Precision Medicine (PM) in Alzheimer's Disease (AD): Observed Efficacy Treatment Effects from Blarcamesine Clinical AD Trial Confirms Identified PM Patient Population

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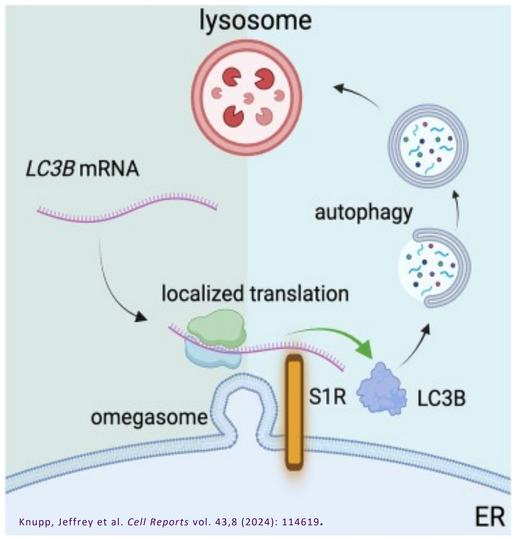
Within a heterogeneous Alzheimer's disease (AD) population, clinical utility of disease-modifying therapeutics could be enhanced via a Precision Medicine (PM) approach of treating those with target-relevant genetic profiles, excluding missense gene populations. This effective targeting with once-daily, oral blarcamesine could alleviate significant medical and economic burdens for up to ~70% of the AD population. With targeting of a prevalent genetic profile, potential improvement in efficacy may be achieved for this drug candidate.

INTRODUCTION

There are no approved ***oral*** disease-modifying treatments for Alzheimer's disease (AD) with the ability to prolong time in the current disease state, with clearly clinically meaningful outcomes to patients, caregivers and clinicians. Blarcamesine is an oral investigational drug having demonstrated promising clinical trial results in a double-blinded placebo-controlled clinical trial, in the intent-to-treat (ITT) population in early AD (1). The mechanistical confirmation of blarcamesine restoring impaired autophagy through SIGMAR1 activation by acting upstream of amyloid and tau pathologies at the molecular level was established both *in vitro* and *in vivo* via enhancing the autophagic flux in human cells and in *C. elegans* as well as increased proteostasis capacity, ultimately ameliorating paralysis caused by protein aggregation in *C. elegans* (2).

A Precision Medicine (PM) approach confirmed the population with deeper clinical responses to blarcamesine, the prespecified SIGMAR1 non-mutated population, termed ABCLEAR1 (up to ~70% of global population). Additional non-mutated populations with potentially enhanced response could also be identified through Genome-Wide Association Study (GWAS) analyses.

Figure 1: Autophagy Restoration Mechanism via SIGMAR1 Activation



Stimulating druggable SIGMAR1 (S1R) to recruit LC3 mRNA represents an attractive therapeutic option for targeting Alzheimer's disease further upstream, preceding amyloid and tau.

METHODS

The Phase IIb/III ANAVEX2-73-AD-004 study was a randomized, double-blind, placebo-controlled, 48-week trial. Blarcamesine was administered orally once-daily in 50mg or 30mg target doses. Clinical endpoint scores in the ITT population were analyzed, as were responses in the prespecified SIGMAR1 non-mutated (ABCLEAR1) gene population, comprising up to ~70% of early AD patients. The fidelity of the pharmacological mechanism of the blarcamesine intervention would provide evidence of improved Precision Medicine (PM) neurology clinical responses through differentiated upstream and constitutional mechanism of action of blarcamesine by enhancing autophagy through SIGMAR1 activation and restoration of cellular homeostasis.

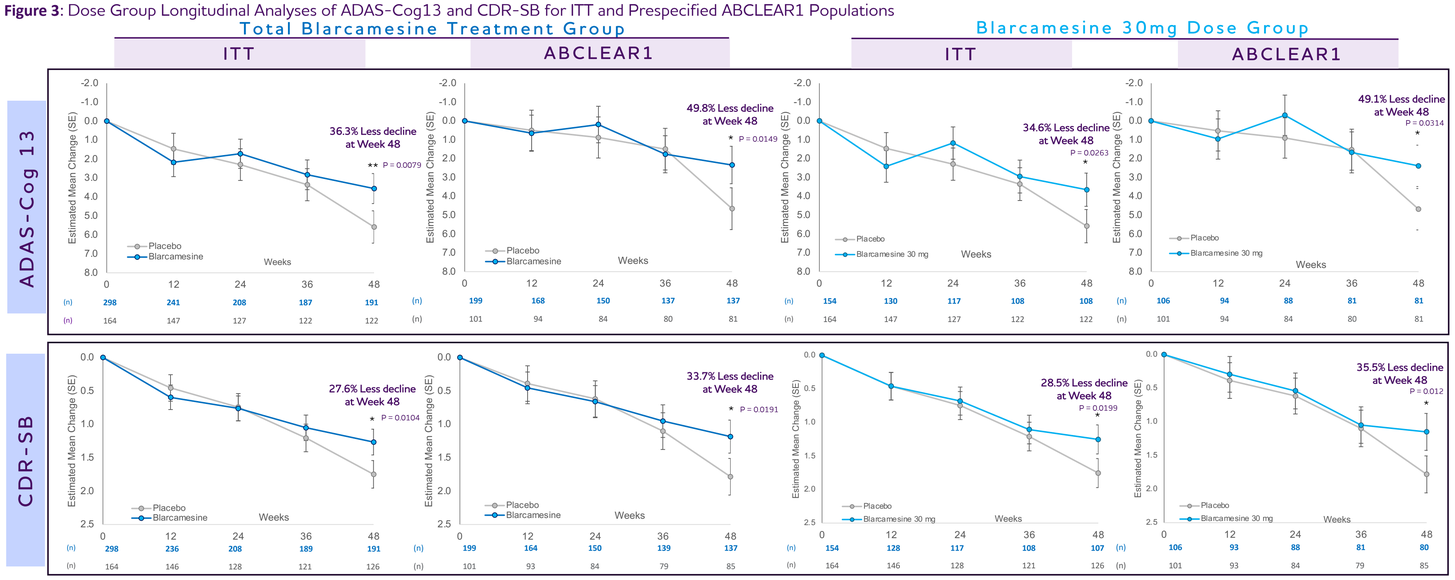
RESULTS

The ITT population (mean age, 73.7 years; 225 [48.7%] women), consisted of 462 randomized participants, with ABCLEAR1 population comprising of 300 participants. While all trial participants improved significantly versus placebo after 48 Weeks (1), 36.3% for ADAS-Cog13 and 27.6% for CDR-SB, respectively, a further, also significant, improvement was observed in the prespecified analysis of SIGMAR1 WT carriers (ABCLEAR1 population). Compared to the ITT population, the ABCLEAR1 population observed further consistent improvement versus placebo. 49.8% and 33.6% for the primary and secondary key endpoints ADAS-Cog13 and CDR-SB total blarcamesine and 49.1% and 35.5% for the 30 mg blarcamesine group, respectively. For the 30 mg blarcamesine group serious TEAEs occurred in 10 participants (12.7%) in the blarcamesine and 6 (9.1%) in the placebo group. Common TEAEs included dizziness, which was transient and mostly mild to moderate in severity. There were no deaths in the blarcamesine 30 mg group and 1 in the placebo group.

Figure 2: Baseline Clinical Characteristics of ABCLEAR1 Population

Clinical Characteristics	Blarcamesine Total (N=199)	Blarcamesine (30 mg) (N=106)	Placebo (N=101)
Baseline clinical scores, Mean (SD)			
ADAS-COG 13 score	28.9 (9.06)	28.6 (8.51)	29.9 (8.87)
ADCS-ADL score	66.8 (7.53)	65.9 (7.53)	67.1 (6.47)
CDR-SB score	3.82 (1.763)	3.96 (1.708)	3.95 (1.727)
MMSE score	23.6 (3.02)	23.6 (3.17)	23.2 (2.79)
Baseline CDR-Global scores, n (%)			
0.5	124 (62.3)	61 (57.5)	61 (60.4)
1	72 (36.2)	43 (40.6)	39 (38.6)
2	2 (1.0)	1 (0.9)	1 (1.0)
3	1 (0.5)	1 (0.9)	0 (0.0)
MMSE score at baseline, n (%)			
≤20	31 (15.6)	16 (15.1)	17 (16.8)
>20	168 (84.4)	90 (84.9)	84 (83.2)
Baseline Plasma p-Tau (181)			
No. of participants evaluated at baseline	183	99	96
Baseline mean (SD), pg/mL	63.9 (26.2)	64.0 (26.7)	66.3 (28.8)
Baseline Plasma p-Tau (231)			
No. of participants evaluated at baseline	132	69	71
Baseline mean (SD), pg/mL	34.4 (48.1)	31.6 (33.6)	24.5 (16.6)

Figure 3: Dose Group Longitudinal Analyses of ADAS-Cog13 and CDR-SB for ITT and Prespecified ABCLEAR1 Populations



Precision Medicine Nomenclature: ABCLEAR = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene; ABCLEAR1 = SIGMAR1 gene variant non-carrier population (Pre-specified)

MMRM analysis of change in score from baseline.
*: P < 0.05; **: P < 0.01

CONCLUSIONS

Chronic Alzheimer's disease (AD) is the most common form of dementia, accounting for 60 to 80% of cases in the elderly. AD is expected to increase worldwide to 66 million by 2030 and 131 million by 2050. Costs of AD and related dementias are projected to reach $384 Billion in 2025 in the U.S. alone.

Oral blarcamesine placebo-controlled Phase IIb/III trial confirmed identified Precision Medicine (PM) patient population (up to ~70% of global population) demonstrating clinically significant improvements for early AD patients, via treating those with target-relevant genetic profiles, excluding missense gene populations. This effective targeting with once-daily, oral blarcamesine could alleviate a significant medical and economic burden for up to ~70% of the AD population. Blarcamesine demonstrated a balanced safety profile with no associated neuroimaging adverse events in the once-daily oral total blarcamesine group as well as in the 30 mg blarcamesine cohort. The ABCLEAR1 population demonstrates further improvement of the already adequate safety profile of the ITT population.

Consistent improvement in clinical effects for the key clinical endpoints was observed, in accordance with significant and further reduced brain atrophy. Latter will be further explored in an upcoming publication.

The Phase IIb/III ANAVEX2-73-AD-004 clinical study demonstrated enhanced efficacy evidenced by the Precision Medicine (PM) paradigm in a pre-specified ABCLEAR1 population. Thus, the specificity of blarcamesine to this genotype underscores the importance of understanding MoA (mechanism of action) and unlocks the potential for further improved Personalized Medicine in AD treatment. The persuasive advantage of blarcamesine's Precision Medicine (PM) approach might lie in the fact that a quite large AD population (up to ~70% of the early AD population) might achieve enhanced clinically meaningful improvements with a scalable and patient friendly convenient once-daily oral pill administration.

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