



Review Article

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Idalopirdine (LY483518, SGS518, Lu AE 58054) in Alzheimer disease: never change a winning team and do not build exclusively on surrogates. Lessons Learned from Drug Development Trials

Jan M Keppel Hesselink*

Department of Molecular Pharmacology, University Witten/Herdecke, Germany

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*Corresponding author: Jan M Keppel Hesselink, Department of Molecular Pharmacology, University Witten/Herdecke, Germany, Email: jan@neuropathie.nu

Abstract

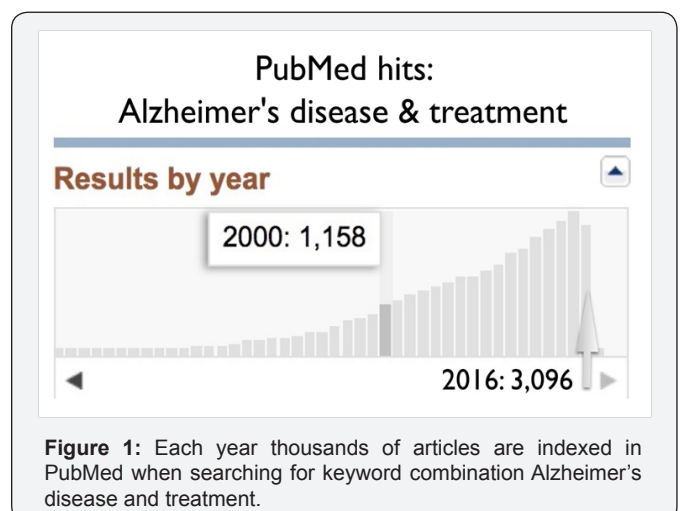
The effect of *Acetylcholinesterase* inhibition on Alzheimer's disease is modest. Augmentation strategies are thus wished for and explored. Idalopirdine is a 5HT₆ antagonist, and was found to augment the efficacy of *acetylcholinesterase* inhibitors in animal pharmacology. A phase II study supported the concept, however the study did not follow a dose-finding design, but focused on one dose only, 90 mg/daily. Currently a phase III program further evaluates the value of such augmentation strategy. The first phase III trial however missed the target. This first phase III trial was underdosed; maximum dose was 60 mg/daily, possibly based on an overly firm belief in surrogate parameters, a PET study. We will discuss the phase II and phase III program of idalopirdine in Alzheimer disease and outline the lessons learned for drug development: always use fixed dose range studies in phase II, first define the lowest effective dose and the no-effect dose, as well as the effective dose (90 mg/day). Subsequently do not change the dose-regime from t.i.d. in phase II to once daily in phase III, even if surrogate parameters support such change, neither reduce the dose, in this case from 90 mg daily (30 mg t.i.d.) in phase II to 60 mg daily (once daily) in phase III. Follow a conservative drug development pattern and avoid cutting corners seems the lesson of this case of idalopirdine in Alzheimer disease.

Keywords: Dose-range; Dementia; Phase III; 5HT₆; Antagonism; Serotonin

Abbreviations: FDA: Food and Drug Administration; NMDA: *N-methyl-D-aspartate*; AChEI: *Acetylcholinesterase* Inhibitor; CIAS: Impairment Associated with Schizophrenia

Introduction

Mid 2016 the U.S. Food and Drug Administration (FDA) granted 'Fast Track Designation' to idalopirdine for the treatment of mild to moderate Alzheimer's disease. [1] Reason to follow this drug in the final phase of her drug development in Alzheimer's disease. Anno 2016 there are at least 24 Alzheimer drugs explored in 36 phase III trials, while 45 agents are explored in 52 phase II trials. [2] Each year thousands of articles are indexed in PubMed when searching for keyword combination Alzheimer's disease and treatment (Figure 1). So far however, only four *cholinesterase* inhibitors and the *N-methyl-D-aspartate* (NMDA) antagonist, memantine, have obtained marketing approval at an international level [3]. Many drugs failed in the past and sunk in oblivion, such as hydergine, lecithine, choline, metrifonate and nimodipine, while reducing A β and tau production was a goal already formulated in the last century, and no disease modifying therapies have been registered yet.



Cholinergic therapy, a kind of substitution therapy, is quite old, and dates from the early 80s. [4] Administered together with the *acetylcholinesterase* inhibitor (AChEI) donepezil, idalopirdine potentiates the effects of the AChEI on acetylcholine levels in the cortex and hippocampus. [5] From AChEI's we know that the treatment effect is relative modest, and treatment may delay cognitive impairment for a short period of time, like 6 months, while none of the compounds could slow the rate of decline in cognitive or functional capacities over the long term. [6] An augmentation strategy, for instance by adding a 5HT6 antagonist on top of an AChEI might lead to a more pronounced therapeutic effect [7]. Antagonism of the 5-HT6 receptor leads to a comparable effects as *acetylcholinesterase* inhibition, increasing acetylcholine concentrations in areas such as the frontal cortex and hippocampus, but of course via a different mechanism of action [8]. Such data suggest a role of 5HT6 antagonism in cognitive processes. [9] Furthermore, 5-HT6 receptor blockade enhances glutamatergic, noradrenergic, and dopaminergic neurotransmission. [10,11] The analysis of the role of the 5HT6 receptor system early on was hampered because of the absence of full agonists. First potent and full 5-HT6 agonists synthesized were WAY-181187 and WAY-208466 [12]. Such agonists and partial agonists are now seen as putative antidepressant and anxiolytic compounds [13,14].

Idalopirdine: a 5HT6 antagonist

Idalopirdine was previously known as SGS518 (Saegis Pharmaceuticals) and Saegis started development in cooperation with Eli Lilly and Company, testing the compound as a treatment for 'Cognitive Impairment Associated with Schizophrenia' (CIAS) [15]. Its first phase I study was completed in 2005. Saegis [16] was later acquired and merged into Lundbeck A/S in December 2006. Lundbeck further designed the clinical program. Idalopirdine was identified in 2002 as a potent antagonist at rat and human 5-HT6 receptors ($K_b=19.4, 19.1$ nM). Administration of the compound dose-dependently inhibited *in vitro* binding of (125I)-SB-258585 to 5-HT6 receptors in rat striatum with an ED50 of 2.2 mg/kg orally [17]. The 5-HT6 receptor was initially cloned from striatal tissue and has been found mainly in the central nervous system [18]. Compared to other 5-HT receptors, the 5-HT6 receptor is seen as an important therapeutic target for CNS-related pathology, because its expression in the CNS and the fact that there are no known isoforms. [19] Peripheral 5HT6 receptors are believed to play a role in nociception [20].

The clinical program of idalopirdine in Alzheimer's disease: bottlenecks

In phase I studies idalopirdine has been shown to be safe and well tolerated in doses of up to 360 mg (single dose) [21]. The clinical efficacy program consists of one fixed dose II study, 90 mg idalopirdine/day and 3 phase III studies, evaluating the dose range of 10-60 mg idalopirdine/day, all studies added the compound on top of an AChEI. In November 24, 2009, a first phase II study was submitted to ClinicalTrials.gov and the

study identifier was: NCT01019421, title: 'Randomised, Double-blind, Parallel-group, Placebo-controlled, Fixed-dose Study of Lu AE58054 in Patients With Moderate Alzheimer's Disease Treated With Donepezil.' The dose tested was 30 mg Lu AE58054 three times daily (90 mg/day). The augmentation strategy tested was further explored in 3 phase III studies and one extension study (identifiers: NCT02006641, NCT01955161, NCT02006654, NCT02079246). The dose-range tested in these phases III studies was 10-60 mg once daily. The results of the phase II study NCT01019421 were reported in 2014 [21]. All patients included were stably treated with donepezil 10 mg per day for 3 or more months. Idalopirdine dose selected in the study was 30 mg thrice daily and was based on available non-clinical and human pharmacokinetic data on file at Lundbeck. Included were 133 patients on placebo and 145 on 90 mg Idalopirdine/day.

25 patients withdrew owing to treatment-emergent adverse events, 18 in the idalopirdine group, of which 13 patients had increased (greater than two times the upper limit of normal) *aspartate aminotransferase* or *alanine amino-transferase* values, with no concurrent increase in total bilirubin. Eleven of the 13 patients with increased values withdrew from the study. At endpoint, week 24, the change from baseline in ADAS-cog total score was +1.38 (SD 0.53) in the placebo group and -0.77 (0.55) in the idalopirdine group (treatment difference of -2.16 points, 95% CI -3.62 to -0.69; $p=0.0040$). Secondary endpoints were negative. It is relevant to note, the dose selected in the phase II study was one dose only, and given the failure of the first phase III trials (see under), this stipulates how important it is in drug development to conduct a dose-finding study in phase II! The authors acknowledged this when they brought forward this issue in the discussion: "the use of a single idalopirdine dose means we could not establish whether lower doses would have been efficacious." (p. 1098). Furthermore, it was pointed out that given the narrow MMSE range this phase II study included relatively severely impaired patients, which tend to respond better to interventions [22]. It was also pointed out that idalopirdine is a potent inhibitor of CYP206 and in this trial bioavailability of donepezil increased by 10%.

The phase III efficacy studies defined in clinicaltrials.gov:

I. NCT02006641

Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with Donepezil (Star beam)

N=858

Dose: Lu AE58054 10 and 30 mg, once daily on top of 10 mg Donepezil.

II. NCT01955161

Lu AE58054 in patients with mild - moderate Alzheimer's disease treated with Donepezil (Star shine)

N=931

Dose: Lu AE58054 30 mg and 60 mg, once daily on top of 10 mg Donepezil

III. NCT02006654

Lu AE58054 in patients with mild to moderate Alzheimer's disease treated with an *Acetylcholinesterase* inhibitor (Star bright)

N=734

Dose: Lu AE58054 60 mg or 30 mg, once daily on top of an unspecified ACHEI

The results of the first phase III study (NCT01955161), conducted by Lundbeck and its collaborator Otsuka, however failed to support the augmentation strategy, due to most probably under dosing. More than 900 patients with mild-to-moderate Alzheimer's disease were randomized to receive placebo or 30 mg or 60 mg idalopirdine on top of 10 mg of donepezil. Both doses failed to improve cognition on the Alzheimer's disease Assessment Scale-cognitive subscale and no difference could be detected between placebo and active drug [23]. In the same press release it was stipulated that Lundbeck designed the phase III study program based on a surrogate, using PET, to predict whether the changes to the dose-regimens would affect efficacy. Rates of 5-HT₆ receptor occupancy achieved by once-daily 30-mg and 60-mg doses of idalopirdine apparently supported the reduction of daily total dose and simplification of the dose regime from t.i.d. dosing to OD dosing. As the efficacy results of the phase II were modest and perhaps explainable based on the selection of a more severely ill cohort or on pharmacokinetic interaction between idalopirdine and donepezil, it seems untimely to explore new leads combining 5HT₆ antagonism with ACEI [24].

Conclusion

The major change between phase II and phase III designs of the drug evaluation program of idalopirdine was the dose-regime: in phase II there was a thrice-daily 30-mg dosing regime, and this was adapted to once-daily dosing of 30-mg or 60-mg doses in the first completed Phase III trial. This adaptation was believed to be a response of the company to the tolerability profile of the drug. This deviation from the dose-regime in phase II might have led to a negative phase III study. The case discussed seems to indicate to always use fixed dose range studies in phase II, and first define the lowest effective dose and the no-effect dose. Subsequently do not change the dose-regime from t.i.d. in phase II to once daily in phase III, even if surrogate parameters support such change. Conservatism in drug development might be a key for its success. Furthermore, results from pharmacological in vivo studies are missing; only one study in a rat model of cognitive impairment in schizophrenia was published [25].

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