

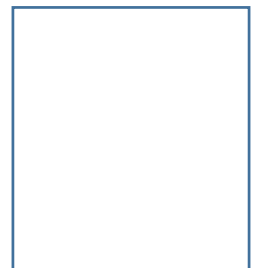
Preliminary data from the 5-year Hungarian fingolimod registry

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K.Bencsik has received travel support,, speaking and participation fees in advisory boards for Biogen, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, Teva. **T.Biernacki** has received travel support from Novartis. **J.Füvesi** has received personal compensation for activities with Teva, Novartis, Genzyme and travel support from Biogen, Sanofi-Genzyme, Teva. **Cs.Rózsa** has received travel support from Biogen, Sanofi-Genzyme, Teva, Merck-Serono, speaker and consultancy honoraria from Teva, Sanofi-Genzyme, Biogen, Roche, compensation fees for participating on advisory board from Biogen, Roche, Merck-Serono, Novartis. Prof **S.Komoly** has received travel support, speaker and consultancy fees, compensation for participating on advisory board from Biogen, Novartis, Teva, Sanofi-Genzyme, Schering, travel support from Merck-Serono, research grant from Teva. **Cs.Botond** has received travel support from Biogen, speaker and consultancy fees from Novartis, compensation for participating on advisory board from Merck-Serono, Sanofi-Genzyme, research grant from Teva. **J.Nikl** has received compensation for participating on advisory board from Novartis. **A.Csányi** has received travel support from Biogen, Novartis, Teva, speaker and consultancy fees from Actelion, Biogen, Novartis, Teva and compensation for participating on advisory board: Merck, Novartis. **G.Rum** has received travel support from Biogen, Sanofi-Genzyme, speaker and consultancy fees from Biogen, Novartis, Merck-Serono, Sanofi-Genzyme, compensation for participating on advisory board from Biogen, Novartis. **Á.Köves** has received travel support from Novartis, Biogen, Sanofi- Genzyme, Teva, Merck-Serono, Roche and speaker and consultancy fees from Novartis, Biogen, Sanofi- Genzyme, compensation for participating on advisory board from Novartis. K.Krisztina has received travel support from Sanofi-Genzyme. **G.Jakab** has received travel support, speaker and consultancy fees from Bayer, Biogen, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, compensation for participating on advisory board from Biogen, Sanofi-Genzyme, Novartis, Merck-Serono, Teva. **M.Simó** has received travel support from Biogen, Sanofi-Genzyme, Roche, speaker and consultancy fees from Biogen, Sanofi-Genzyme, Merck-Serono, Novartis. **T.Csépány** received speaker honoraria/ conference travel support from Bayer Schering, Biogen, Merck , Novartis, Roche, Sanofi-Aventis and Teva. **Z.Jobbágy** has received travel support from Bayer, Biogen, Novartis, Merck-Serono, Roche, Sanofi-Genzyme, Teva, speaker and consultancy fees from Bayer, Biogen, Novartis, Merck-Serono, Sanofi-Genzyme, Teva, compensation for participating on advisory board from Novartis, Biogen. **E.Dobos** has received travel support from Bayer, Biogen, Novartis, Merck-Serono, Sanofi-Genzyme and compensation for activities from Novartis, Merck-Serono, Teva, **Sz.Péntek** has received travel support from Bayer, Biogen, Novartis, Merck-Serono, Sanofi-Genzyme and speaker honoraria from Novartis, Biogen. **A.Szentesi** has been employe of Novartis. **Prof L.Vécsei** has received travel support from Sanofi-Genzyme, Biogen, Teva, speaker and consultancy fees from Novartis, Merck-Serono, Sanofi-Genzyme, Biogen, Teva, Roche, compensation for participating on advisory board from Novartis, Sanofi-Genzyme, Biogen, Teva, Merck-Serono, Roche, research grant from Novartis.

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Study background, objective, design

Background

- Fingolimod is a sphingosine 1-phosphate receptor modulator approved by the European Medicines Agency in 2011.
- Fingolimod has been reimbursed in Hungary since 2014 for both first-line and second-line treatment in patients (by reference to the summary of product characteristics) with relapsing-remitting multiple sclerosis (RRMS) to reduce disease activity.

Objective

This non-interventional study aims to collect long-term data on real-world effectiveness in patients treated with fingolimod in Hungary.

Design/ Methods

- This study combines retrospective and prospective methods from fingolimod treated patients in order to obtain long term 5 year dataset from 23 multiple sclerosis centers. The preliminary analysis on the dataset was available on the 2nd of April, 2020.
- A total of 720 patients have been enrolled to the study and have received at least one dose of fingolimod.

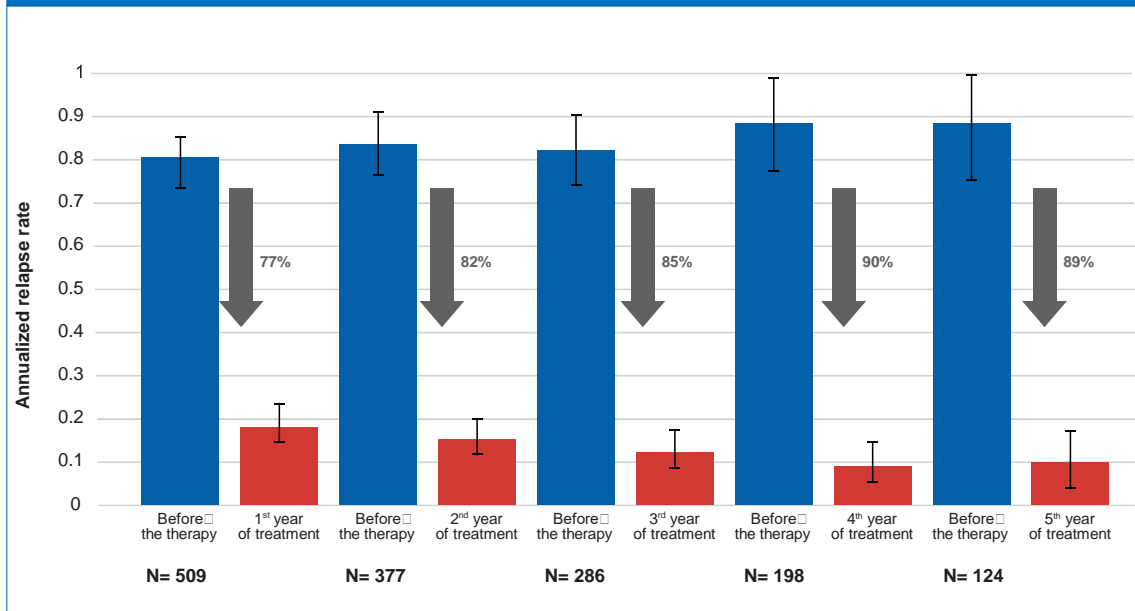
Outcomes and statistical analysis

- Of the 720 patients enrolled (safety population, SP), 570 completed (Intention To Treat population, ITT) at least 1 year follow-up by the end of study. A total of 570 (100.0%), 420 (73.7%), 314 (55.1%), 213 (37.4%) and 132 (23.2%) patients had received fingolimod for 1, 2, 3, 4 or 5 years, respectively.
- The ITT population consisted of 178 (31.2 %) men and 392 (68.8 %) women, mean age was 39.14±9.79 years, age at disease onset was 28.7±8.5 years, mean disease duration was 10.2±6.7 years.
- 89.5% of pts. were previously treated with a disease modifying therapy, most commonly with glatiramer acetate (175 pts).
- For patients switching from injectables the most common reason for the discontinuation and change to fingolimod was the lack of effectiveness of the previous treatment (53-65%). For switchers from natalizumab the main drive for the change was the increased risk of progressive multifocal leukoencephalopathy (75%) For other immunomodulants the reasons for the change were mixed (etc. side effects for dimethyl fumarate – 71.4%, lack of efficacy for teriflunomide –66.6%).
- The vast majority (565, 99.1%) of patients in the ITT population suffered at least 1 relapse before study start, megadose steroid therapy was necessary for the treatment of 553 (97.0%) patients' relapses. The mean number of relapses before study start was 4.93 ± 3.01 (median 4.0).
- In total 237 patients have terminated the study early, the leading cause of permanent discontinuation was the lack of effectiveness (31.2%), adverse events (5.4%), pathological laboratory findings (3.8%), lost to follow-up (3.2%), informed consent withdrawal (1.0%), administrative problems (0.1%) and other reasons (9.2%).

The persistence with fingolimod after 60 months was 73.4%.

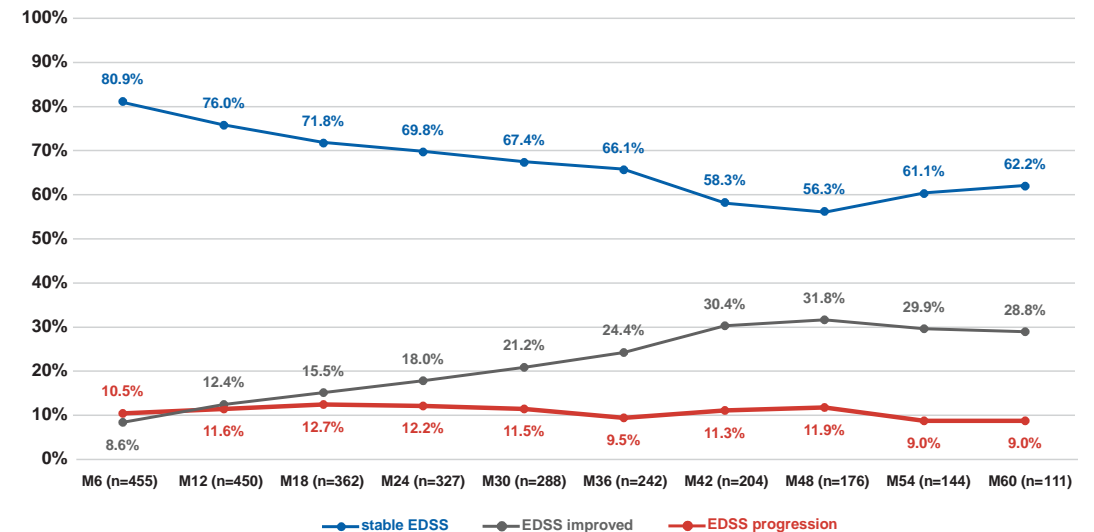
Efficacy: ARR and EDSS

Change in ARR during 5 years treatment



The annual relapse rate (ARR) of patients treated with fingolimod was substantially reduced from 0.80 ± 0.69 (baseline) to 0.19 ± 0.51 ($p < 0.001$) at first, 0.15 ± 0.41 ($p < 0.001$) at second, 0.12 ± 0.38 ($p < 0.001$) at third, 0.09 ± 0.34 ($p < 0.001$) at fourth, and 0.10 ± 0.37 ($p < 0.001$) at fifth year of treatment

Change in EDSS over 5 years



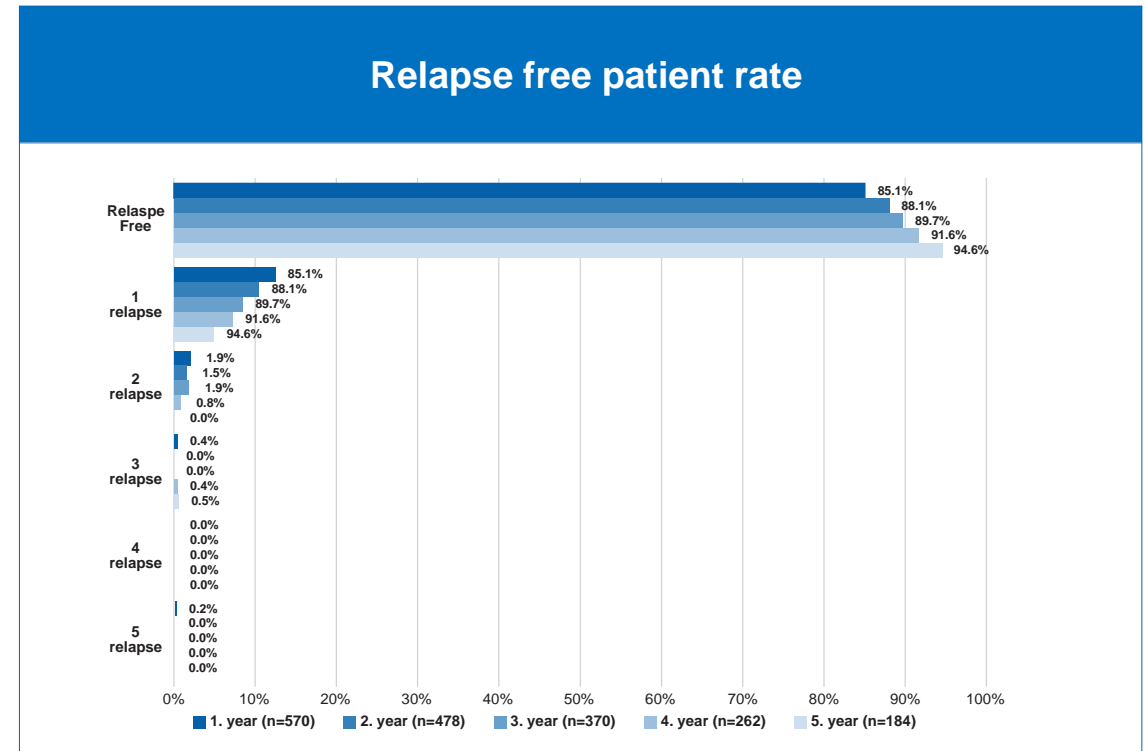
The proportion of patients with an EDSS score lower than, or equal to that seen before the study start was near, or over 70% at any time point during the observation period. Among the patients who completing the study 62.2% had stable, 9.0% had improving and 28.8% had worsening EDSS scores through the study

Efficacy: Relapse free rate

ARR and CDP					
	Proportion of patients free from relapse	Cumulative proportion of patients free from relapse	Proportion Of patients free from 6 month CDP	ARR	Reduction in ARR compared tobaseline, %
Year 1	85.1%	85.1%	87.6%	0.185	77.0%
Year 2	88.1%	77.6%	81.9%	0.149	82.1%
Year 3	89.7%	73.8%	75.6%	0.122	85.2%
Year 4	91.6%	71.0%	68.2%	0.091	89.7%
Year 5	94.6%	69.6%	71.2%	0.097	89.0%

RR: annualized relapse rate, CDP: confirmed disability progression.

After 1, 2, 3, 4, and 5 years of treatment 85.1%, 77.6%, 73.8%, 71.0%, and 69.6% of the patients were completely relapse-free.



In the 1st, 2nd, 3rd, 4th, and 5th year 85.10%, 88.10% 89.70%, 91.60% and 94.60% of the patients did not experience a relapse.

Efficacy: long term outcome

- **The annual relapse rate (ARR)** of patients treated with fingolimod was substantially reduced from 0.80 ± 0.69 (baseline) to 0.19 ± 0.51 ($p < 0.001$) at first, 0.15 ± 0.41 ($p < 0.001$) at second, 0.12 ± 0.38 ($p < 0.001$) at third, 0.09 ± 0.34 ($p < 0.001$) at fourth, and 0.10 ± 0.37 ($p < 0.001$) at fifth year of treatment
- **The mean Expanded Disability Status Scale (EDSS)** score of all enrolled patients at baseline was 2.67 ± 1.52 , which rose to 3.32 ± 1.92 by the end of the 5th year
- The vast majority (486, 85.30%) of the subjects has **remained radiologically stable** during the study period, progression was reported in the case of only 32 (5.60%) patients. No radiological data was supplied about 52 (9.10%) patients

Change in value during study		
ARR	prior to study start (mean, 95% CI)	0.80 (0.74-0.86)
	Year 1	0.19 (0.14-0.23)
	Year 2	0.15 (0.11-0.19)
	Year 3	0.12 (0.08-0.17)
	Year 4	0.09 (0.04-0.14)
	Year 5	0.10 (0.03-0.16)
EDSS Score	Baseline	2.67 (± 1.52)
	Year 1	2.66 (± 1.66)
	Year 2	2.85 (± 1.75)
	Year 3	2.96 (± 1.86)
	Year 4	3.16 (± 1.89)
	Year 5	3.32 (± 1.92)
MRI	Progression	32
	Stable	483
	No data	52

Safety

Adverse Events

- At first dose monitoring pathological findings were seen on the ECG in 6 cases (1-1 case of 1st degree AV block, incomplete right bundle branch block, complete bundle branch block, and sinus arrhythmia, and 2 cases of sinus bradycardia).
- No patients presented with any kind of cardiac adverse event and no patients were diagnosed with any, previously unknown rhythm abnormalities during the study.
- The first dose of fingolimod had a clinically meaningless, however statistically significant effect on both systolic, and diastolic blood pressure and heart rate of the patients (122/77 Hgmm vs. 119/77 Hgmm, $p < 0.001$), concomitantly the mean heart rate fell from 77/min to 67/min ($p = 0.001$).
- During follow-up, 467 patients (64.86%) had experienced at least one adverse event, in total 1057 AEs have been documented.
- Mainly infections (167, 15.79%, mostly urinary tract – 12, 1.7% and upper respiratory tract infections – 68, 9.4%), liver enzyme elevations (54, 5.10%), lymphopenia (61, 5.77%) and leukopenia (17, 1.60%), gastrointestinal and chest discomfort (11, and 12 cases, 1.05% and 1.13%, respectively), dizziness and headache (24-24 cases, 2.27%) have been reported.
- Long-standing bradycardia was reported 9 times (0.85%), herpes zoster infection occurred 6 times (0.56%). No patients were identified with macular edema or PML.
- Temporary treatment suspension due to an adverse event was necessary in 199 of the 1057 cases. Reasonable causality with fingolimod was assumed in only 218 (20.6%) cases. The vast majority of events resolved deterioration was observed only in 3 patient's state.

Safety

Serious Adverse Events

- Of the 1057 adverse events, 124 (36 severe relapses, 88 other events) have been classified as SAEs, reported by 93 patients (12.92%).
- Temporary treatment discontinuation was necessary in 27 cases, causality with fingolimod was presumed in 99 occasions.
- Most patients recovered completely (107, 86.2%), deterioration or recovery with residual symptoms was seen in only a fraction of the cases (5, 4.0%), the fate of the remaining events were left unreported.
- During the observation period four patients have deceased, no causality was assumed with fingolimod in either of the cases. The causes of death were breast cancer, septicemia with concomitant paralytic ileus secondary to cholangiocarcinoma, status epilepticus with subsequent cardiorespiratory failure, and the consequences of long-term bedriddenness.
- Fourteen participants have been diagnosed with a tumor 9 patients had benign masses; 1 hemangioma, 2 lipomas, 1 thyroid adenoma, 1 breast adenoma, 1 unspecified benign tumor, and 3 skin papillomas were reported.
- Five malignant neoplasms have been detected; 1 malignant melanoma, 1 breast cancer, 1 cholangiocarcinoma, 1 bladder transitional cell carcinoma, and 1 anogenital wart, which is within the range of expected malignancies in the general and MS populations.

Conclusions

Real-world evidence data from the preliminary analysis results from the 5-year Hungarian fingolimod registry further support the positive effectiveness profile of fingolimod in RRMS as demonstrated in the Phase 3 clinical trials.