NOVARTIS

CBAF312AIT04 Study Results Abstract for Public Disclosure

Title

Impact of mayzenT (siponimod) on active secondAry progressive multiple Sclerosis patients in a long-term non-Interventional study in ItAly (ITASIA)

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NIS Type

NIS with Primary Data Collection; Novartis Drug NIS

Keywords

Multiple sclerosis, siponimod, disability progression, patient reported outcomes

Rationale and background

Physical disability measured by the Expanded Disability Status Scale (EDSS) and cognitive processing speed measured by the Symbol Digit Modalities Test (SDMT) are functional domains of high clinical relevance for patients with secondary progressive multiple sclerosis (SPMS). Both EDSS- and SDMT-based events can be used and represent a clinically meaningful functional composite endpoint. Confirmed disability progression (CDP) is usually based on changes in EDSS sustained over 3 or 6 months; 6-month CDP is the more robust indicator of permanent disability progression and was used in this study assessed by composite endpoint EDSS or SDMT, defined as a worsening from baseline of either for at least 6 months.

MS reduces quality of life (QoL) by interfering with the ability to work, pursue leisure activities, and carry on usual life roles. Thus, in addition to optimizing symptom management and delaying disability progression, assessing and promoting QoL should be a principal goal of treatment. The effects of siponimod treatment on QoL offer highly relevant and important insights into the benefit of therapy beyond clinical parameters.

The purpose of this study was to produce real-world evidence showing that siponimod is able to provide relevant clinical benefits that comprehensively encompass disability progression, cognitive impairment and QoL.

Research question and objectives

The primary objective of this study is to assess the long-term benefit of siponimod on disability progression in routine clinical practice.

The secondary objectives are to assess:

- Other long-term benefits of siponimod in routine clinical practice.
- Long-term benefits of siponimod on QoL.
- Long-term safety and tolerability of siponimod in routine clinical practice.
- Need for First Dose Observation (FDO) in participants starting siponimod.

Study design

This is a multicenter, single-arm, prospective observational study. Primary data were to be collected over a period of three years. The study was, however, terminated prematurely on 1 July 2025 considering that the analysis of the data collected for up to 2 years of treatment provides sufficiently robust information for the evaluation of the primary and secondary endpoints. Furthermore, studies (EXPAND) show that differences in the parameters evaluated at 24 and 36 months are marginal. Finally, the high dropout rate in the study could have compromised the integrity and reliability of the final analysis.

After the decision to start siponimod treatment as routine clinical care regardless of study participation, an initial baseline visit took place no later than 7 days after the start of treatment. Treatment followed the indications in the EMA approved SmPC. Starting from initial siponimod dose titration, participants who provided informed consent entered the initially planned three-year observation period, during which evaluations of clinical parameters, functional domains, and PROs were documented on a regular basis.

Setting

The study took place in Italy and was to involve 200 participants with active SPMS treated with siponimod as per label and local clinical practice. Data were collected at on-site visits. Prospective data were originally to be collected over a period of 3 years for each participant. The study was however closed in July 2025 (a time when all enrolled participants were to reach 24 months of follow-up).

Subjects and study size, including dropouts

Inclusion criteria

1. Signed informed consent.
2. Male/female participants aged between 18 and 60.
3. Documented diagnosis of active SPMS.
4. Patients newly treated with siponimod (starting not more than 7 days before baseline visit). The decision to start treatment had already been made regardless of study inclusion based on clinical practice and according to SmPC and AIFA criteria.

Exclusion criteria

1. Patients treated outside the approved label or with any contraindication indicated in the SmPC.
2. Pregnant or breastfeeding women.
3. Patients with any clinical condition that could have interfered with their ability to cooperate and comply with the study procedures based on investigator judgement.
4. Participation in an interventional trial.
5. Treatment with siponimod prior to inclusion in this study.

Study size

To have a sample size large enough to describe the impact of siponimod on EDSS or SDMT progression in a real-world clinical setting, a total of 122 patients should be evaluated after 36 months of treatment. This number would provide a precision (measured as the distance from the proportion to the two-sided 95% confidence limit) of roughly 8.6%. To adjust for an expected dropout rate of approximately 13% per year, 200 patients needed to be recruited initially, leaving about 122 patients at month 36 for the assessment of the primary composite endpoint.

Variables and data sources

Variables

Demographic and baseline characteristics

- Demographics: age, sex, weight, height, employment status, education, origin /ethnicity.
- Smoking and alcohol status.

- Physical examination.
- MS history including last disease modifying therapy (DMT) and relapses.
- Non-MS medical history and prior and concomitant medications.
- CYP2C9 genotyping.
- Pregnancy status in women of childbearing age.

Siponimod treatment

- Dosage and dose interruptions.
- First dose observation.

Disease status

- MRI parameters: number of new/newly enlarging T2 (neT2) lesions and gadolinium-enhancing T1 lesions (T1Gd+).
- MS relapse documentation: MS activity status (MS-AS) including timing, duration, treatment, intensity and recovery of relapses.
- Expanded Disability Status Scale (EDSS)
- Confirmed Disability Progression
- Symbol Digit Modality Test (SDMT)
- Timed 25-foot walk (T25-FW)
- Nine-hole peg test

Physician reported outcomes

- Clinical Global Impression (CGI)
- MS Progression Discussion Tool (MSProDiscuss)

Patient reported outcomes

- United Kingdom Neurological Disability Scale (UKNDS)
- Fatigue Scale for Motor Skills and Cognition (FSMC)
- EuroQuol-5D, (EQ-5D)
- Treatment Satisfaction Questionnaire for Medication (TSQM-9)
- Hospital Anxiety and Depression Scale (HADS)

Safety

- Adverse events
- Laboratory findings: WBC, liver test (AST, ALT, bilirubin)
- Vital signs: heart rate, systolic and diastolic pressure
- Pregnancy status

<u>Outcomes</u>

<u>Primary endpoint</u>

The proportion of participants with 6-month CDP assessed by composite endpoint EDSS or SDMT. CDP is defined as a ≥1.0-point worsening of EDSS score from ≤5.0 at baseline or a 0.5-point worsening from >5.0 at baseline OR a ≥4.0-point worsening from baseline of SDMT for at least 6 months.

<u>Secondary endpoints</u>

- Long-term benefits of siponimod in routine clinical practice:
  - Treatment response in terms of relapse (ARR, annualized relapse rate) and MRI parameters.
  - Treatment response after 36 months based on EDSS scores.

  - Treatment response by differentiating participants who stabilized from those who experienced an increase of EDSS score. Moreover, participants with progression were categorized as having continuous disability accrual (CDA) or one-step worsening (OneS-wors), defined as:
    - OneS-wors: one single episode of confirmed EDSS deterioration.
    - CDA: at least two episodes of OneS-wors between at least two time points.
  - Proportion of participants with No Evidence of Disease Activity (NEDA)-3 at end of the study. NEDA-3 is defined as no CDP, no confirmed relapse and absence of T1Gd+ lesions.
  - Summary measures of the following questionnaires and functional tests: UKNDS, FSMC, HADS, SDMT, CGI, MS-AS, T25-foot-walk, 9-Hole peg test.
  - Long-term benefit on QoL and treatment satisfaction assessed by EQ-5D and TSQM-9.
- Long-term safety and tolerability of siponimod in routine clinical practice:
  - Exposure adjusted proportion of participants with adverse event (AE) or serious adverse event (SAE) per 100 subject-years.
  - Discontinuation rates due to AE or other reasons.
- Proportion of participants who required FDO when starting siponimod and the reason.

Statistical methods

The primary endpoint was analyzed considering two time-windows: the first 2 years and the entire study. The proportion of participants with and without 6-month CDP in the first 2 years is provided together with 95% CI computed with the exact Clopper-Pearson method. For participants with 6-month CDP, details related to which parameter led to progression are provided considering the categories “only EDSS”, “only SDMT” or “both EDSS and SDMT”.

For many endpoints, results were broken down according to three categories of EDSS score at baseline: EDSS < 4.0, 4.0 ≤ EDSS ≤5.0, and EDSS > 5.0.

Results

One hundred thirty-four patients were enrolled in the study. At the end of the study, 105 (78.36%) participants were still on siponimod treatment while 29 (21.64%) discontinued. At 24 months, 106 (79.10%) participants were still on siponimod treatment and 28 (20.90%) discontinued.

Primary endpoint

Considering data over the first two years, the proportion of participants with 6-month CDP as composite EDSS and SDMT endpoint was 23.66% (95% CI: 15.46%; 33.60%). Among the 22 participants with 6-month CDP, 11 (50.00%) had worsening of only SDMT, 10 (45.45%) had worsening of only EDSS, and 1 (4.55%) had worsening of both. The proportion of participants with 6-month CDP increased with the increase of EDSS at baseline: 16.67% (95% CI 5.64%; 34.72%) in the EDSS < 4.0 group, 21.88% (95% CI: 9.28%; 39.97%) in the 4.0 ≤ EDSS ≤ 5.0 group, and 32.26% (95% CI: 16.68%; 51.37%) in the EDSS > 5.0 group.

Considering all data collected during the study, only one additional participant experienced 6-month CDP, providing an overall proportion equal to 24.73% (95% CI: 16.37%; 34.76%).

Secondary endpoints

- Annualized Relapse Rate

Considering all data collected, 87 participants (93.55%) did not experience a confirmed MS relapse, and the remaining 6 (6.45%) had one. The estimated ARR was 0.027 (95% CI: 0.012; 0.060), and similar among EDSS classes at baseline. All relapses occurred in the first year of observation.

- MRI parameters

In the first two years of observation, 49 participants (52.69%) underwent at least one MRI assessment. Of them, 4 (8.16%) had at least one new lesion: all reported at least one neT2 lesion and 1 (2.04%) also had T1Gd+ lesions.

- Expanded Disability Status Scale

Mean EDSS value remained stable over the visits overall and within EDSS class at baseline. Overall, 13.98% (95% CI: 7.66%; 22.72%) of participants had at least one confirmed EDSS deterioration in the first two years: 7.69% were One-step worsening (OneS-wors) and 92.31% were classified as CDA.

- No evidence of disease activity-3 (NEDA-3)

Only 18 out of 93 participants (19.35%) were evaluable for NEDA-3 response at 24 months. Of them, 2 were NEDA-3 responders (11.11%).

- United Kingdom Neurological Disability Scale (UKNDS)

An improvement in disability was observed for most of the 12 functional systems of the UKNDS, both overall and in each EDSS class at baseline. Greater disability was observed in the EDSS > 5.0 group. UKNDS total score decreased across all visits both overall and within EDSS class at baseline, except in the EDSS > 5.0 group, where values were stable. Overall, the mean total score was 11.1 ± 5.97 at baseline and 9.2 ± 5.92 at 12 months, resulting in a mean change of -1.9 ± 5.17 (95% CI: -3.0; -0.8); and 9.2 ± 7.03 at 24 months, with a mean change of -2.4 ± 6.77 (95% CI: -3.9; -0.9).

The mean UKNDS total score was lower in the EDSS at baseline <4.0 group, indicating lower disability for participants with lower EDSS score at baseline, when the mean total score was 8.0 ± 4.69 in the EDSS < 4.0 group, 12.6 ± 6.49 in the 4.0 ≤ EDSS ≤5.0 group, and 12.5 ± 5.56 in the EDSS > 5.0 group. At 12 months, the score was 5.6 ± 4.25 in the EDSS < 4.0 group, 9.4 ± 5.26 in the 4.0 ≤ EDSS ≤ 5.0 group, and 12.6 ± 6.10 in the EDSS > 5.0 group. At 24 months, the score was 5.6 ± 5.17 in the EDSS < 4.0 group, 8.1 ± 5.29 in the 4.0 ≤ EDSS ≤ 5.0 group, and 14.1 ± 7.81 in the EDSS > 5.0 group.

- Fatigue Scale for Motor Skills and Cognition (FSMC)

All FSMC scores decreased from baseline to 12 and 24 months. The mean motor score was 34.7 ± 8.77 at baseline and 31.6 ± 10.02 at 12 months, with a mean change of -3.0 ± 9.40; and 31.5 ± 10.66 at 24 months with a mean change of -3.1 ± 10.38. The mean cognitive score was 30.9 ± 10.95 at baseline and 28.0 ± 11.01 at 12 months, with a mean change of -2.6 ± 9.46; and 28.5 ± 10.81 at 24 months, with a mean change of -2.4 ± 10.32; the mean total score was 65.6 ± 18.73 at baseline and 59.7 ± 20.26 at 12 months, with a mean change of -5.6 ± 17.58; and 60.0 ± 20.73 at 24 months, with a mean change of -5.5 ± 19.34. Similar trends were observed in each EDSS class at baseline. The same conclusion can be drawn from the proportion of participants falling into classes (no fatigue, mild, moderate or extreme).

- Hospital Anxiety and Depression Scale (HADS)

HADS-A and HADS-D sub-scores had small fluctuations from baseline to 12 and 24 months. Most participants were classified as having normal status for both anxiety (HAD-A sub-score ≤ 7 points) and depression (HAD-D sub-score ≤ 7 points) at each visit, both overall and in each EDSS class at baseline.

- Symbol Digit Modality Test (SDMT)

SDMT score increased slightly across all visits. The mean score was 39.14 ± 11.350 at Baseline and 41.78 ± 12.753 at 12 months, with a mean change of 2.58 ± 7.088; and 42.58 ± 12.936 at 24 months, resulting in a mean change of 3.92 ± 9.705. Mean SDMT score was greater in the EDSS < 4.0 group.

- Clinical global impression (CGI)

Overall, small fluctuations in the severity of illness (CGI-S) were observed, and considering EDSS class at baseline, the proportion of “normal, not at all ill” participants was greater in the EDSS < 4.0 group.

At 12 and 24 months, most participants had no change. At 24 months, a small improvement was observed in 22 participants (26.83%): 7 (8.54%) were considered much improved and 9 (10.98%) very much improved. Worsening was observed in 13 participants (15.85%) and much worsening in 4 participants (4.88%).

Greater improvement was observed in the EDSS < 4.0 and 4.0 ≤ EDSS ≤ 5.0 groups, while the proportion of worsening participants was greater in the EDSS > 5.0 group at both 12 and 24 months.

At 24 months, physicians reported minimal (35.37%) or moderate (32.93%) therapeutic effect, followed by unchanged or worse status (15.86%), and by marked effect (14.86%). Concerning side effects, only 1 participant (1.22%) had side effects that significantly interfered with functioning, even if a marked therapeutic effect was seen, and 1 participant had side effects that outweighed the unchanged therapeutic effect observed.

- MS activity status (MS-AS)

Overall, a total of 5 MS relapses were observed in 5 participants (5.38%), and their median duration was 4.0 days (Q1; Q3: 3.0; 5.0 days).

- Timed 25-foot walk test (T25-FW) and Nine-hole peg test (9HPT)

Overall, the average time to complete the trial was stable from baseline to 12 and 24 months, and increased with the increase of EDSS class at baseline. Similar results were observed considering the time to complete the 9HPT both with dominant and non-dominant hand.

- EuroQol-5D-3L

A slight improvement was observed in each of the 5 EQ-5D-3L dimensions both overall and in each EDSS class at baseline, and is supported by the increase of EQ-5D VAS value: overall, mean value was 60.4 ± 21.89 at Baseline and 66.4 ± 15.87 at 12 months, with a mean change of 6.7 ± 22.02; and 63.6 ± 18.47 at 24 months, with a mean change of 3.6 ± 20.73. Similar trends were observed in each EDSS class at baseline, but the greater difficulties were reported by participants in the EDSS > 5.0 group.

- Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Overall, the median value for the effectiveness domain was 61.11 (Q1; Q3: 50.00; 72.22) at 12 months, indicating that at least 50% of participants were satisfied with the effectiveness of siponimod, while around 25% reported low satisfaction (score ≤ 50). Satisfaction was greater in the EDSS < 4.0 at baseline group. Similar results were observed at 24 months.

Satisfaction with convenience was high in all EDSS classes at baseline. At 12 months, the median value was 94.44 (Q1; Q3: 77.78; 100.00), indicating that most participants were satisfied, while around 25% reported satisfaction lower than 77.78 points. Similar results were observed at 24 months.

The median value of global satisfaction was 57.14 (Q1; Q3: 50.00; 71.43), again indicating that at least 50% of the participants were globally satisfied with siponimod, while around 25% reported low satisfaction (score ≤ 50). Median global satisfaction was similar between EDSS groups. Similar results were observed at 24 months.

Safety results

Most participants started siponimod at 2 mg (109, 81.34%), 16 (11.94%) started with 1 mg, and 9 with another dose. Mean exposure was 23.18 ± 10.206 months (min; max: 0.1; 36.9 months).

Twenty-nine participants (21.64%) permanently discontinued siponimod: 14 (48.28%) due to adverse event, 7 (24.14%) due to lack of efficacy, and 8 (27.59%) for other reasons.

Thirty-nine participants (29.10%) experienced at least one suspected drug-related AE. The most frequent were “blood and lymphatic system disorders” (18 participants, 13.43%) (all “lymphopenia”) followed by “investigations” (8 participants, 5.97%) (most commonly “lymphocyte count decreased”).

A total of 20 serious adverse events were observed in 18 participants (13.43%) and one participant had bladder cancer that led to death.

Discussion

Siponimod was the first DMT that significantly reduced the risk of disability progression and decline in

cognitive processing speed (CPS) in a large Phase 3 study in SPMS patients (EXPAND), in addition to reducing inflammatory disease activity. Nearly two-thirds of the EXPAND study population had not relapsed in the 2 years before enrolment. At baseline, only about 20% of patients had focal inflammatory activity and more than 50% needed assistance for walking. The patients in the EXPAND study belonged to the least active populations with the most advanced disability at baseline, as 56% of patients had a baseline EDSS of 6 or more.

In the ITASIA study, nearly one-third of the study population had not relapsed in the 2 years before enrolment, whereas nearly two thirds presented evidence of disease activity (presence of MS relapse in the last year and/or presence of gadolinium enhancing lesions). EDSS at baseline was 5 or more for 36.5% of the population, suggesting that the patients were treated at less advanced stages of the disease than in the EXPAND study. Participants included in the ITASIA study had a longer history of disease, with a difference of almost 3 years in time since both diagnosis and onset of MS symptoms compared to patients treated in the EXPAND study. The time since conversion to SPMS was shorter in the ITASIA study (2.18 years vs 3.6 years).

The primary objective of the ITASIA study was to evaluate a novel functional composite endpoint based on disability progression measured by EDSS score and cognitive processing speed measured by the SDMT to characterize disease progression in patients with SPMS more effectively. We analyzed clinically meaningful changes in EDSS and SDMT, i.e., 6-month CDP on EDSS and/or SDMT.

In the first two years of observation, the proportion of participants free of 6-month CDP and that of participants with 6-month CDP was respectively 76.34% and 23.66%. Among the 22 participants with 6-month CDP, 50% had CDP related to worsening of only SDMT, 45.45% had worsening of only EDSS, and 4.55% had worsening of both EDSS and SDMT. The proportions of participants with 6-month CDP increased with increased EDSS score at baseline: 16.67% in the EDSS < 4.0 at baseline group, 21.88% in the 4.0 ≤ EDSS ≤ 5.0 group, and 32.26% in the EDSS > 5.0 group.

Of the 1645 overall patients in the EXPAND study, 358 (21.76%) had EDSS-progression, of whom 279 (78%) had no progression on SDMT; 287 (17.44%) had SDMT-progression, of whom 208 (72%) had no progression on EDSS; 79 (4.8%) progressed on both EDSS and SDMT. At the end of the core study, 62% of siponimod-treated patients versus 52% on placebo remained free of 6-month CDP.

In ITASIA, mean EDSS value remained stable across visits overall and in each EDSS group at baseline. This contrasts with the results of another observational study conducted on SPMS patients in Germany, in which the group with EDSS > 4 at baseline remained stable, whereas the EDSS ≤ 4 group had a significant increase in EDSS from baseline to 12 months. Time to complete the T25-FW and 9HPT was stable from baseline to 12 and 24 months in both this study and ITASIA.

As in the EXPAND trial, we did not observe any overall deterioration in SDMT.

In another observational study conducted by Stavrogianni et al on 50 patients with active SPMS treated with siponimod, no significant change during the follow-up period was observed in EDSS or SDMT, suggesting a stabilization in physical disability progression and lack of significant changes in information processing speed. The results were consistent for the entire sample of patients as well as for the subgroups of patients with EDSS score ≤ 4.5 and ≥ 5.0.

Overall, treatment with siponimod appeared to have beneficial effects on disability (activity limitations measured by UKNDS), fatigue (measured by FSMC), and quality of life (measured by EuroQoL-5D). Most participants were satisfied with siponimod treatment.

In terms of safety, 39 participants (29.10%) experienced at least one drug-related AE (most commonly lymphopenia). Seven participants (5.22%) experienced at least one suspected drug-related SAE.

Conclusion

This study highlights the potential benefits of siponimod treatment in patients with SPMS. In addition, the findings of this study suggest that siponimod offers benefits not only in patients with moderate disability but also in those in more-advanced stages of SPMS where activity may be less evident. In such cases, the efficacy of siponimod results from its effects on a wide spectrum of clinical parameters.

These findings contribute to the evolving landscape of MS therapeutics and underline the importance of exploring novel outcome measures in future research focused on SPMS.

List of abbreviations

AE	Adverse Event
ARR	Annualized Relapse Rate
CI	Confidence Interval
CDA	Continuous Disability Accrual
CDP	Confirmed Disability Progression
CGI	Clinical Global Impression
CGI-S	Clinical Global Impression-Severity of illness
CPS	Cognitive Processing Speed
DMT	Disease Modifying Therapy
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQuol-5D
FDO	First Dose Observation
FSMC	Fatigue Scale for Motor Skills and Cognition
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depression
MS	Multiple Sclerosis
MS-AS	MS Activity Status
MSProDiscuss	MS Progression Discussion Tool
NEDA	No Evidence of Disease Activity
neT2	New/newly enlarging T2
NIS	Non-Interventional Study
OneS-wors	One-Step worsening
PRO	Patient-Reported Outcome
QoL	Quality of Life
SAE	Serious Adverse Event
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SmPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
T1Gd+	Gadolinium-enhancing T1
T25-FW	Timed 25-Foot Walk
TSQM	Treatment Satisfaction Questionnaire for Medication
UKNDS	United Kingdom Neurological Disability Scale