A 5-HT$_6$ antagonist in advanced development for the treatment of mild and moderate Alzheimer's disease: idalopirdine (Lu AE58054)

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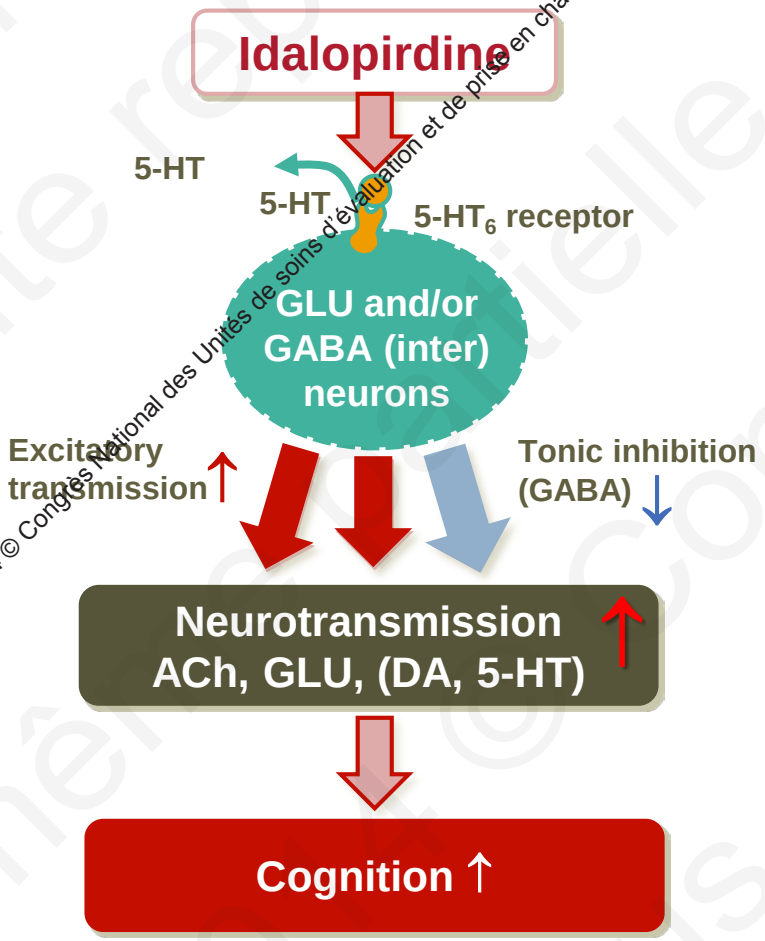
Overview

- Preclinical data and rationale for 5-HT_6 receptor antagonism via novel compound idalopirdine
- Results of idalopirdine (Lu AE58054) Phase II study in moderate Alzheimer's disease (AD)
- Overview of Phase III safety and efficacy program in mild and moderate AD

Hypothesized MoA of idalopirdine



In the frontal cortex and hippocampus of rats, 5-HT$_6$ antagonism by idalopirdine:

- **Impacts multiple neurotransmitters**
  - Facilitation of cholinergic, glutamatergic and, likely, monoaminergic signaling
  - Suppression of GABAergic transmission
- **Facilitates neuronal activity**
  - Induces, augments and prolongs cortical theta and gamma oscillations in association with donepezil
- **Added effects in combination with donepezil**

5-HT=serotonin; GABA=gamma aminobutyric acid; ACh=acetylcholine; DA=dopamine; MoA=mode of action

Idalopirdine Phase II study – objectives

Primary objective

- To explore the effect of a fixed dose of idalopirdine (90 mg/day) on cognitive performance (ADAS-Cog) after 24 weeks, compared with placebo (parallel group design), in donepezil-treated patients with moderate AD

Secondary objectives

- Safety and tolerability
- Efficacy outcomes including:
  - Global impression (ADCS-CGIC)
  - Activities of daily living (ADCS-ADL_{23})
  - Behavioral symptoms (NPI)

Power/sample size objectives

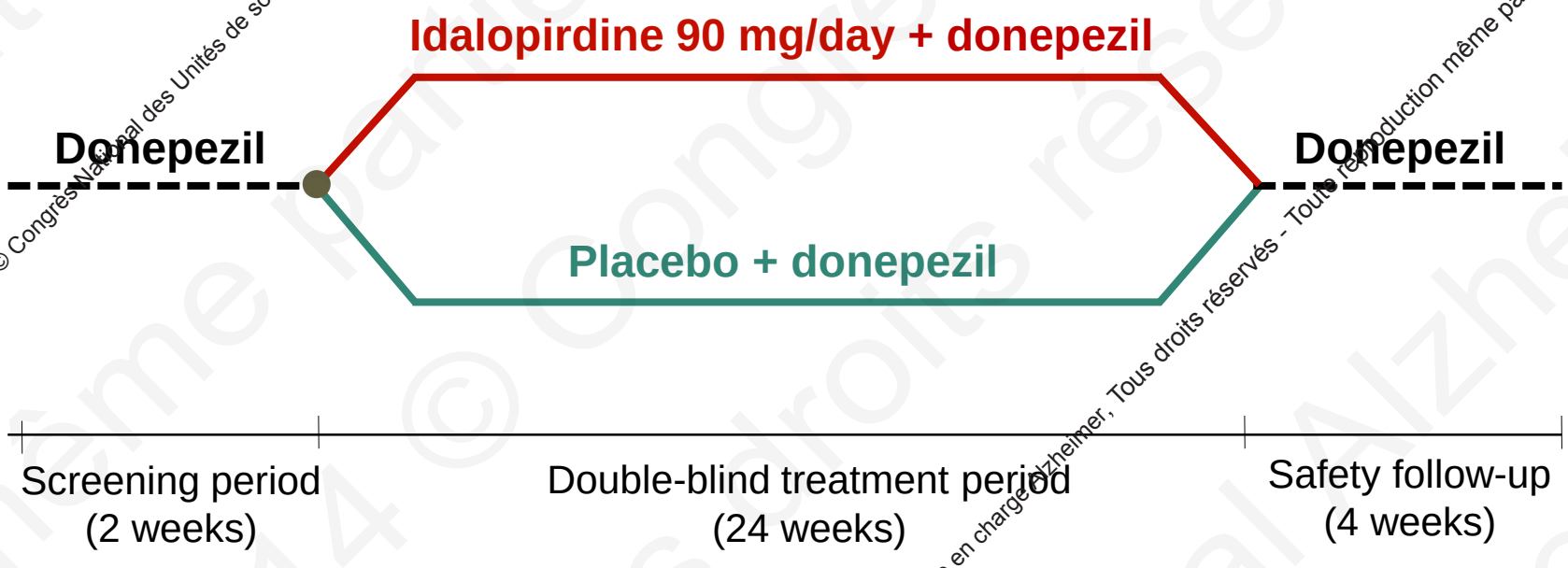
- To **detect a 2 point ADAS-Cog (primary measure)** change from baseline at Week 24 for completers (based on MMRM analysis SD of 6, a withdrawal rate of 15%, p=0.05 (2-sided), with power of 72%) – need minimum of 135 patients in each treatment group
- **Exploratory analysis of secondary measures**

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

Wilkinson et al. Lancet Neurology 2014;13(11):1092–1099

Idalopirdine in Alzheimer's disease – Phase II study design

- **Baseline/randomisation:** n=278
- Patients with moderate AD (MMSE 12–19)
- On stable donepezil treatment (10 mg/day)



MMSE=Mini-Mental State Examination

Wilkinson et al. Lancet Neurology 2014;13(11):1092–1099

Baseline characteristics

	Donepezil + placebo (n=133)	Donepezil + idalopirdine (n=145)
Age, years[a]	75 (7.2)	74 (7.5)
Gender, % male	33	26
Duration of AD, years[a]	2.2 (1.9)	2.1 (1.8)
Duration of donepezil use, years[a]	1.5 (1.6)	1.4 (1.6)
MMSE[b]	17 (16; 19)	17 (15; 18)
ADAS-Cog[b]	28 (20; 36)	28 (21; 34)

[a]Mean (SD); [b]Mean (25%; 75% percentile)

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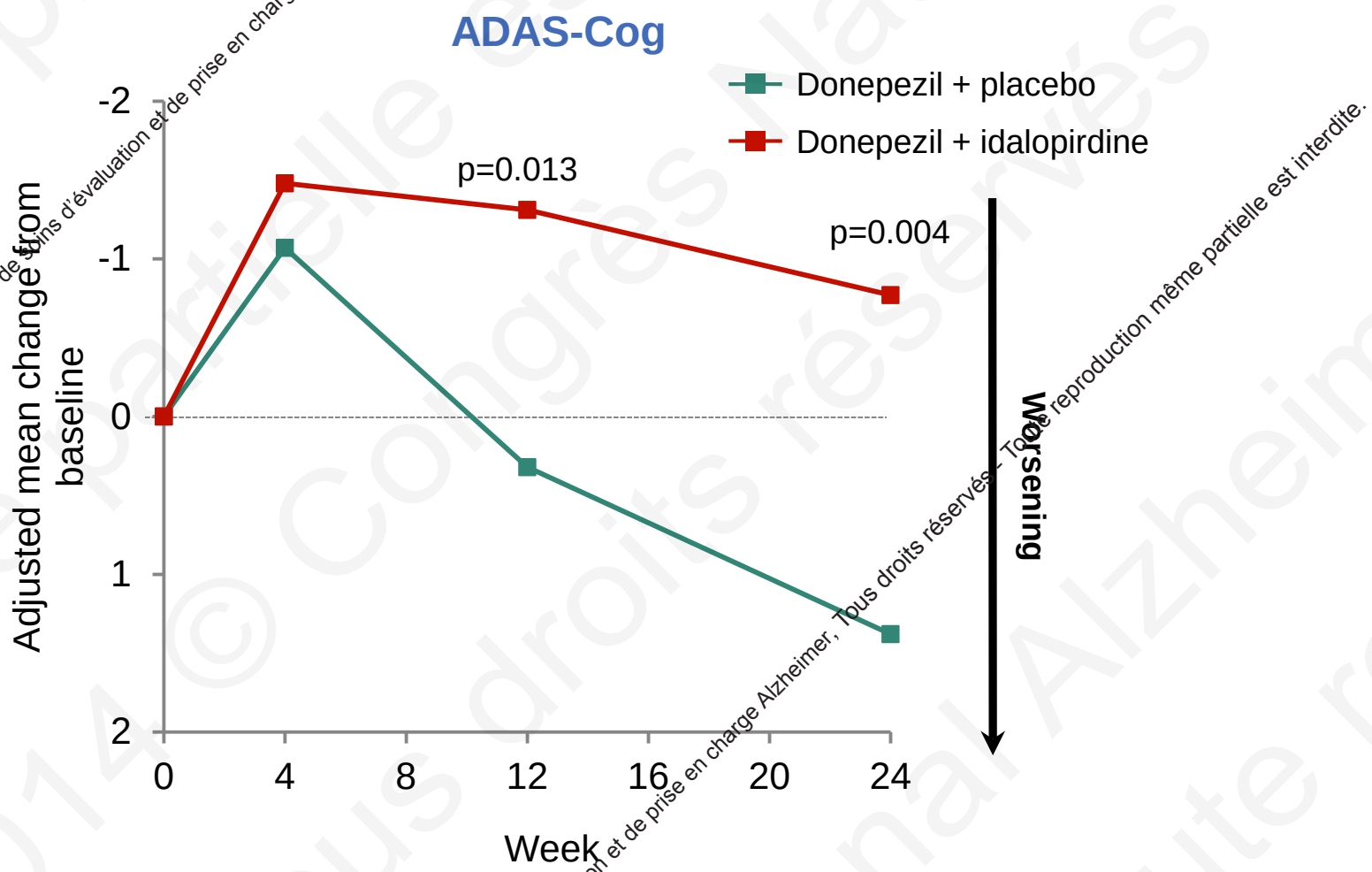
Primary endpoint – cognition



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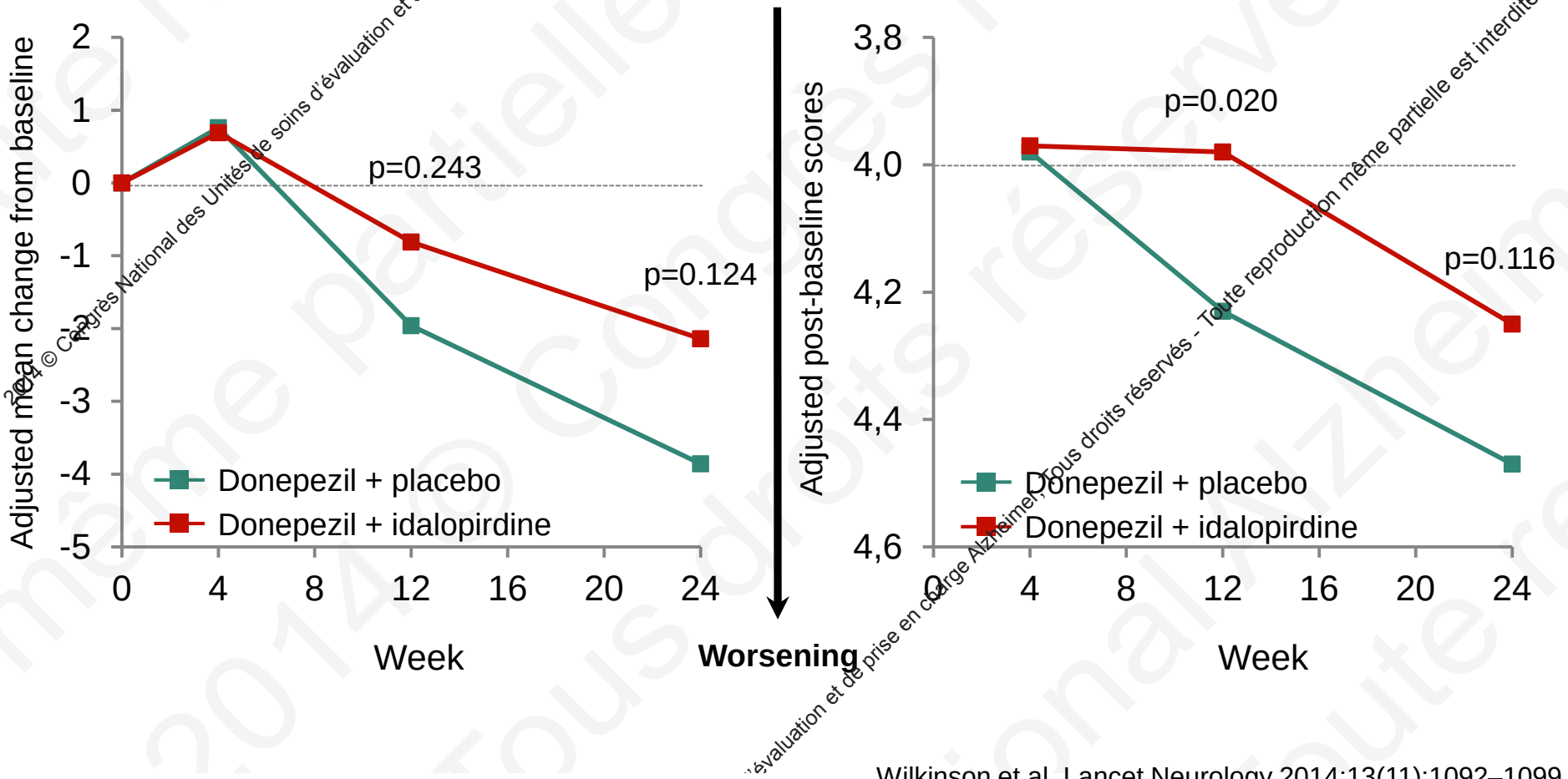
Secondary endpoints – functional and global outcomes



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Safety

- Generally safe and well tolerated
- Comparable incidence of SAEs in the two treatment arms

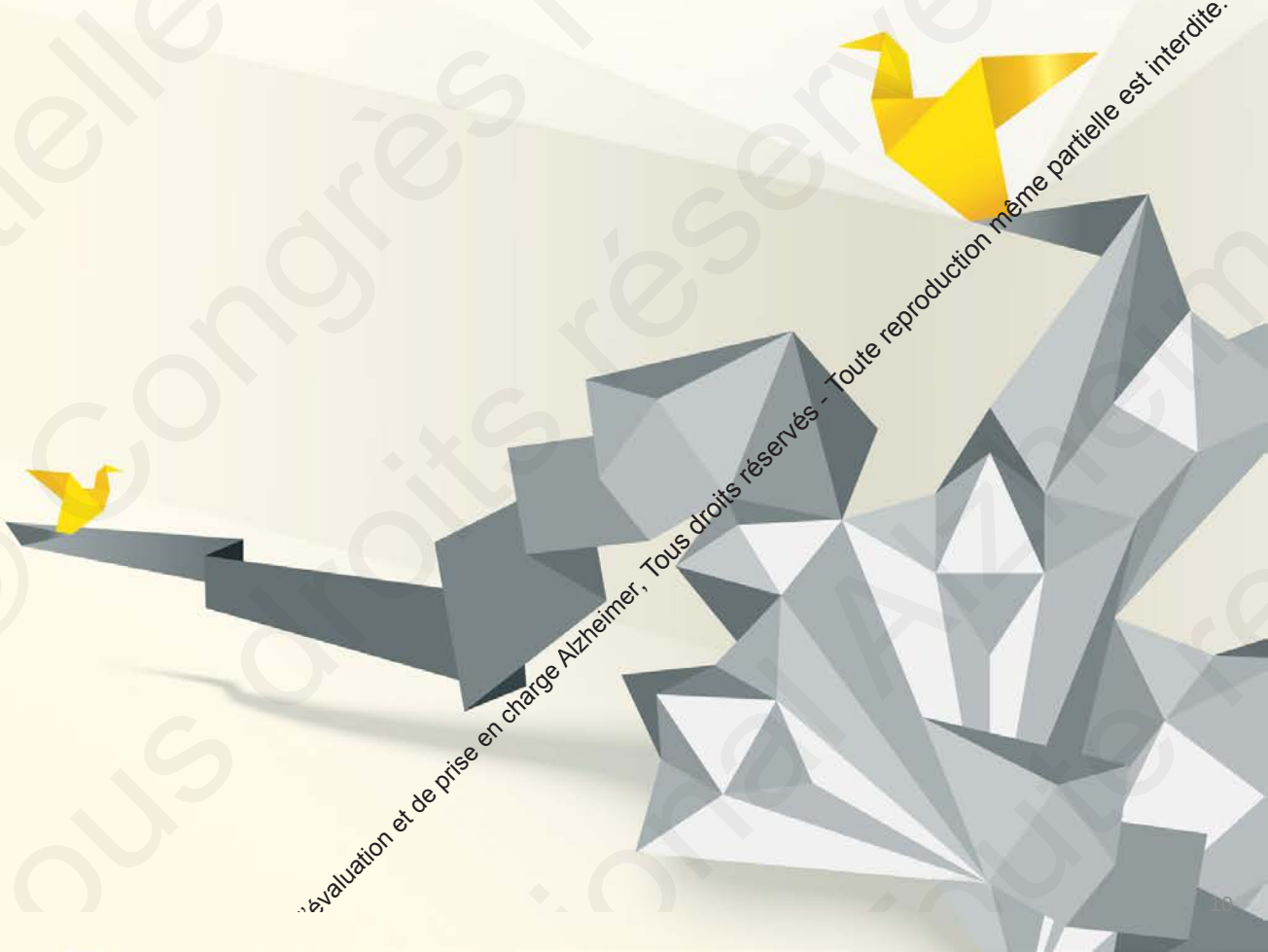
Safety – most common adverse events (≥5%)

	No. patients (%)	
	Donepezil + placebo (n=133)	Donepezil + idalopirdine (n=145)
GGT increased	2 (2)	14 (10)
ALAT increased	0 (0)	9 (6)
Diarrhea	9 (7)	6 (4)
Fall	8 (6)	3 (2)
Urinary tract infection	9 (7)	3 (2)
Benign prostatic hyperplasia (% men)	0 (0)	2 (5)

ALAT=alanine aminotransferase;
GGT=gamma-glutamyltransferase; SAE=serious adverse event

Wilkinson et al. Lancet Neurology 2014;13(11):1092–1099

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



Idalopirdine Phase III safety & efficacy program

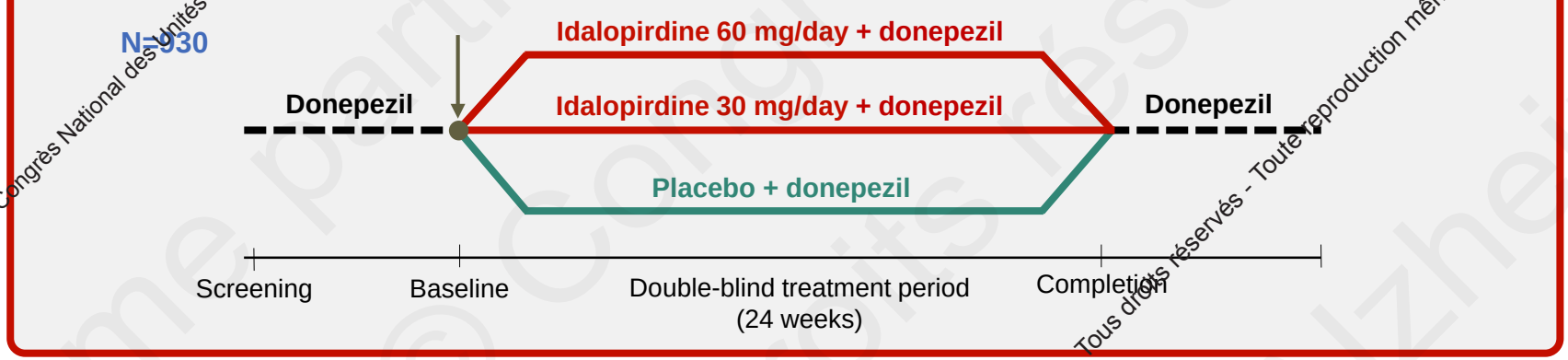
- In mild and moderate AD (MMSE 12–22)
- As add-on to any ChEI (not just donepezil – in one study)
- Lower dosing than Phase II

ChEI=cholinesterase inhibitor

Phase III program – 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, ADL, CGIC



RCT=randomised, controlled trial;
CGIC=Clinical Global Impression of Change; ADL=Activities of Daily Living

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

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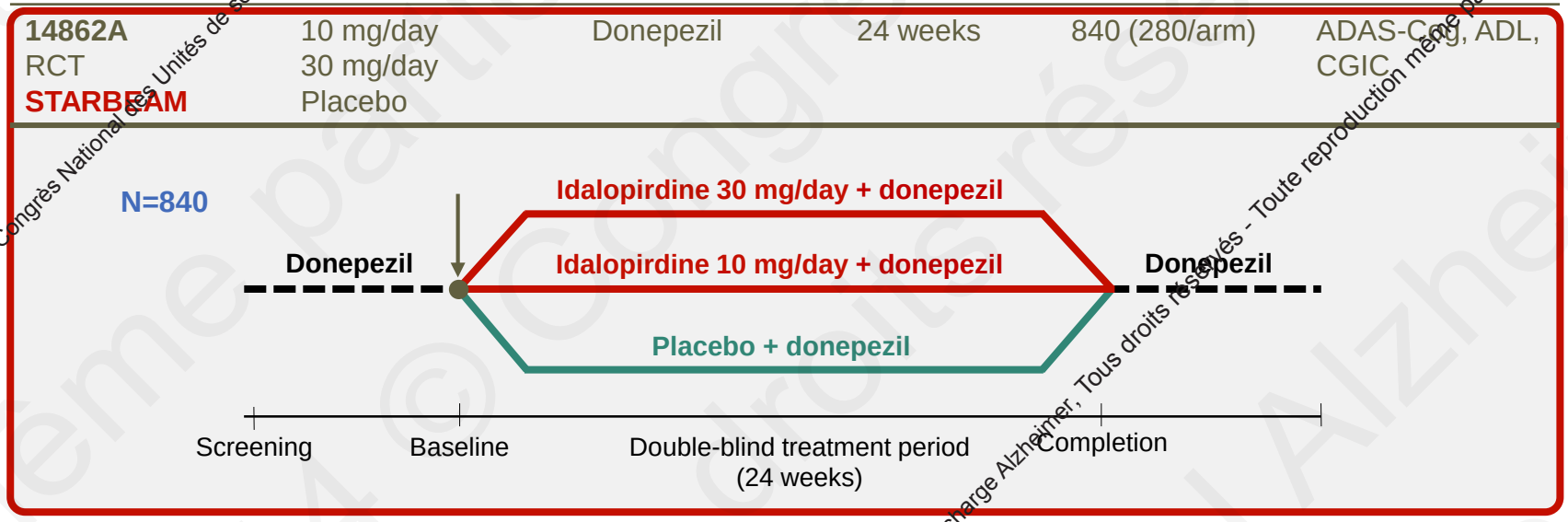

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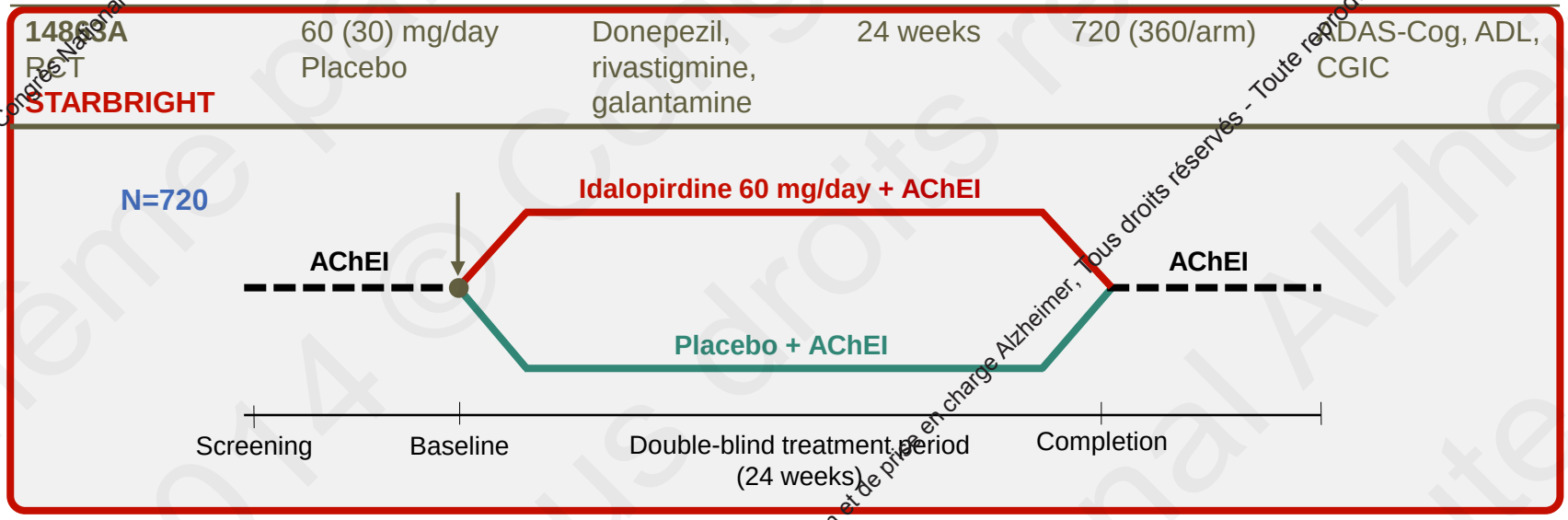

AChEI=acetylcholinesterase inhibitor; RCT=randomised, controlled trial; CGIC=Clinical Global Impression of Change; ADL=Activities of Daily Living

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14861B Open-label extension[a]	60 (30) mg/day	Donepezil	28 weeks	Up to 1,770	ADAS-Cog, ADL, CGIC

[a]Extension of 14861A, and 14862A; RCT=randomised, controlled trial; CGIC=Clinical Global Impression of Change; ADL=Activities of Daily Living

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Conclusion

- 5-HT$_6$ receptor antagonism represents a novel approach to the treatment of AD that likely affects several neurotransmitter systems (ACh, glutamate, dopamine, GABA), and networks that support cognition, function and behavior

- In Phase II, idalopirdine (Lu AE58054), when administered as adjunctive treatment to donepezil in patients with moderate AD, over 24 weeks:
  - Improved cognition
  - Showed trends toward ameliorating decline in function (ADL) and global clinical status/clinically meaningful change (CGIC)
  - Was generally safe and well tolerated

- A large Phase III program in mild–moderate AD is ongoing to confirm and further elucidate the beneficial effects and safety profile of idalopirdine

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