Design and baseline characteristics of Phase 3, double-blind, randomised trials evaluating the efficacy and safety of evobrutinib versus teriflunomide in relapsing multiple sclerosis (evolutionRMS 1 and 2)

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CONCLUSIONS

- **The demographics and baseline characteristics were similar across the Phase 3 evolutionRMS 1 and 2 trials, and the combined trial cohort (n=2285) will allow for a robust assessment evaluating the safety and efficacy of evobrutinib in RMS**
- **In addition to an assessment of ARR, CDP and CDI, the evolutionRMS 1 and 2 trials will be the first Phase 3 RMS trials that include both fluid biomarkers and MS-specific patient-reported outcomes measuring fatigue and physical function as key secondary endpoints**

INTRODUCTION

Evobrutinib

- An oral, CNS-penetrant, highly selective covalent BTK inhibitor[1–3]
- Designed to target both CNS-compartmentalised and peripherally-driven inflammation through dual effects on B cells and microglia. Both are important drivers of neurodegeneration and disability progression in MS[4–6]

Phase 2
NCT02975349

- The efficacy and safety of evobrutinib was shown in a Phase 2, double-blind, randomised controlled trial in patients with RMS[7]
  - BID dosing was identified as the most efficacious dosing regimen versus QD to achieve maximal sustained BTK occupancy, likely due to the continuous turnover of endogenous BTK protein and rapid clearance from the system[8]
  - Evobrutinib met its primary endpoint (reduction in total cumulative T1 Gd^+ lesions at Weeks 12–24)[7]
  - The clinical efficacy and safety profile of evobrutinib has remained consistent over 4.5 years of treatment in the ongoing open-label extension[9,10]

Phase 3
NCT04338022
NCT04338061

- Based on the results from the Phase 2 trial, the Phase 3 evolutionRMS trials were initiated to investigate the efficacy and safety of evobrutinib versus teriflunomide in RMS
- Evobrutinib 45 mg BID with food used in the Phase 3 trials is predicted to be comparable with respect to exposure and BTK occupancy to 75 mg BID fasted used in the Phase 2 trial[8]

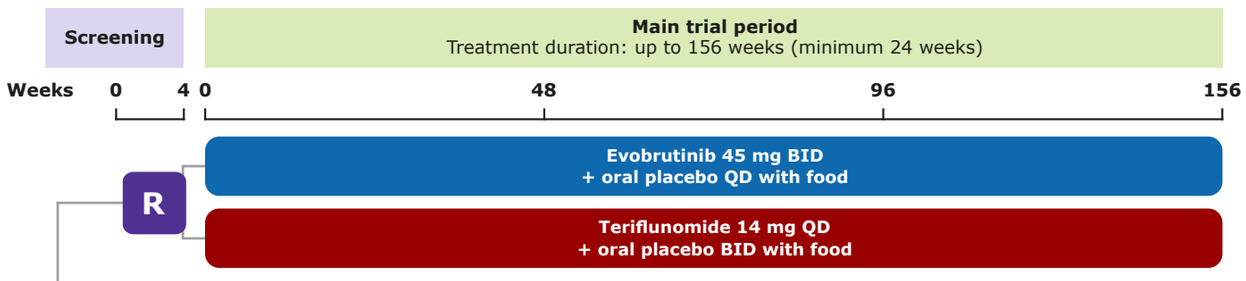
OBJECTIVE

To describe the trial design and baseline characteristics of evolutionRMS 1 and 2, two Phase 3 trials of evobrutinib in patients with RMS

METHODS

TRIAL DESIGN

Multicentre, randomised, double-blind, double-dummy, active comparator-controlled trials conducted in parallel



Inclusion criteria
- 18–55 years
- RRMS or active SPMS (i.e., with superimposed relapses)
- ≥1 relapse in <2 years
- EDSS 0–5.5

Exclusion criteria
- PPMS or SPMS (without superimposed relapses)
- >10 years with EDSS ≤2
- Other neurological disorders

Primary
• ARR based on qualified and adjudicated relapses up to 156 weeks
Secondary
• Time to first occurrence of 12-/24-week CDP (EDSS) up to 156 weeks*†
• Time to first occurrence of 24-week CDI (EDSS) up to 156 weeks*†
• Change from baseline in PROMIS physical function and fatigue scores over 96 weeks*†
• Total number of T1 Gd^+ lesions* • Number of new/enlarging T2 lesions*
• NfL concentration at 12 weeks*
• Adverse events
Exploratory
• Included, but not limited to PIRA, NEDA-3, slowly expanding lesions, paramagnetic rim lesions, brain/grey matter/thalamic volume, SDMT, anti-SARS-CoV-2 antibodies

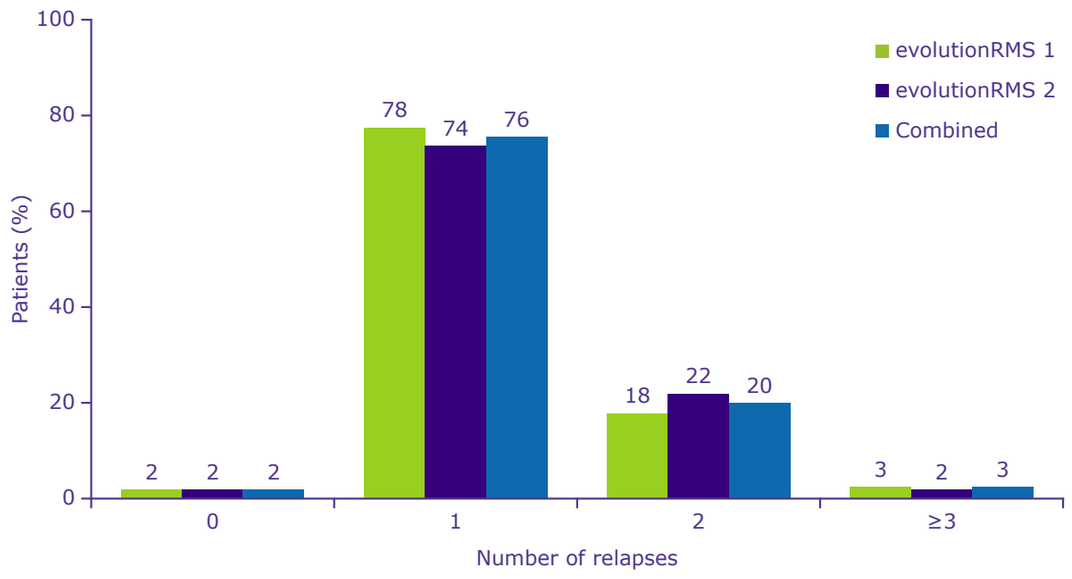
*Hierarchical testing structure
†Pooled across the two trials

RESULTS

Baseline characteristics	evolutionRMS 1 N=1122	evolutionRMS 2 N=1163	Combined N=2285
Age, years	37.7 [±9.5]	36.7 [±9.3]	37.2 [±9.4]
Female, n (%)	751 (66.9)	781 (67.2)	1532 (67.0)
White, n (%)	1051 (93.7)	1104 (94.9)	2155 (94.3)
Not Hispanic/Latino, n (%)	995 (88.7)	1081 (92.9)	2076 (90.9)
MS type, n (%)			
RRMS	1080 (96.3)	1116 (96.0)	2196 (96.1)
SPMS	42 (3.7)	47 (4.0)	89 (3.9)
Time since symptom onset, years	6.7 [±6.8]	6.7 [±6.7]	6.7 [±6.7]
Time since diagnosis, years	4.7 [±5.8]	4.8 [±5.7]	4.7 [±5.7]
≥1 relapse in the year before randomisation, n (%)	1101 (98.1)	1142 (98.2)	2243 (98.2)
EDSS score			
Mean [±SD]	2.7 [±1.3]	2.8 [±1.2]	2.8 [±1.3]
Median (IQR)	2.5 (2.0–3.5)	2.5 (2.0–3.5)	2.5 (2.0–3.5)
MRI			
T1 Gd+ lesions: Mean **n** [±SD]	1.4 [±3.60]	1.4 [±3.51]	1.4 [±3.55]
T2 lesions: Mean **vol.** [±SD], cc	14.33 [±13.77]	14.98 [±13.49]	14.66 [±13.62]

Data from an ongoing trial: data cut-off 8 December, 2022
Data are mean [±SD], unless stated otherwise

Relapses in year prior to randomisation



Data from an ongoing trial: data cut-off 8 December, 2022

Key results

- Baseline characteristics are similar across both evolutionRMS trials
  - **96.1%** diagnosed with RRMS
  - **67.0%** female
  - **4.7 [±5.7]** years since diagnosis*
  - **2.8 [±1.3]** EDSS score*
  - **63.5%** treatment naïve (evolutionRMS 1: 64.0%; evolutionRMS 2: 63.1%)

Data from an ongoing trial: data cut-off 8 December, 2022
*Data are mean [±SD]

Prior DMTs	evolutionRMS 1 N=1122	evolutionRMS 2 N=1163	Combined N=2285
Any prior DMTs, %	36.0	36.9	36.5
Interferons	22.2	23.6	22.9
Glatiramer acetate	13.0	9.8	11.4
Dimethyl fumarate/diroximel fumarate	6.5	7.1	6.8
Fingolimod/siponimod/ozanimod/ponesimod	2.0	1.9	2.0
Teriflunomide	2.0	1.8	1.9
Ocrelizumab/ofatumumab/rituximab/ublituximab	1.2	0.9	1.1
Natalizumab	0.4	1.8	1.1
Cladribine	0.1	0.3	0.2
Mitoxantrone	0.2	0.0	0.1
Other	5.3	4.4	4.9

Data from an ongoing trial: data cut-off 8 December, 2022

Abbreviations: ARR, annualised relapse rate; **BID**, twice daily; **BTK**, Bruton's tyrosine kinase; **cc,** cubic centimetres; **CDI/CDP**, confirmed disability improvement/progression; **CNS**, central nervous system; **DMT**, disease-modifying treatment; **EDSS**, Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **IQR**, interquartile range; **MS**, multiple sclerosis; **n,** number; **NEDA**, no evidence ofdisease activity; **NfL**, neurofilament light chain; **PPMS**, primary progressive MS; **PIRA**, progression independent of relapse activity; **PROMIS**, Patient-Reported Outcomes Measurement Information System; **QD**, once daily; **R**, randomisation; **RMS**, relapsing MS; **RRMS**, relapsing–remitting MS; **SARS-CoV-2**, severe acute respiratorysyndrome coronavirus 2; **SD**, standard deviation; **SDMT**, Symbol Digit Modalities Test; **SPMS**, secondary progressive MS; **vol,** volume

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XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Bayer, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Genzyme, F. 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