Short- and long-term predictors of relapses or disability worsening in patients with multiple sclerosis in the phase 3 TRANSFORMS study

Aaron Boster,[1] Pavle Repovic,[2] Xiangyi Meng,[3] Daniela Piani Meier,[4] Fernanda Boulos,[3] Till Sprenger,[5] Frederik Barkhof[6]

[1]OhioHealth Neurological Physicians, Columbus, OH, United States; [2]Multiple Sclerosis Center, Swedish Neuroscience Institute, Seattle, WA, United States; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; [4]Novartis Pharma AG, Basel, Switzerland; [5]Medical Image Analysis Center and Department of Neurology, University Hospital Basel, Basel, Switzerland and DKD HELIOS Klinik, Wiesbaden, Germany; [6]Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, Netherlands

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Introduction

- Evidence suggests that long-term clinical outcomes in multiple sclerosis (MS) may be predicted by the treatment and disease histories of patients.[1-3]
- Patients with MS at risk of suboptimal response to first-line therapy may need to have their treatment modified to slow accumulation of inflammation and neurodegeneration and to maximize therapeutic benefit in the long term.[3]
- Several studies investigated the value of measuring inflammatory magnetic resonance imaging (MRI) disease activity or clinical parameters or combinations of these parameters early in MS to predict clinical outcomes.[1-3]

Objective

- Assess whether parameters at baseline and during the 1-year TRANSFORMS study[4] predict relapses, an Expanded Disability Status Scale (EDSS) score >6, or 6-month confirmed disability progression (6MCDP) in the short term and long term during the trial's extension phases.

Methods

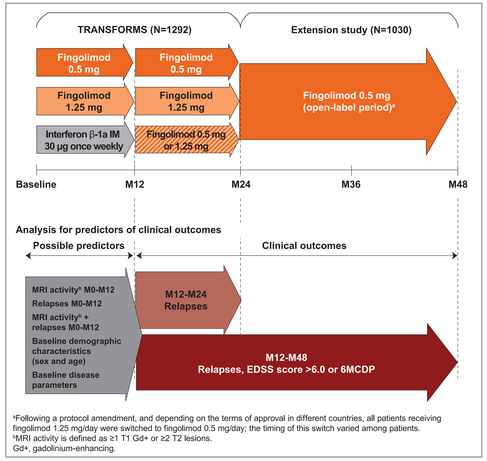
Study design

- TRANSFORMS was a 1-year, double-blind, randomized, phase 3 study of fingolimod compared with intramuscular (IM) interferon (IFN) β-1a.[4]
  - Enrolled patients with relapsing MS were randomized 1:1:1 to receive fingolimod 0.5 mg or 1.25 mg once daily, or IFNβ-1a IM 30 µg once weekly.
- At 1 year, patients randomized to IFNβ-1a IM were re-randomized to fingolimod 0.5 mg or 1.25 mg on entering a 1-year extension phase.[5,6]
- All patients then received fingolimod 0.5 mg in an ongoing open-label extension[7,8] (**Figure 1**).

Analyses

- This was a *post hoc* analysis of TRANSFORMS and its extension over 48 months (M).
- Unadjusted logistic regression analyses assessed which patient variables or disease variables at baseline or between baseline and M12 predicted relapses during M12-24 and M12-48, or predicted disability (EDSS score >6 or 6MCDP) during M12-48.
  - Relapses were confirmed when accompanied by an increase in EDSS score of ≥0.5 points, or an increase of 1 point in two different functional systems (FS), or of 2 points in one FS (excluding bowel/bladder or cerebral FS).
  - 6MCDP was defined as an increase in EDSS score from baseline confirmed at 6M of: 1.5 points if baseline score was 0; 1.0 point if baseline score was 1.0-5.0; or 0.5 points if baseline score was ≥5.5.

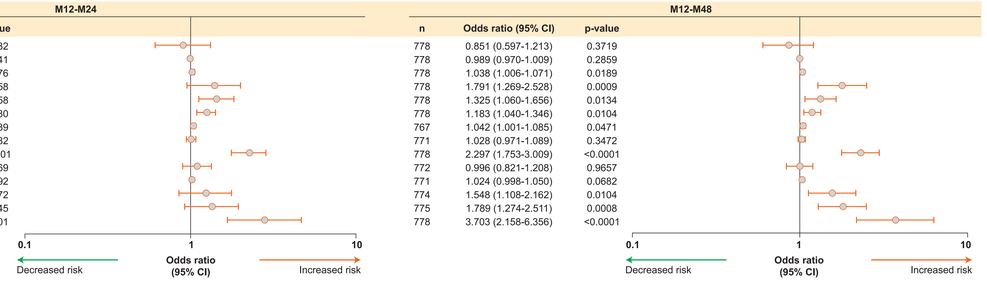
Figure 1. Study design and analysis summary



[a]Following a protocol amendment, and depending on the terms of approval in different countries, all patients receiving fingolimod 1.25 mg/day were switched to fingolimod 0.5 mg/day; the timing of this switch varied among patients.
[b]MRI activity is defined as ≥1 T1 Gd+ or ≥2 T2 lesions.
Gd+, gadolinium-enhancing.

Figure 2. Odds ratios for prediction of relapse activity during the short term (M12-M24) and long term (M12-M48) of TRANSFORMS and its extension phases

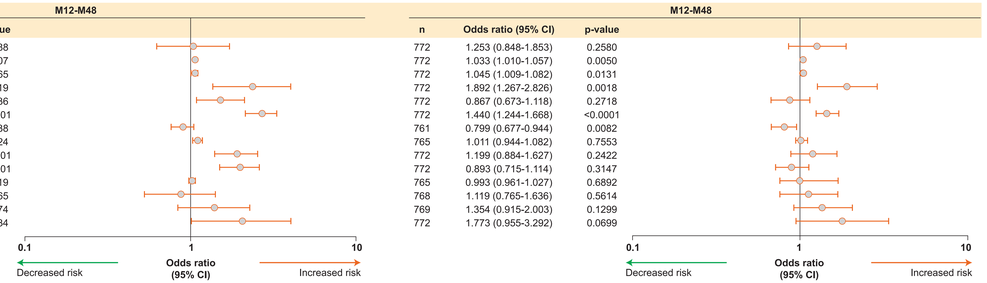
Parameter	M12-M24 n	M12-M24 Odds ratio (95% CI)	M12-M24 p-value	M12-M48 n	M12-M48 Odds ratio (95% CI)	M12-M48 p-value
Sex[a]	973	0.895 (0.602-1.330)	0.5832	778	0.851 (0.597-1.213)	0.3719
Age at core baseline (years)	973	0.996 (0.975-1.018)	0.7341	778	0.989 (0.970-1.009)	0.2859
Duration of MS since diagnosis (years)	973	1.022 (0.987-1.057)	0.2176	778	1.038 (1.006-1.071)	0.0189
Previous treatment for MS	973	1.382 (0.944-2.022)	0.0958	778	1.791 (1.269-2.528)	0.0009
Number of relapses in 2 years before baseline	972	1.428 (1.109-1.839)	0.0058	778	1.325 (1.060-1.656)	0.0134
EDSS score at baseline	973	1.237 (1.075-1.423)	0.0030	778	1.183 (1.040-1.346)	0.0104
Number of Gd+ lesions at baseline	958	1.031 (0.992-1.073)	0.1239	767	1.042 (1.001-1.085)	0.0471
T1 hypointense lesion volume at baseline (cm^3)	964	1.002 (0.934-1.074)	0.9632	771	1.028 (0.971-1.089)	0.3472
Number of confirmed relapses (M0-M12)	973	2.240 (1.751-2.866)	<0.0001	778	2.297 (1.753-3.009)	<0.0001
EDSS score change (M0-M12)	965	1.089 (0.882-1.344)	0.4269	772	0.996 (0.821-1.208)	0.9657
T2 lesion volume at baseline (cm^3)	964	1.018 (0.990-1.046)	0.2092	771	1.024 (0.998-1.050)	0.0682
New T2 lesions at M12 compared with M0	965	1.224 (0.843-1.777)	0.2872	774	1.548 (1.108-2.162)	0.0104
MRI lesion activity (M0-M12)	968	1.336 (0.914-1.952)	0.1345	775	1.789 (1.274-2.511)	0.0008
MRI lesion activity and ≥1 confirmed relapse (M0-M12)	973	2.776 (1.649-4.674)	0.0001	778	3.703 (2.158-6.356)	<0.0001



[a]An odds ratio >1 implies an increased risk in men.
Odds ratios are derived from individual regression models with the respective variable and study as predictors. For continuous variables, the odds ratio corresponds to a unit increase in the explanatory variable. MRI lesion activity is defined as ≥1 T1 Gd+ lesion or ≥2 T2 lesions at any post-baseline assessment up to M12.

Figure 3. Odds ratios for prediction of EDSS score >6 (left panel) and 6-month confirmed disability progression (right panel) in the long term (M12-M48) of TRANSFORMS and its extension phases

Parameter	M12-M48 n	M12-M48 Odds ratio (95% CI)	M12-M48 p-value	M12-M48 n	M12-M48 Odds ratio (95% CI)	M12-M48 p-value
Sex[a]	955	1.037 (0.627-1.714)	0.8888	772	1.253 (0.848-1.853)	0.2580
Age at core baseline (years)	955	1.052 (1.022-1.083)	0.0007	772	1.033 (1.010-1.057)	0.0050
Duration of MS since diagnosis (years)	955	1.056 (1.015-1.098)	0.0065	772	1.045 (1.009-1.082)	0.0131
Previous treatment for MS	955	2.348 (1.369-4.026)	0.0019	772	1.892 (1.267-2.826)	0.0018
Number of relapses in 2 years before baseline	954	1.517 (1.090-2.112)	0.0136	772	0.867 (0.673-1.118)	0.2718
EDSS score at baseline	955	2.669 (2.158-3.300)	<0.0001	772	1.440 (1.244-1.668)	<0.0001
Number of Gd+ lesions at baseline	940	0.896 (0.768-1.046)	0.1638	761	0.799 (0.677-0.944)	0.0082
T1 hypointense lesion volume at baseline (cm^3)	946	1.103 (1.035-1.175)	0.0024	765	1.011 (0.944-1.082)	0.7553
Number of confirmed relapses (M0-M12)	955	1.889 (1.408-2.535)	<0.0001	772	1.199 (0.884-1.627)	0.2422
EDSS score change (M0-M12)	955	1.984 (1.514-2.601)	<0.0001	772	0.893 (0.715-1.114)	0.3147
T2 lesion volume at baseline (cm^3)	946	1.019 (0.984-1.056)	0.2919	765	0.993 (0.961-1.027)	0.6892
New T2 lesions at M12 compared with M0	948	0.864 (0.531-1.407)	0.5565	768	1.119 (0.765-1.636)	0.5614
MRI lesion activity (M0-M12)	951	1.383 (0.845-2.266)	0.1974	769	1.354 (0.915-2.003)	0.1299
MRI lesion activity and ≥1 confirmed relapse (M0-M12)	955	2.027 (1.021-4.023)	0.0434	772	1.773 (0.955-3.292)	0.0699



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- The patient or disease variables used to predict relapses, EDSS score >6 or 6MCDP were:
  - sex, age, duration of MS since diagnosis, previous treatment for MS, number of relapses in the previous 2 years, EDSS score, number of gadolinium-enhancing (Gd+) lesions, T1 hypointense lesion volume and T2 lesion volume (all at baseline)
  - number of confirmed relapses, change in EDSS score, number of new T2 lesions, MRI lesion activity (≥1 T1 Gd+ or ≥2 new T2 lesions),[9] MRI lesion activity and ≥1 confirmed relapse (all from baseline to M12).

Results

- In total, 1292 patients were randomized in TRANSFORMS (analysis sets: M12-M24, n=973; M12-M48, n=778).

Predictors of relapses

- Strongest predictors of relapses in both the short (M12-M24) and long (M12-M48) term were (**Figure 2**):
  - MRI lesion activity and ≥1 confirmed relapse between baseline and M12
  - number of confirmed relapses between baseline and M12.
- Other strong predictors of relapse activity in the long term were (**Figure 2**):
  - previous treatment for MS
  - MRI lesion activity between baseline and M12
  - number of new T2 lesions at M12 compared with baseline.
- Other predictors of relapses in both timeframes were (**Figure 2**):
  - number of relapses in the 2 years before baseline
  - EDSS score at baseline.

Predictors of disability worsening

- Baseline parameters that predicted disability reaching an EDSS score >6 and 6MCDP in the longer term were (**Figure 3**):
  - EDSS score
  - duration of MS
  - age
  - previous treatment for MS.
- Other predictors of an EDSS score >6 in the longer term were (**Figure 3**):
  - EDSS score change between baseline and M12
  - number of relapses in the 2 years before baseline
  - number of confirmed relapses between baseline and M12
  - T1 hypointense lesion volume at baseline
  - MRI lesion activity and ≥1 confirmed relapse between baseline and M12.

Conclusions

- Combined MRI lesion and relapse activity in the 1-year TRANSFORMS study was the strongest predictor of relapses at up to 4 years.
- Longer-term predictors of disability worsening based on an EDSS score >6 or on 6MCDP were EDSS score, previous treatment, disease duration and age at baseline.

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Disclosures

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Text: Qe1f3e
To: 8NOVA (86682) US only
+18324604729 North, Central and South Americas; Caribbean; China
+447866024038 UK, Europe and Russia
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Presenter email address:
aaron.boster@ohiohealth.com