Cumulative effects of idalopirdine, a 5-HT_6 antagonist in advanced development for the treatment of mild and moderate Alzheimer's disease

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Background

- A 24-week, double-blind, placebo-controlled Phase II clinical trial demonstrated a pro-cognitive effect of idalopirdine, as adjunct to donepezil, in patients with moderate AD dementia (MMSE 12–19)[1]
- With supportive trends in the functional and global clinical domains[1]
- This was based on an MMRM analysis of changes from baseline in efficacy assessments, the primary endpoint being defined at Week 24
- AUC analysis of the individual clinical domains and several clinical domain composites to assess cumulative effects of treatment over a 24-week period[2]

AD=Alzheimer's disease; AUC=area under the curve;
MMRM=mixed model for repeated measures;
MMSE=Mini Mental State Evaluation

1. Wilkinson et al. Lancet Neurology 2014;13(11):1092–1099;
2. Atri et al. J Prev Alzheimers Dis 2015;2(4):325

Methods

- AUC analyses for cognition (ADAS-Cog), function (ADCS-ADL_{23}), and global clinical status (ADCS-CGIC) were computed by applying the trapezoidal rule to the estimated visit-wise means from the change-score MMRM used in the analysis in the published study[1,2]

- Two composite measures were also evaluated:[1,3]
  - A 2-domain (2D) composite consisting of equal weightings of ADAS-Cog and ADCS-ADL
  - A 3-domain (3D) equally-weighted composite that also included the ADCS-CGIC

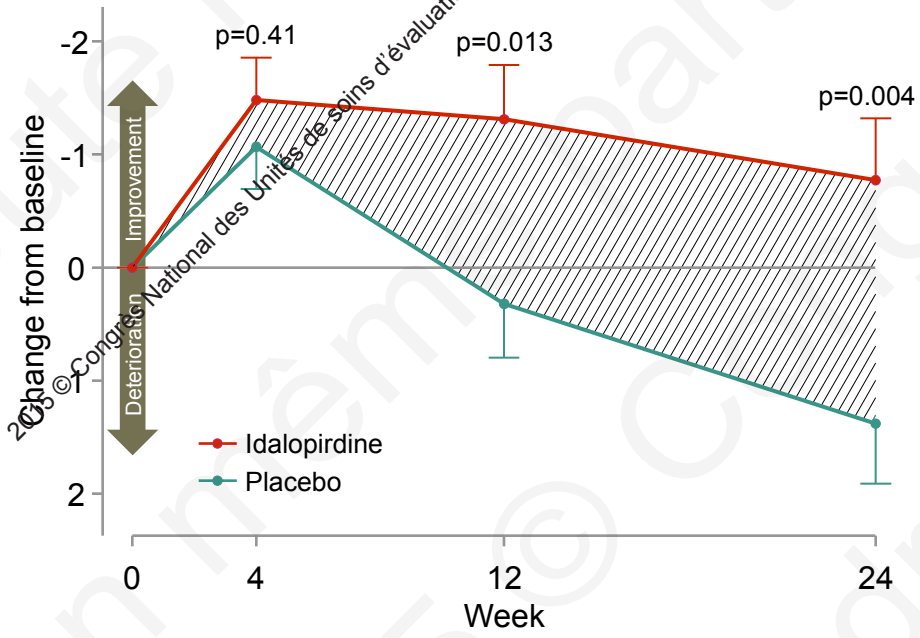
- Cumulative treatment effects in the different domains and composites were compared to results from the published study[1,3]

ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive subscale; ADCS-CGIC=Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; ADCS-ADL_{23}=Alzheimer's Disease Cooperative Study–Activities of Daily Living, 23-item scale; MMRM=mixed model for repeated measures; NPI=Neuropsychiatric Inventory

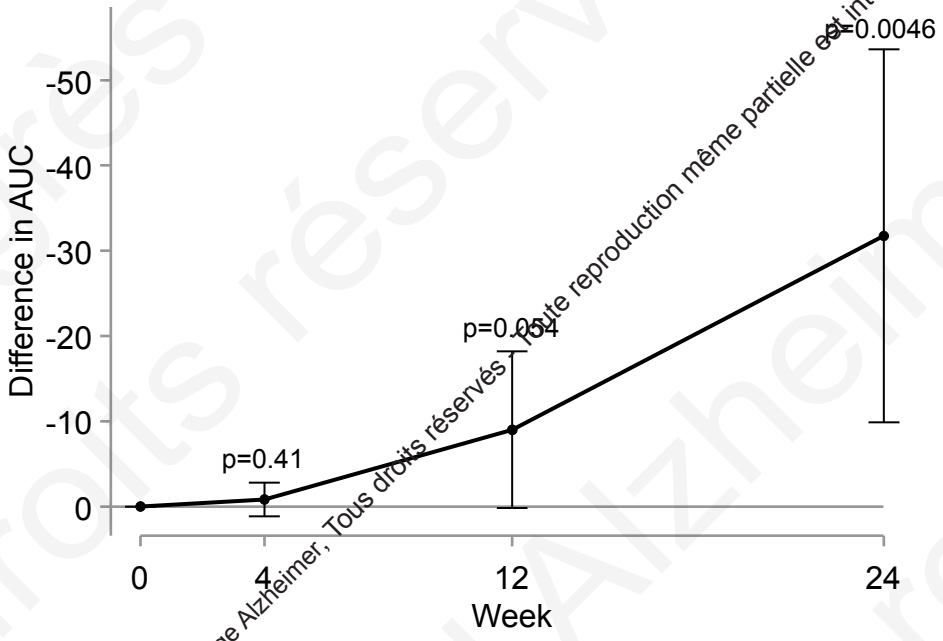
1. Atri et al. J Prev Alzheimers Dis 2015;2(4):325;
2. Wilkinson et al. Lancet Neurology 2014;13(11):1092–1099;
3. Atri et al. Poster at CTAD 2015

Cumulative effects on ADAS-Cog

ADAS-Cog change from baseline (LSM ± SEM)



Difference in cumulative AUC of ADAS-Cog change from baseline (mean, 95% CI)

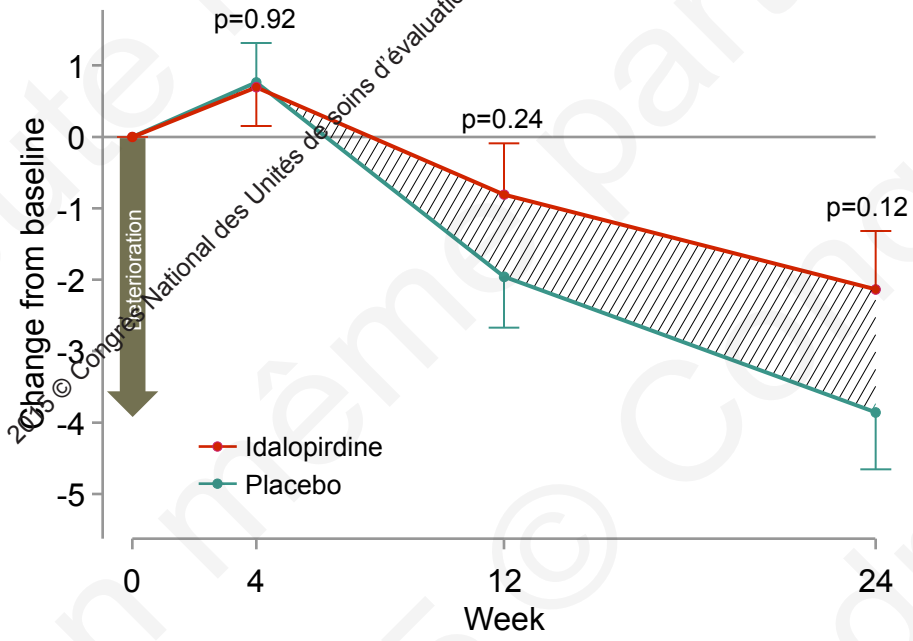


ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive subscale;
AUC=area under the curve; LSM=least squares mean;
CI=confidence interval; SEM=standard error of the mean

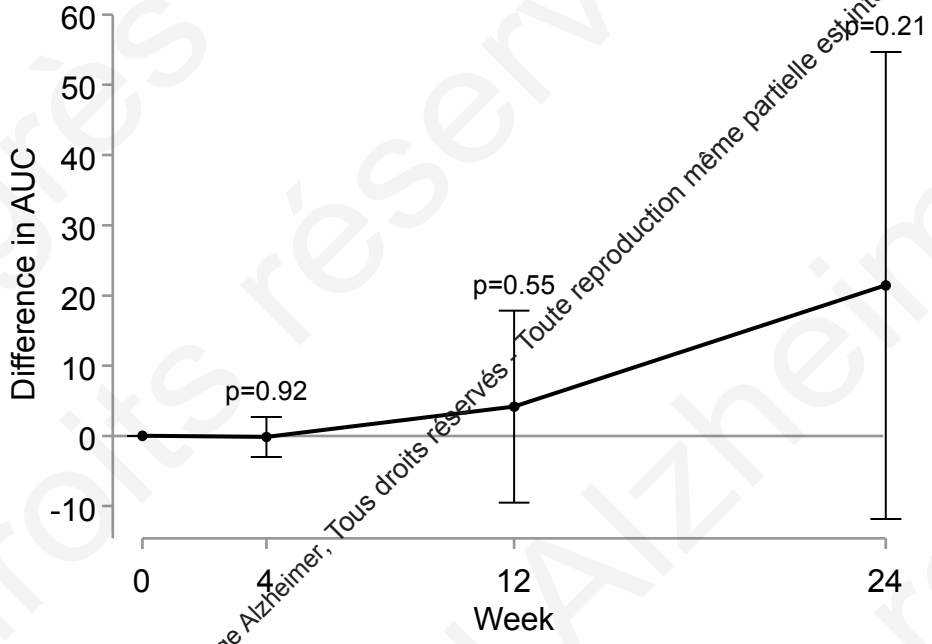
Atri et al. Poster at CTAD 2015

Cumulative effects on ADCS-ADL$_{23}$

ADCS-ADL$_{23}$ change from baseline (LSM ± SEM)



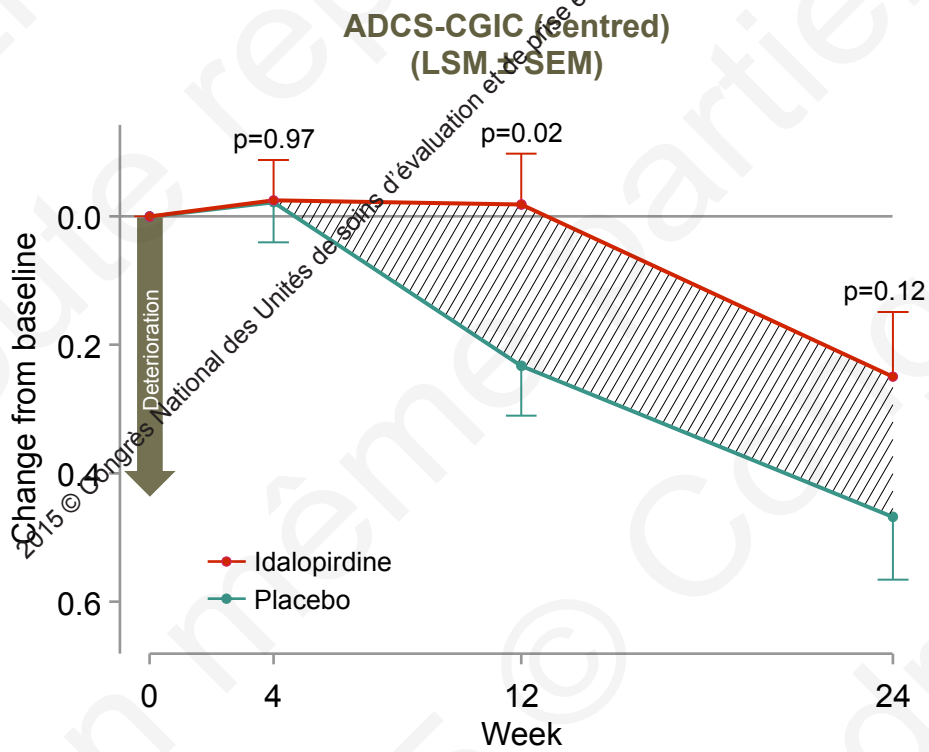
Difference in cumulative AUC of ADCS-ADL$_{23}$ change from baseline (mean, 95% CI)

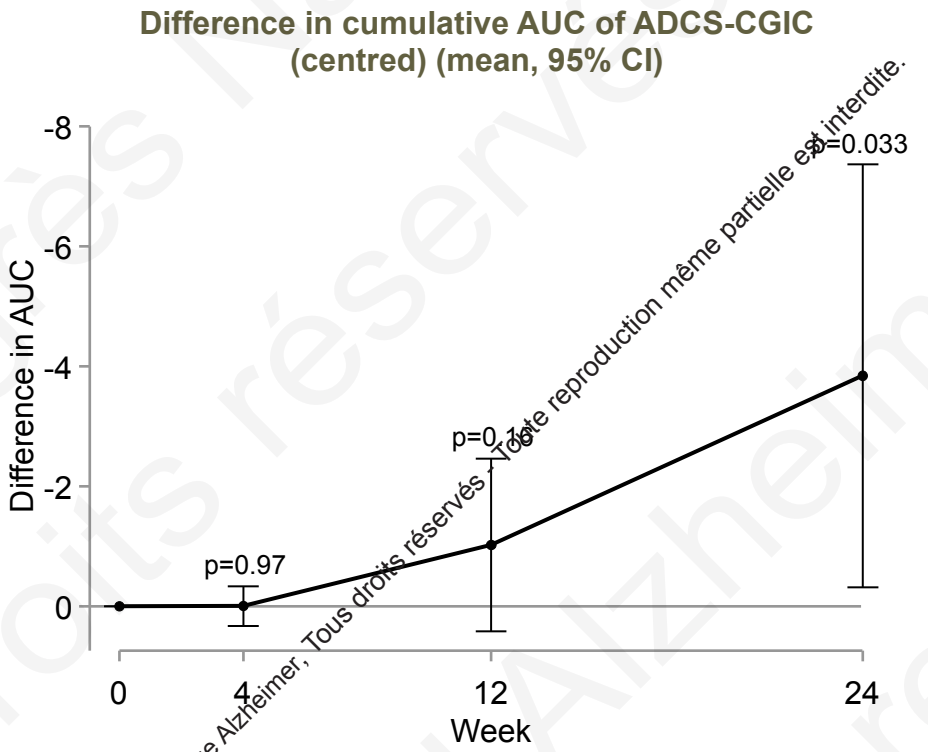


ADCS-ADL$_{23}$=Alzheimer's Disease Cooperative Study–Activities of Daily Living, 23-item scale; AUC=area under the curve; LSM=least squares mean; CI=confidence interval; SEM=standard error of the mean

Atri et al. Poster at CTAD 2015

Cumulative effects on ADCS-CGIC

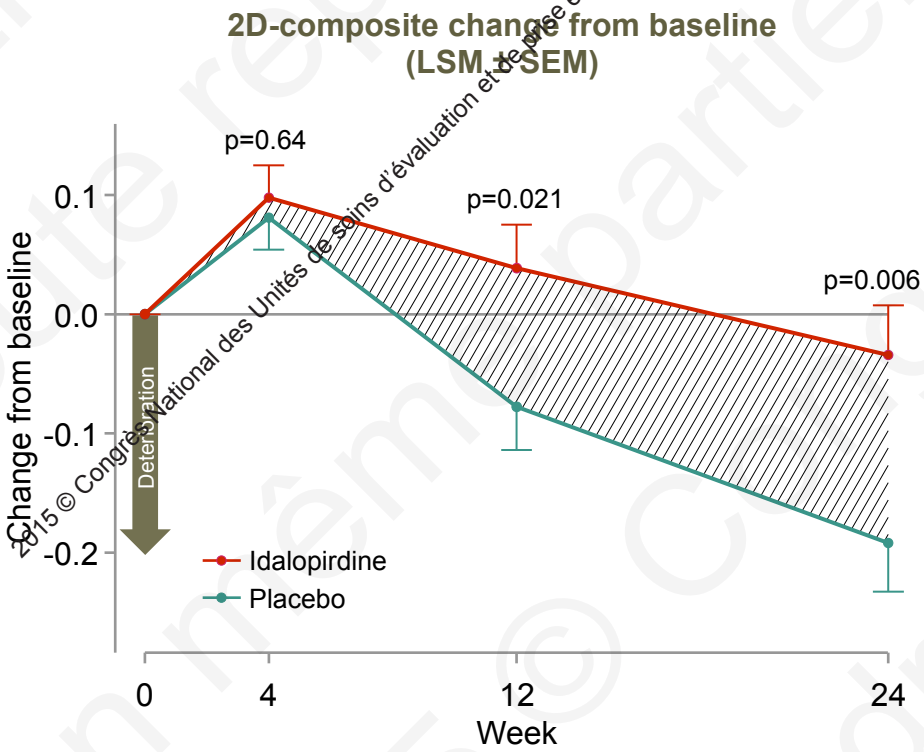


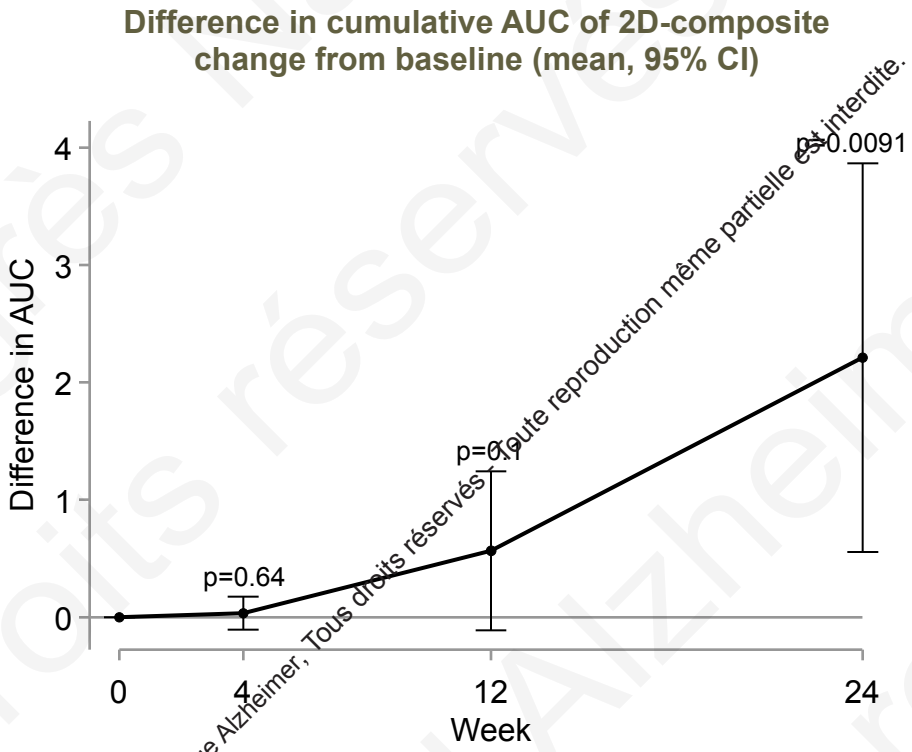


ADCS-CGIC=Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; AUC=area under the curve; LSM=least squares mean; CI=confidence interval; SEM=standard error of the mean

Atri et al. Poster at CTAD 2015

Cumulative effects on ADAS-Cog/ADCS-ADL – 2D-composite

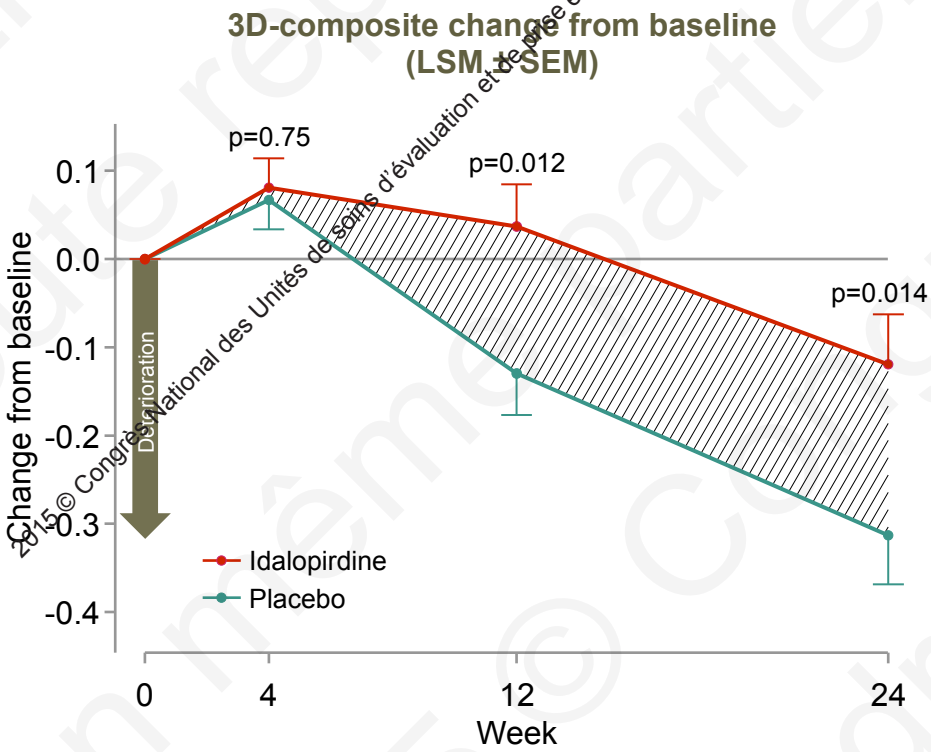


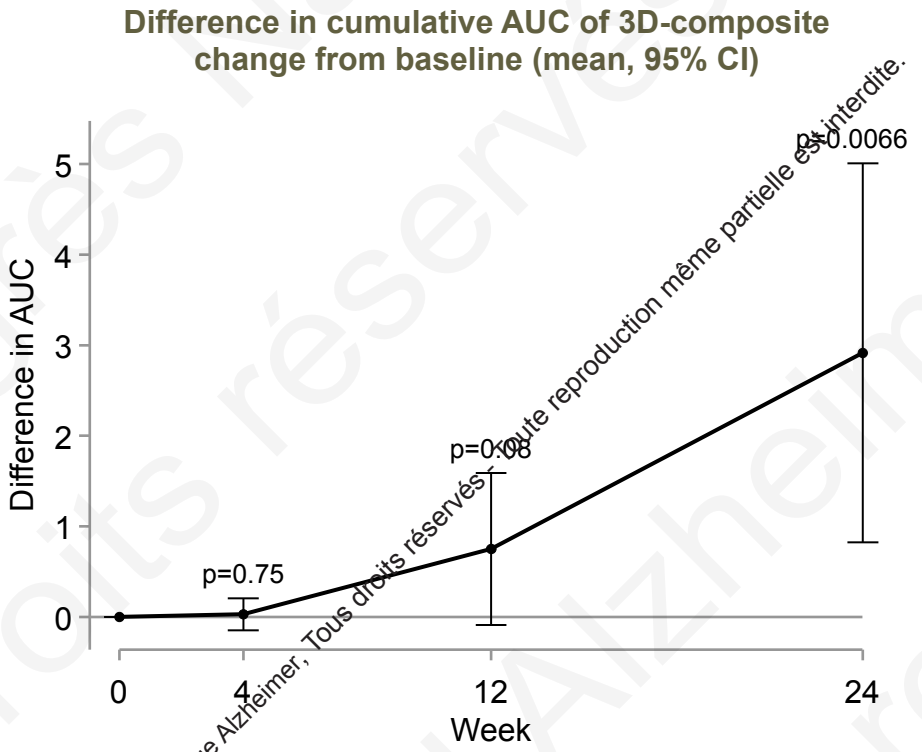


ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living; AUC=area under the curve; LSM=least squares mean; CI=confidence interval; SEM=standard error of the mean

Atri et al. Poster at CTAD 2015

Cumulative effects on ADAS-Cog/ADCS-ADL/ADCS-CGIC – 3D-composite





ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive subscale;
ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living;
ADCS-CGIC=Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; AUC=area under the curve; LSM=least squares mean;
CI=confidence interval; SEM=standard error of the mean

Atri et al. Poster at CTAD 2015

Conclusion

- AUC analyses of 24-week response profiles showed robust and progressively accumulating effects of idalopirdine treatment, as adjunct to donepezil, compared with donepezil–placebo treatment effects[1]
- For the global clinical evaluation, the cumulative 24-week idalopirdine treatment effect was significant for the ADCS-CGIC AUC analysis; this had not been previously observed with the traditional change-score analysis[1,2]
- The effects on the 2D-composite (ADAS-Cog and ADCS-ADL) were consistent with the effects on ADCS-CGIC and on the 3D-composite (ADAS-Cog, ADCS-ADL, ADCS-CGIC)[3]
- AUC single- and composite-domain analyses provided complementary and additional information to traditional change-score analyses[1,3]

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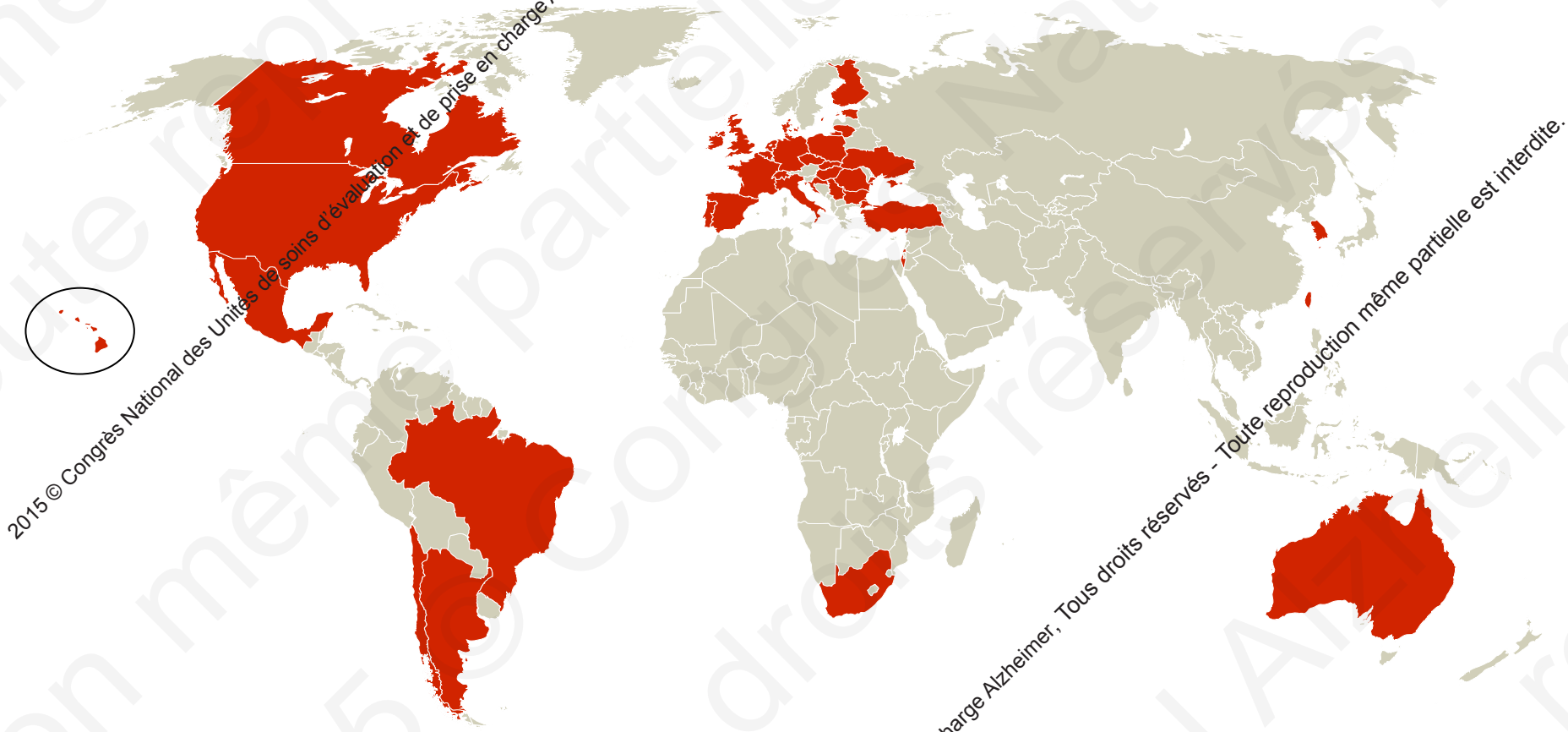
Idalopirdine Phase III programme



A Phase III efficacy and safety clinical trial programme of the selective 5-HT_6 antagonist, idalopirdine, in mild and moderate Alzheimer's disease is progressing as planned

Phase III programme – Lundbeck & Otsuka
Clinical development plan (ongoing trials)

Treatment population: mild to moderate AD (MMSE 12–22)

Study	Doses, comparator	Background treatment	Treatment duration	Total population	Key efficacy endpoints
14861A RCT **STARSHINE**	30 mg/day 60 mg/day Placebo	Donepezil	24 weeks	930 (310/ arm)	ADAS-Cog, ADCS-ADL$_{23}$, ADCS-CGIC
14862A RCT **STARBEAM**	10 mg/day 30 mg/day Placebo	Donepezil	24 weeks	840 (280/ arm)	ADAS-Cog, ADCS-ADL$_{23}$, ADCS-CGIC
14863A RCT **STARBRIGHT**	60 (30) mg/day Placebo	Donepezil, rivastigmine, galantamine	24 weeks	720 (360/ arm)	ADAS-Cog, ADCS-ADL$_{23}$, ADCS-CGIC
14861B Open-label extension[a]	60 (30) mg/day	Donepezil	28 weeks	Up to 1,770	ADAS-Cog, ADCS-ADL$_{23}$, ADCS-CGIC

[a]Extension of 14861A and 14862A

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ClinicalTrials.gov; Study identifiers: NCT02006641; NCT01955161; NCT02006654

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