Phase 2 Trial of SAR443820 (RIPK1 Inhibitor) in Relapsing and Progressive Multiple Sclerosis: K2 Study Design and Baseline Characteristics

P332

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BACKGROUND

- Receptor-interacting serine/threonine-protein kinase 1 (RIPK1), a critical signalling protein involved in regulating neuroinflammation and cell death, is suggested to play an important role in multiple sclerosis (MS) biology[1,2]
- Neurofilament light chain (NfL), a marker of neuronal damage, is known to increase in MS[3,4]
- Therapeutic administration of a brain-penetrant RIPK1 inhibitor reduced neurofilament levels and disease progression in experimental autoimmune encephalomyelitis[5] and cuprizone animal models[1]
- SAR443820 (DNL788) is an oral, brain-penetrant, selective inhibitor of RIPK1 that regulates inflammatory signalling and cell death pathways[6]
- A Phase 1 trial of healthy volunteers demonstrated that SAR443820 has favourable safety and tolerability, high brain-penetrance and peripheral target engagement[6]
- K2 (NCT05630547) is a Phase 2 study to assess the effects of SAR443280 on serum NfL (sNfL), safety, and tolerability, compared to placebo in participants with relapsing and progressive MS[7]

OBJECTIVE

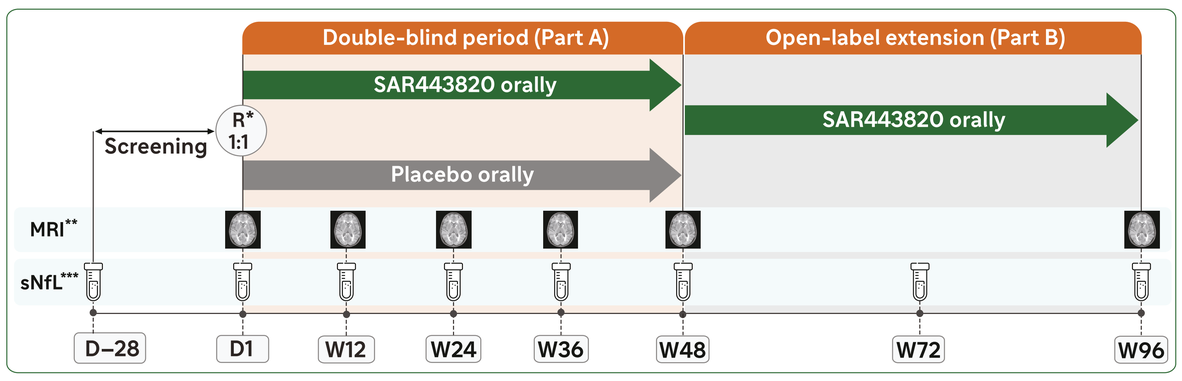
- To present the study design and baseline characteristics of participants enrolled in K2

METHODS

Study design[7]

- K2 is a Phase 2, randomised, double-blind, placebo-controlled, 2 parallel-arm trial, consisting of 2 parts (A and B) (**Figure 1**)
- Part A: 48-week double-blind period, where participants were randomised (1:1) to receive SAR443820 or matching placebo. A minimum of 50% of study participants are required to have progressive MS
- Part B: 48-week open-label extension period (Week 48 through Week 96), where all eligible participants who completed Part A (without disruption of investigational medicinal product) rolled over to receive SAR443820
- Participants were permitted to continue prespecified standard-of-care disease modifying therapies (DMTs) throughout the study

Figure 1: Study design



*Randomisation was stratified by MS clinical subtypes (i.e., RRMS, SPMS, or PPMS) in order to ensure a balance between the treatment and placebo arms within each MS clinical subtype.
**Baseline MRI scan was conducted within 7 days prior to randomisation after completing all other screening assessments. Brain MRI was to be performed at early discontinuation visit only if the previous MRI was done more than 4 weeks ago.
***Serum NfL was collected as part of the blood specimen according to the schedule of activities, with the mean of the screening and Day 1 predose sample levels serving as the baseline value for calculating NfL changes.
In Part A, participants were scheduled to attend in-clinic study assessments at baseline (Day 1) and Weeks 2, 12, 24, 36, and 48. In Part B, participants will attend in-clinic study assessments at Weeks 48, 60, 72, 84, and 96.
D, day; MS, multiple sclerosis; MRI, magnetic resonance imaging; PPMS, primary progressive MS; R, randomisation; RRMS, relapsing-remitting MS; sNfL, serum neurofilament light chain; SPMS, secondary progressive MS; W, Week.

Table 1: Participant eligibility criteria

Key inclusion criteria
• Age 18–60 years
• Diagnosis of RRMS, SPMS (relapsing or non-relapsing), or PPMS
• EDSS score of 2–6 at screening
• Untreated or stable on allowed DMT (interferons, glatiramer acetate, dimethyl fumarate, teriflunomide) for past 3 months and not anticipated to require a change in MS treatment for the duration of the double-blind treatment phase (Part A); In Part B, changes in dose or transition to other allowed DMTs are permitted
Key exclusion criteria
• History of seizures or epilepsy
• Known clinical relapse within 8 weeks of screening
• Any immunodeficiency syndromes or other disease requiring immunosuppressive therapy
• Abnormal laboratory test indicative of chronic infection, liver disease or kidney disease

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

Table 2: Study endpoints

Primary endpoints	
Part A	• W48 sNfL* levels relative to baseline
Part B	• W96 sNfL* levels relative to baseline
Secondary endpoints (Part A)	
Imaging endpoints	• Cumulative number of new Gd-enhancing T1 hyperintense lesions at W48 • Cumulative number of new and/or enlarging T2 hyperintense lesions at W48 • Percent change from baseline in BVL at W48 • Change from baseline in the volume, number, and intensity (T1) of SELs at W12, 24, 36, and 48 • Change from baseline in the total number and volume of non-enhancing lesions at W12, 24, 36, and 48 • Change from baseline in the number of PRL at W12, 24, 36, and 48
Clinical endpoints	• Time to onset of 12 weeks CDP from baseline as assessed by the EDSS score • Time to onset of sustained 20% increase in 9-HPT confirmed over at least 12 weeks • Time to onset of sustained 20% increase in timed T25-FW confirmed over at least 12 weeks • Change from baseline in EDSS-Plus at W48 • ARR of RMS population (relapsing SPMS and RRMS) up to W48
Safety and tolerability	• Incidence of AE, SAE, TEAE, PCSA in laboratory tests
PK	• Plasma concentration of SAR443820
Secondary endpoints (Part B)	
Similar endpoints from Part A will be evaluated in Part B at W96 relative to baseline	

*Serum NfL will be collected as part of the blood specimen according to the schedule of activities, with the mean of the screening and Day 1 predose sample levels serving as the baseline value for calculating NfL changes.
AE, adverse event; ARR, annualized relapse rate; BVL, brain volume loss; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd, gadolinium; 9-HPT, 9-hole peg test; PCSA, potentially clinically significant abnormality; PK, pharmacokinetic; PRL, phase rim lesion; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; SEL, slowly expanding lesion; SPMS, secondary progressive multiple sclerosis; sNfL, serum neurofilament light chain; T1 and T2, intensity; TEAE, treatment-emergent adverse event; T25-FW, timed 25-foot walk test; W, week.

CONCLUSIONS

K2 is a Phase 2, randomised, double-blind, placebo-controlled trial (Part A), followed by an open-label, long-term extension period (Part B)

174 participants with relapsing and progressive MS were randomised to receive either SAR443820 or placebo in this trial. The goal of enrolling at least 50% of participants with progressive MS was achieved

At baseline, participants had a mean age (SD) of 47.7 (8.9) years, 39.7% participants were using concomitant DMTs, 90.8% participants had no Gd-enhancing T1 lesions; mean time (SD) since the last relapse was 6.5 (5.5) years, and 89% participants were relapse-free within the past year

This ongoing Phase 2 trial in participants with relapsing and progressive MS is investigating the safety, tolerability, and effect of SAR443820 on neuroaxonal damage and disease progression as measured by sNfL, MRI, and clinical disability

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RESULTS

- As of data cut-off date, May 16, 2024, 191 participants were screened, and 174 participants were randomised to receive either SAR443820 or placebo (on top of their allowed standard-of-care DMTs)
- Of the 174 randomised participants, at baseline 48% had relapsing MS and 52% had progressive MS

Table 3: Baseline demographics and characteristics - Randomised study population

Category	All (N=174)
Age, mean (SD), years	47.7 (8.9)
Female gender, n (%)	106 (60.9)
Race, n (%)	
White	156 (89.7)
Asian	10 (5.7)
American Indian or Alaska Native	1 (0.6)
Not reported	7 (4.0)
Weight, mean (SD), kg	74.2 (17.8)
Ethnicity, n (%)	
Hispanic/Latino	19 (10.9)
BMI, mean (SD), kg/m²	26 (5.6)

BMI, body mass index; SD, standard deviation.

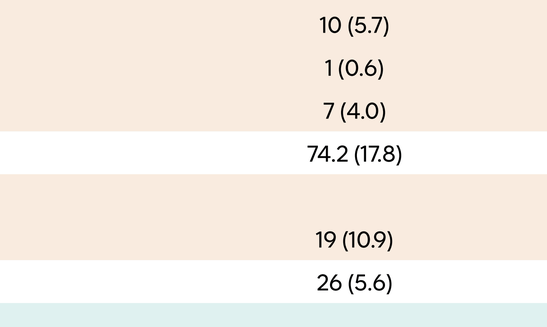
Table 4: Baseline disease characteristics - Randomised study population

Characteristics	All (N=174)
MS clinical subtype, n (%)	
RRMS	76 (43.7)
SPMS	
Relapsing	8 (4.6)
Non-relapsing	67 (38.5)
PPMS	23 (13.2)
Time since most recent relapse, years, mean (SD)	6.5 (5.5)
Number of relapses in past year, mean (SD)	0.1 (0.4)
Number of relapses in past 2 years, mean (SD)	0.3 (0.6)

MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SD, standard deviation; SPMS, secondary progressive MS.

Table 5: Concomitant DMT use at baseline - Randomised study population

Characteristics	All (N=174)
Participants on DMTs, n (%)	69 (39.7)
DMTs by MS subtype, n (%)	
RRMS	49 (28.2)
SPMS	
Relapsing	1 (0.6)
Non-relapsing	18 (10.3)
PPMS	1 (0.6)



*N=69 (% population on DMTs).
DMT, disease-modifying therapy; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SD, standard deviation; SPMS, secondary progressive MS.

Table 6: MRI findings at baseline - Randomised study population

Characteristics	All (N=174)
Number of participants with no Gd-positive T1 lesions at baseline, n (%)	158 (90.8)
Count of Gd-positive T1 lesions at baseline (N=173), mean (SD)	0.2 (1.1)
Count of T2 lesions at baseline (N=173), mean (SD)	49.5 (31.2)

Gd, gadolinium; MRI, magnetic resonance imaging; SD, standard deviation; T1 and T2, intensity.

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