Estimating the Profile of Responders to Treatment: Do Different Patients Show Benefits on Different Outcomes?

Francesca Bovis[1], Ludwig Kappos[2], Sophie Arnould[3], Goeril Karlsson[3], Daniela Piani Meier[3], Maria Pia Sormani[1,4]

[1]Department of Health Sciences (DISSAL), University of Genova, Via Pastore 1, 16132, Genova, Italy; [2]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Head, Spine and Neuromedicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [3]Novartis Pharma AG, Basel, Switzerland; [4]IRCCS Policlinico San Martino Hospital, Genoa, Italy

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Introduction & Objective

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Introduction

- There is a consensus that disability progression in multiple sclerosis (MS) is multi-dimensional; however, the primary outcome of clinical studies in progressive MS is usually one measure, the Expanded Disability Status Scale (EDSS)[1,2], which captures several but not all functional domains affected by MS
- MS is a heterogeneous disease and patients with different clinical and demographic profiles may respond differently across a range of MS clinical outcomes depending on the underlying pathophysiology and the treatment's mechanism of action (MoA)
- Siponimod is a selective S1P1 and S1P5 receptor modulator with a proposed dual MoA, targeting both inflammation and neurodegeneration in MS[3]
- The EXPAND study evaluated the safety and efficacy of siponimod versus placebo in a broad range of patients with secondary progressive MS (SPMS)[4] – a population where other disease-modifying therapies (DMTs) have failed
- In EXPAND, siponimod versus placebo was shown to reduce the risk of disability progression[4], risk of 6-month confirmed clinically meaningful worsening in cognitive processing speed,[5] and reduce grey matter atrophy[6] and magnetization transfer ratio[7]

Objective

- To identify the baseline profile characteristic of super-responders to siponimod in the Phase 3 EXPAND study on four domains of progression (EDSS; upper limb function using the 9-hole peg test [9HPT]; ambulation using the timed-25-foot walk test [T25FWT]; and cognitive processing speed using the single digit modalities test [SDMT])

1. Lublin FD, et al. *Neurology*. 1996;46:907-11. 2. Lublin FD, et al. *Neurology*. 2014;83:278-86. 3. Bigaud M, et al. Poster Presentation at the 8th Joint ACTRIMS-ECTRIMS Meeting, September 11–13, 2020; P0317. 4. Kappos L, et al. *Lancet*. 2018;391:1263-1273. 5. Penner IK, et al. Poster Presentation at the 8th Joint ACTRIMS-ECTRIMS Meeting, MSVirtual2020; September 11–13, 2020; P0806. 6. Fox R, et al. Poster Presentation at the 72nd Annual meeting of AAN, April 25th–May 1st, 2020; P1130. 7. Arnold DL et al. Poster Presentation at the 8th Joint ACTRIMS-ECTRIMS Meeting, September 11–13, 2020; P0587.

Methods

EXPAND study design

- EXPAND was a randomized, double-blind, placebo-controlled, event- and exposure-driven study that investigated the efficacy and safety of siponimod versus placebo in patients with SPMS[1]

Progression domain outcomes

- The outcomes were time to 3-month confirmed progression on each of the following three domains
  - EDSS progression: 1-point increase in EDSS if the baseline score was 3.0–5.0, or a 0.5-point increase in EDSS if the baseline score was 5.5–6.5, confirmed at a scheduled visit at least three months later
  - T25FW, 9HPT progression: worsening of at least 20% from baseline confirmed at a scheduled visit at least three months later
- For SDMT, the outcome was time to 6-month confirmed clinically meaningful worsening of ≥4pt vs baseline

Identification and profiling of super-responders

- A response score derived from baseline characteristics describing participants with a more pronounced treatment effect on each of four domains was generated (EDSS; T25FW; 9HPT; SDMT)[2]
- Super-responder profiles (SRPs) were identified based on the Zhao et al. 2013 approach[3] and by applying the same stringent cut-off of 25% (representing the first quartile of response score) to all outcomes
  - Note: The data reported in the abstract, adopted a variable cut-off ranging between 21% to 55% depending on the outcome

9HPT, 9-hole peg test; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; SDMT, single digit modalities test; SPMS, secondary progressive MS; T25FWT, timed-25-fooot walk test.

1. Kappos L, et al. *Lancet*. 2018;391:1263-1273. 2. Fox R, et al. Poster Presentation at the 72nd Annual meeting of AAN, April 25th–May 1st, 2020; P1130. 3. Zhao L, et al. *J Am Stat Assoc*. 2013;108:527-539.

Methods: Statistical analysis

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Validation of the statistical procedure

- The EXPAND population was randomly split into a training set (70%) and validation set (30%)
- Response scores were generated on the training set by running all the possible models built with the 15 available baseline variables representing 32,767 possible combinations
- For each model, the expected hazard ratio (HR) comparing treatment groups in the training set for non-SRPs and SRPs (1st quartile) was determined, and their ratio was calculated
- The models were ranked in ascending order according to the ratio calculated. The model with the highest ratio was tested on the validation dataset and the p-value of the treatment by score interaction was calculated[1]
- For good generalization performance, training-validation was replicated on 500 bootstrap samples and the procedure was considered validated if at least 70% of the models on the validation set had a ratio >1.2 or a p-value <0.2

Selection of final models and derivation of response scores

- Once the procedure was validated, we used the whole EXPAND dataset to create one response profile for each outcome

SRPs, super-responder profiles.

1. Zhao L, et al. *J Am Stat Assoc*. 2013;108:527-539.

Results: Siponimod treatment effect in super-responders

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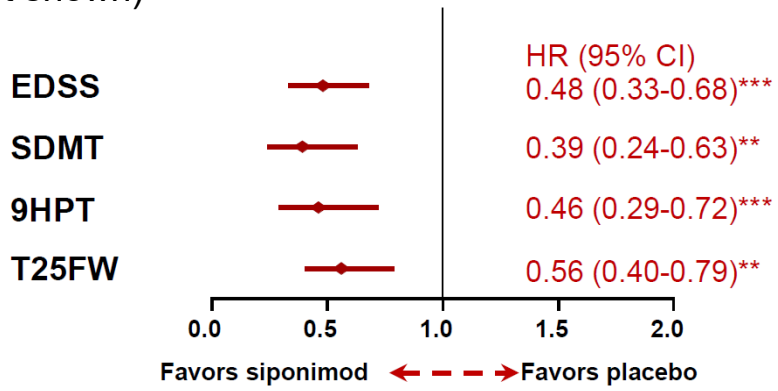
- Of the 1651 patients with SPMS randomized in the EXPAND study, 1645 (~99.6%) patients (full analyses set, i.e., received at least one dose of study drug and had at least one post baseline assessment) were included in this post hoc analysis (siponimod, n=1099 and placebo, n=546)
- For the whole cohort, the risk of 3-month confirmed disability progression was reduced by 21% for EDSS (HR=0.79, p=0.013); 25% for SDMT (HR=0.75, p=0.001); 14% for 9HPT (HR=0.86, p=0.23); and 5% for T25FW (HR=0.95, p=0.53)

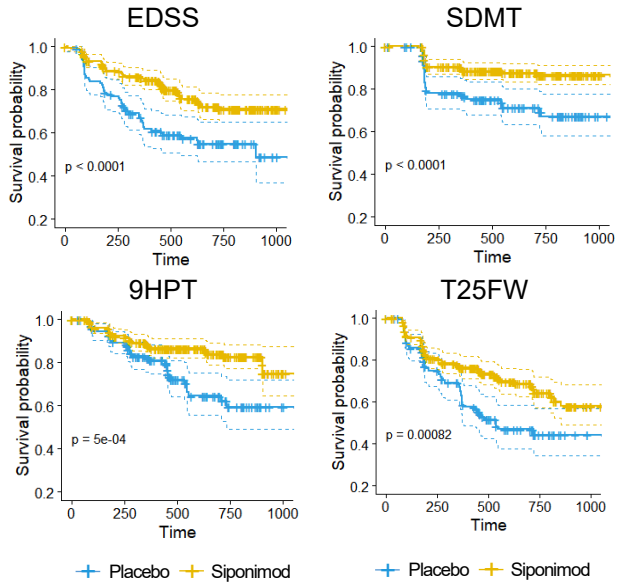
Treatment response of the super-responders for each outcome

- The HR for the non-responders ranged between 0.91 and 1.14
- Applying the variable cut-off of 21-55%, the HR for the SRPs ranged between 0.48, and 0.74 and for the non-SRP between 0.89, and 1.23 (data not shown)



**, p≤.01; ***, p≤.001
9HPT, 9-hole peg test; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; SDMT, symbol digit modalities test; SRPs, super-responder profiles; T25FW, timed 25-foot walk test.

Kaplan-Meier curves of the super-responders for each outcome



Results: Proportion of patients who were super-responders by outcome and patient profiles

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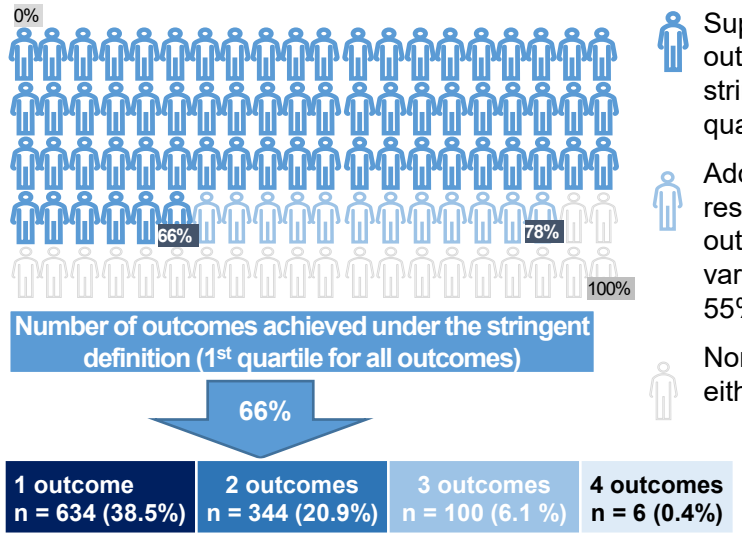
- Applying the stringent cut-off of 25% for all outcomes, 66% of patients were classified as super-responders on at least one outcome with an HR ranging between 0.39 (61% risk reduction) and 0.56 (44% risk reduction)
  - 78% of patients were classified as super-responders applying the variable cut-off
- Notably, different baseline profiles (baseline variables) were associated with each outcome

Proportion of patients achieving super-responder status on ≥1 outcome



Variables predictive of the treatment response on each of the outcomes in order of importance*

EDSS	Age, Gd+ lesions, EDSS, pre-study relapse, SDMT, prior DMT
SDMT	Gender, T25FW, log(disease duration), T1/T2 ratio
T25FW	T1/T2 ratio, $\log_{(\text{disease duration})}$, 9HPT, GM atrophy, logGFAP, EDSS
9HPT	Gd+ lesions, T1/T2 ratio, logGFAP, age

**Predictions > 9% variable importance*

9HPT, 9-hole peg test; EDSS, Expanded Disability Status Scale; Gd, gadolinium; logGFAP, glial fibrillary acidic protein; GM, grey matter; SDMT, symbol digit modalities test; T1/T2, T1 hypointense lesions volume/T2 lesions volume; T25FW, timed 25-foot walk test; TAL, normalized thalamus volume.

Conclusions

- The majority of patients with SPMS treated with siponimod were identified as super-responders on at least one of the outcomes with risk reductions between 44 and 61% on EDSS, SDMT, 9HPT and T25FW

- The super-responders on each domain had distinct baseline characteristic profiles supporting the concept that different pathophysiological processes drive the response on different outcomes and may be related to siponimod's proposed dual MoA, targeting both inflammatory and neurodegenerative pathophysiological processes

- This study also emphasizes the relevance of evaluating treatment response on different aspects of MS and the feasibility of defining patient super-responder profiles by applying innovative methodology as a step towards an optimized and personalized treatment approach to manage MS

9HPT, 9-hole peg test; EDSS, expanded disability status scale; MoA, mechanism of action; MS, multiple sclerosis; SDMT, symbol digit modalities test; SPMS, secondary progressive MS; T25FW, timed 25-foot walk test.