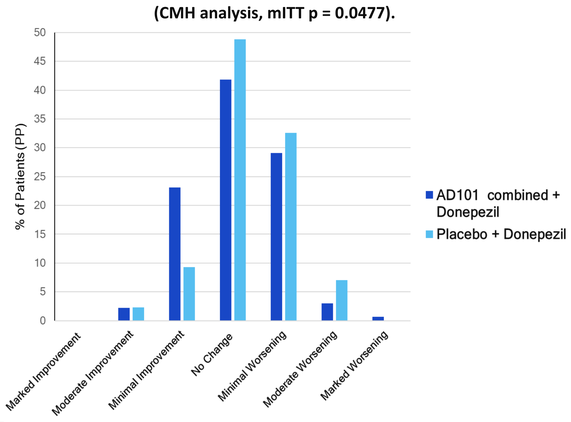


Table 1: The pharmacokinetics of AD101 are linear and support once-daily administration.

Parameters on Study Day 8	Dose (mg/day) n = 8 per dose group			
	10 mg	60 mg	120 mg	180 mg
C_{max} (ng/mL)	348 ± 62.2	2200 ± 345	4410 ± 516	6490 ± 1570
Dose Normalized C_{max} (ng/mL)	348	367	367	356
t_{max} (h)	1	1	1	1.25
AUC_{0-t} (ng·h/mL)	5578 ± 964	34038 ± 8605	77901 ± 25205	111460 ± 31179
Dose normalized AUC_{0-t} (ng·h/mL)	5578	5673	6492	6192
$t_{1/2}$ (h)	12.4 ± 1.95	11.9 ± 1.85	12.5 ± 2.73	12.2 ± 1.88
$Cl_{T/F}$ (L/h/kg)	0.0339 ± 0.137	0.331 ± 0.0083	0.0297 ± 0.0065	0.0306 ± 0.0042

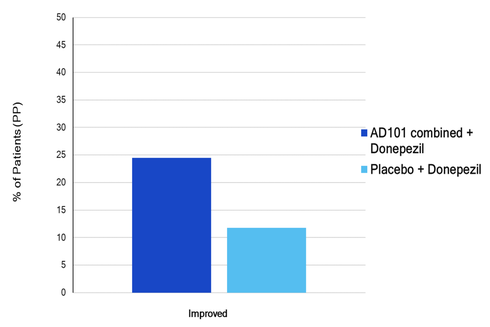
Table 2: Treatment emergent adverse events reported in ≥5% of patients.

System Organ Class/ Preferred Term	Placebo+ Aricept (N=53) n (%)	Combined (N=157) n (%)	10mg (N=52) n (%)	60 mg (N=53) n (%)	120 mg (N=52) n (%)
Subjects with any AE	28 (52.8)	91 (58.0)	32 (61.5)	31 (58.5)	28 (53.8)
Infections & Infestations	7 (13.2)	23 (14.6)	8 (15.4)	9 (17.0)	6 (11.5)
Urinary Tract Infection	2 (3.8)	12 (7.6)	3 (5.8)	4 (7.5)	5 (9.6)
Nervous System Disorders	3 (5.7)	18 (11.5)	7 (13.5)	6 (11.3)	5 (9.6)
Somnolence	0 (0)	5 (3.2)	3 (5.8)	1 (1.9)	1 (1.9)
Syncope	1 (1.9)	4 (2.5)	0 (0)	1 (1.9)	3 (5.8)
Injury, Poisoning and Procedural Complications	4 (7.5)	15 (9.6)	6 (11.5)	2 (3.8)	7 (13.5)
Fall	4 (7.5)	10 (6.4)	6 (11.5)	1 (1.9)	3 (5.8)
Psychiatric Disorders	6 (11.3)	15 (9.6)	4 (7.7)	3 (5.7)	8 (15.4)
Confusional State	3 (5.7)	3 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)
Delusion	1 (1.9)	3 (1.9)	0 (0)	0 (0)	3 (5.8)
General Disorders & Administration Site Cond	7 (13.2)	11 (7.0)	3 (5.8)	6 (11.3)	2 (3.8)
Oedema Peripheral	4 (7.5)	3 (1.9)	0 (0)	2 (3.8)	1 (1.9)

Table 3: Change from Baseline at Week 12 for ADAS-cog 11 in Study 202 (mITT and PP population).

	AD101 combined			Placebo			AD101 versus Placebo		
	n	Adjusted change for baseline	SE	n	Adjusted change for baseline	SE	LS mean difference	SE	p-value (one-sided)
ADAS-cog (PP)	134	0.19	0.42	43	-1.28	0.74	1.46	0.85	0.0434
ADAS-cog (mITT)	142	0.01	0.4	47	-1.04	0.69	1.05	0.8	0.0957

Figure 6: Percentage of patients considered improved on the ADCS-CGIC after 12 weeks of treatment (mITT p = 0.0382).



Phase 1 profile of AD101

- Phase 1 studies across 70 healthy subjects demonstrated that AD101 was well tolerated at doses up to 180 mg/day.
- There were no significant differences across treatment groups with respect to adverse events or laboratory values.
- Interval analyses demonstrated that higher plasma concentrations of AD101 were not associated with increased QTc duration (Figure 2).
- PK across a dose range of 10 to 180 mg/day were proportional after both single- and multiple-dose (Table 1) administration.
- Mean half-life was 13 hours. Steady-state was achieved by Day 5 of multiple-dose administration.

Phase 2 Profile of AD101

- Including the OLE, 356 patients with AD were exposed to AD101 at doses up to 180 mg/day for up to 6 months.
- AD101 was well tolerated, including when administered in combination with donepezil.
- Most frequent treatment emergent adverse events reported across the full Phase 2 program were:
  - Dizziness [21/356 (5.9%) AD101 vs. 8/93 (8.6%) Placebo].
  - Urinary tract infection [30/356 (8.4%) AD101 vs. 6/93 (6.5%) Placebo].
  - Falls [22/356 (6.2%) AD101 vs. 4/93 (4.3%) Placebo].
- In this preliminary study AD101, when added on to a stable dose of 10 mg/day donepezil, significantly improved ADCS-CGIC and ADAS-cog vs. donepezil monotherapy.

Conclusions

AD101 has been well tolerated without identification of adverse events, abnormal laboratory values or safety signals of potential clinical concern in either healthy subjects or patients with AD.

A double-blind, placebo-controlled, Phase 2 proof-of-concept trial demonstrated promising evidence of additive efficacy when AD101 was added on to a stable 10 mg/day dose of donepezil.

References:

Effects of the Acetylcholine Release Agent ST101 with Donepezil in Alzheimer's Disease: A Randomized Phase 2 Study

S. Gauthier, S. Rountree, B. Finn, B. LaPlante, E. Weber and T. Oltersdorf

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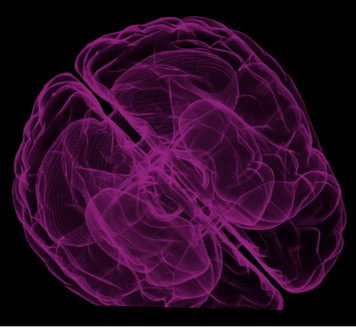

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