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Results of the First-in-Human, Randomized, Double-Blind, Placebo-Controlled Phase 1b Study of Lumbar Intrathecal Bolus Administrations of Antisense Oligonucleotide (ISIS 814907; BIIB080) Targeting Tau mRNA in Patients with Mild Alzheimer's Disease

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Intrathecal bolus administration of multiple ascending doses of ISIS 814907 (BIIB080) over 3 months was well-tolerated in patients with mild AD. The robust lowering of CSF total tau and phospho-tau warrants further investigation for the treatment of AD

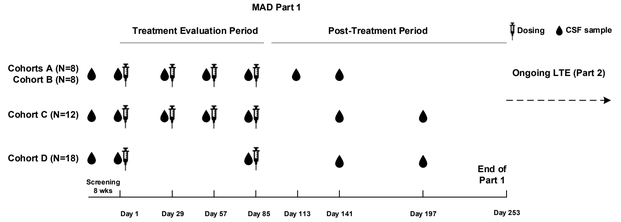
INTRODUCTION

ISIS 814907 (BIIB080) is an antisense oligonucleotide (ASO) that hybridizes to a complementary nucleotide sequence of mRNA of the human microtubule-associated protein tau (*MAPT*) gene, preventing production of tau protein. Accumulation of hyperphosphorylated tau is associated with cognitive decline and brain atrophy in Alzheimer's disease (AD). The placebo-controlled period of the Phase 1b multiple ascending dose (MAD) study of ISIS 814907 in patients with mild AD is complete and the open-label long term extension (LTE) is ongoing in the UK, Canada, Germany, Sweden, Netherlands and Finland (EudraCT: 2016-002713-22; NCT03186989). Results from the placebo-controlled MAD portion of the study are presented.

METHODS

The study is divided into 2 parts. Part 1 is the MAD study, comprising a 3-month Treatment Evaluation (TE) Period and a 6-month Post-Treatment (PT) Period. Part 2 is the open-label LTE, comprising a 12-month TE Period and a 4- or 6-month PT Period. Four ascending dose cohorts were enrolled sequentially and randomized 3:1 to intrathecal bolus (ITB) administrations of ISIS 814907 or placebo. Male or female patients aged 50-74 years with mild AD defined by a Clinical Dementia Rating Overall Global Score of 1 or Global Score of 0.5 with a Memory Score of 1, MMSE score of 20-27 inclusive, and confirmed amyloid positivity (via CSF) at Screening were considered eligible. The primary endpoint was assessment of safety and tolerability of multiple ITB administrations of ISIS 814907. The key exploratory endpoint was CSF total tau.

STUDY DESIGN



At the conclusion of the screening period, eligible patients were randomly assigned in a 3:1 ratio to receive the antisense oligonucleotide drug ISIS 814907 (BIIB080) or placebo: Cohort A (low dose ISIS 814907 or placebo every 4 weeks), Cohort B (medium dose ISIS 814907 or placebo every 4 weeks) and Cohort C (high dose Q4W ISIS 814907 or placebo every 4 weeks) and Cohort D (Q12W dose ISIS 814907 or placebo). All subjects (N=46) completed the MAD TE Period and 43 subjects completed the PT Period.

Cumulative ISIS 814907 dose level during Treatment Evaluation period is as follows: low dose Q4W < medium dose Q4W < Q12W dose < high dose Q4W.

The CSF samples obtained during Screening and on Day 1 were analyzed and results averaged to serve as the baseline sample for CSF biomarker analyses.

RESULTS

Characteristics of Patients at Baseline*

	POOLED PLACEBO (N=12)	TOTAL ISIS 814907 GROUPS (N=34)	ISIS 814907 COHORT A (LOW DOSE Q4W) (N=6)	ISIS 814907 COHORT B (MEDIUM DOSE Q4W) (N=6)	ISIS 814907 COHORT C (HIGH DOSE Q4W) (N=9)	ISIS 814907 COHORT D (Q12W DOSE) (N=13)
Age – year	66±4.6	66±6.1	64±5.2	65±6.1	66±6.8	67±6.3
Female, no. (%)	6 (50)	17 (50)	2 (33)	4 (67)	5 (56)	6 (46)
Race – White, no. (%)	12 (100)	34 (100)	6 (100)	6 (100)	9 (100)	13 (100)
MMSE Total Score	24.2±1.7	23.5±2.4	21.5±1.6	24.5±1.4	24.6±2.5	23.2±2.5
RBANS Total Score	64.9±10.2	68.2±12.1	58.8±11.2	69.2±12.1	69.9±9.1	70.9±13.4
CDR Global Score, no. (%)						
0.5	7 (58)	23 (68)	0 (0)	3 (50)	9 (100)	11 (85)
1	5 (42)	11 (32)	6 (100)	3 (50)	0 (0)	2 (15)
CDR Sum of Boxes	4.1±1.3	3.7±1.1	4.8±0.5	4.7±1.0	2.9±0.6	3.3±1.1
Concomitant Medications no. (%)						
Anticholinesterases	7 (58)	21 (62)	4 (67)	5 (83)	4 (44)	8 (62)
Memantine	1 (8)	7 (21)	2 (33)	0 (0)	3 (33)	2 (15)
Estrogen Replacement	0 (0)	3 (9)	1 (17)	0 (0)	1 (11)	1 (8)
APOE4 Carrier (%)	8 (67)	25 (74)	5 (83)	3 (50)	6 (67)	11 (85)
t-tau Concentration in CSF – pg/mL	387.3±120.9	405.6±132.7	364.6±98.1	386.4±152.3	391.0±111.8	443.4±153.8
p-tau concentration in CSF – pg/mL	38.7±13.0	40.7±14.2	39.1±13.0	38.6±16.6	39.5±12.6	43.2±15.9
t-tau/Aβ42	0.6±0.2	0.6±0.2	0.6±0.2	0.6±0.1	0.5±0.1	0.6±0.2

All subjects (N=46) completed the MAD TE Period and 43 subjects completed the PT Period.

* Plus–minus values are means ±SD. CSF (cerebrospinal fluid); MMSE (Mini Mental State Examination); RBANS (Repeatable Battery for the Assessment of Neuropsychological Status); CDR (Clinical Dementia Rating); APOE4 (Apolipoprotein E4); t-tau (total tau); p-tau (phosphorylated tau); Aβ42 (amyloid β 42).

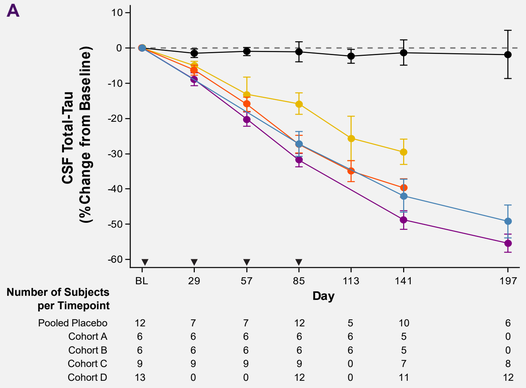
Top 5 Adverse Events (AEs) Reported

All AEs were considered mild (Grade 1) or moderate (Grade 2).
No patients discontinued the study due to an AE

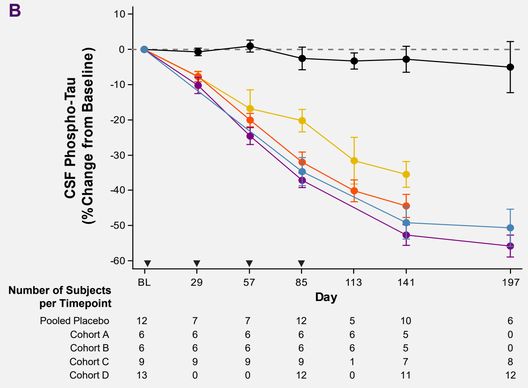
	POOLED PLACEBO (N=12)	ISIS 814907 LOW DOSE Q4W (N=6)	ISIS 814907 MEDIUM DOSE Q4W (N=6)	ISIS 814907 HIGH DOSE Q4W (N=9)	ISIS 814907 Q12W DOSE (N=13)	TOTAL ISIS 814907 (N=34)
MedDRA Preferred Term[1]	**Patients (%)**	**Patients (%)**	**Patients (%)**	**Patients (%)**	**Patients (%)**	**Patients (%)**
Subjects Reporting at Least One Adverse Event	9 (75.0)	6 (100.0)	5 (83.3)	9 (100.0)	12 (92.3)	32 (94.1)
Headache	3 (25.0)	2 (33.3)	3 (50.0)	3 (33.3)	2 (15.4)	10 (29.4)
Post lumbar puncture syndrome	3 (25.0)	3 (50.0)	1 (16.7)	2 (22.2)	3 (23.1)	9 (26.5)
Procedural pain	1 (8.3)	2 (33.3)	0	3 (33.3)	2 (15.4)	7 (20.6)
Musculoskeletal pain	0	1 (16.7)	1 (16.7)	1 (11.1)	1 (7.7)	4 (11.8)
Vomiting	0	0	1 (16.7)	2 (22.2)	1 (7.7)	4 (11.8)

[1] Subjects reporting more than one adverse event were counted only once for the incidence.

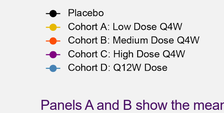
Effect of ISIS 814907 (BIIB080) on CSF Concentrations of Total Tau and Phospho-Tau Protein



Number of Subjects per Timepoint	BL	29	57	85	113	141	197
Pooled Placebo	12	7	7	12	5	10	6
Cohort A	6	6	6	6	6	5	0
Cohort B	6	6	6	6	6	5	0
Cohort C	9	9	9	9	0	7	8
Cohort D	13	0	0	12	0	11	12



Number of Subjects per Timepoint	BL	29	57	85	113	141	197
Pooled Placebo	12	7	7	12	5	10	6
Cohort A	6	6	6	6	6	5	0
Cohort B	6	6	6	6	6	5	0
Cohort C	9	9	9	9	1	7	8
Cohort D	13	0	0	12	0	11	12



Panels A and B show the mean percentage change from baseline over time according to dose group for total-tau and phospho-tau concentration, respectively. Error bars indicate the standard error of the mean. Arrowheads indicate the days on which ISIS 814907 (BIIB080) or placebo was administered.

Cumulative ISIS 814907 dose level during Treatment Evaluation period is as follows: low dose Q4W < medium dose Q4W < Q12W dose < high dose Q4W.

CONCLUSIONS

- Only mild and moderate AEs were reported in MAD Part 1 following ITB administrations of the ASO drug ISIS 814907 (BIIB080) every 4 or 12 weeks (total of 4 and 2 doses, respectively) to adults with mild AD
- ISIS 814907 treatment resulted in a time and dose-dependent reduction in the concentration of CSF t-tau and phospho-tau
- This study demonstrated antisense-mediated tau protein suppression in the central nervous system of patients with mild AD
- These results warrant further investigation of ISIS 814907 (BIIB080) for the treatment of AD and suggest that antisense-mediated suppression of tau protein may be a feasible therapeutic approach for other tauopathies

DISCLOSURES

Dr. Mummery: Advisory board - IONIS, Roche/Genentech, Biogen Research/Clinical Trials – Biogen, IONIS, Roche/Genentech, Lilly, Alector, Prevail, Wave, AC Immune, Eisai

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