DMT08

Evobrutinib efficacy is maintained over two years in an open-label Phase II study extension in patients with relapsing multiple sclerosis

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CONCLUSION

- **With evobrutinib 75 mg BID, the efficacy observed at Week 48 (ARR, 0.11) was maintained at 108 weeks (ARR, 0.12)**
- **Probability of and time to QR highlighted that, despite switching to evobrutinib 75 mg QD/BID in the OLE, patients treated with evobrutinib 25 mg QD, 75 mg QD, or placebo in the DBP did not achieve the same level of efficacy as those initiated on 75 mg BID**
- **The maximum efficacy observed at the 75 mg BID dose correlated with optimal BTK occupancy of >95% achieved in 98% of patients with BID dosing**
- **These long-term efficacy data in patients with relapsing MS are the first to be reported for the class of agents that inhibit BTK**

ARR, annualized relapse rate; **BID**, twice daily; **BTK**, Bruton's tyrosine kinase; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily; **QR**, qualifying relapse

INTRODUCTION

- Evobrutinib is a highly selective BTKi with a dual mode of action targeting both B cells and myeloid cells, including macrophages and microglia, which are known to play a key role in the pathogenesis of autoimmune diseases such as MS[1,2]
- Clinical efficacy of evobrutinib in relapsing MS was shown in a Phase II randomized controlled trial (NCT02975349) with a significant reduction of T1 Gd-enhancing lesions compared with placebo at Week 24 (the primary endpoint of the study) and continued efficacy through Week 48[3]

BTKi, Bruton's tyrosine kinase inhibitor; **Gd,** gadolinium

OBJECTIVE

- To report the long-term efficacy of evobrutinib measured as:

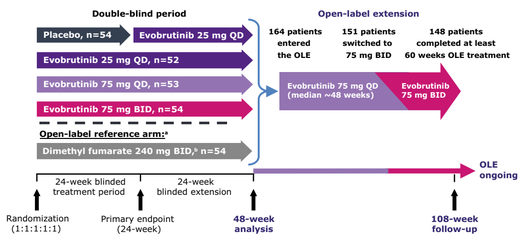
ARR	QR[a]
Annualized relapse rate	Cumulative probability of and time to qualifying relapse

[a]QR defined as a change in neurological symptoms or Expanded Disability Status Scale score increase attributed to MS lasting ≥24 hours preceded by a stable or improving neurological status ≥30 days
ARR, annualized relapse rate; **QR**, qualifying relapse

METHODS

- In the 48-week DBP, patients received evobrutinib 25 mg QD, 75 mg QD, 75 mg BID, or placebo for the first 24 weeks; all arms continued with the original treatment assignment until 48 weeks, except placebo patients who were switched to evobrutinib 25 mg QD (**Figure 1**)
- At Week 48, all patients could enter the OLE, where treatment was initially evobrutinib 75 mg QD (for a median of ≈48 weeks) before switching to 75 mg BID. Efficacy was assessed at the data cut-off of December 31, 2019, when all patients had completed at least 60 weeks of the ongoing OLE or discontinued (**Figure 1**)

Figure 1. Study design



[a]Only patients treated with evobrutinib are included in the current analysis
[b]120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment
BID, twice daily; **DBP,** double-blind period; **OLE,** open-label extension; **QD,** once daily

RESULTS

Patient disposition

- Of 213 patients randomized to evobrutinib or placebo, 164 (77%) entered the OLE; of these, 148 (90%) completed at least 108 weeks of treatment (**Table 1**)

Table 1. Patients entering the OLE

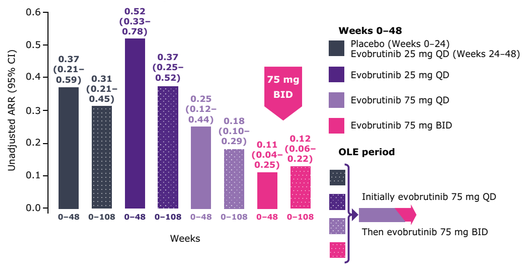
Patients, n (%)	Placebo/ evobrutinib 25 mg QD	Evobrutinib 25 mg QD	Evobrutinib 75 mg QD	Evobrutinib 75 mg BID
Entered OLE period	39 (72.2)	39 (75.0)	42 (79.2)	44 (81.5)
Switched to 75 mg BID during OLE	35 (64.8)	35 (67.3)	37 (69.8)	44 (81.5)
Discontinued treatment during OLE	5 (9.3)	9 (17.3)	5 (9.4)	3 (5.6)

BID, twice daily; **OLE**, open-label extension; **QD**, once daily

ARR maintained with long-term evobrutinib treatment

- In patients receiving evobrutinib 75 mg BID in the DBP, the efficacy at Week 48 (ARR, 0.11) was maintained at 108 weeks (ARR, 0.12; **Figure 2**)
- Patients starting on evobrutinib 75 mg BID in the DBP had a lower ARR compared with those starting on 75 mg QD, 25 mg QD or placebo in the DBP (**Figure 2**)

Figure 2. Annualized relapse rate



ARR, annualized relapse rate; **BID**, twice daily; **CI**, confidence interval; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily

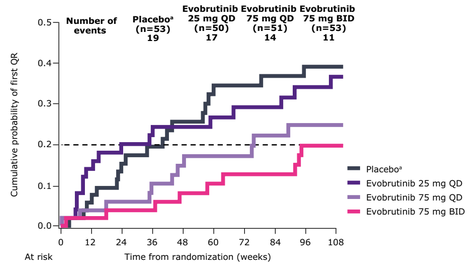
Lower probability of first QR with evobrutinib 75 mg BID

- The estimated time from randomization by which 20% of patients had a QR was (**Figure 3**, **Table 2**):
  - Three times longer for those treated with evobrutinib 75 mg BID in the DBP than for those who received placebo
  - Longer for those treated with evobrutinib 75 mg BID than with evobrutinib 25 mg QD and 75 mg QD

Evobrutinib BTK occupancy is highly correlated with efficacy

- BTK occupancy increased in a dose-dependent manner based on pre-dose (steady state trough) observations at Weeks 4, 12, and 24 (**Figure 4**)
- The highest pre-dose BTK occupancy was observed with the 75 mg BID dose
- Lower trough occupancy observed at 25 mg QD and 75 mg QD doses resulted in no efficacy (25 mg) or lower efficacy (75 mg) than 75 mg BID (**Figure 4**)
  - No efficacy for 25 mg QD despite 51% of trough samples having >90% BTK occupancy

Figure 3. Estimated time from randomization to first QR



At risk

Placebo[a]	53	50	43	39	35	30	29	28	26	26
Evobrutinib 25 mg QD	50	43	39	36	35	30	29	29	26	24
Evobrutinib 75 mg QD	51	49	46	41	38	35	34	30	29	29
Evobrutinib 75 mg BID	53	52	48	46	41	39	38	38	35	35

[a]Patients switched from placebo to evobrutinib 25 mg QD for the second 24-week treatment period
BID, twice daily; **DBP**, double-blind period; **QD**, once daily; **QR**, qualifying relapse

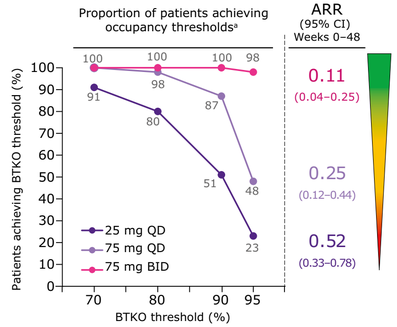
Table 2. Probability of first QR

Treatment	Time to 20% of patients with first QR, weeks (95% CI)	Cumulative probability of first QR at Week 48 (95% CI)	Cumulative probability of first QR at Week 96 (95% CI)
Placebo/evobrutinib 25 mg QD	40.1 (14.1; 58.1)	0.26 (0.14; 0.38)	0.39 (0.25; 0.53)
Evobrutinib 25 mg QD	23.7 (8.7; 86.6)	0.24 (0.12; 0.36)	0.34 (0.20; 0.48)
Evobrutinib 75 mg QD	75.7 (34.9; 119.7)	0.15 (0.05; 0.25)	0.25 (0.12; 0.38)
Evobrutinib 75 mg BID	118.1 (46.7; NE)	0.08 (0.00; 0.16)	0.20 (0.08; 0.31)

BID, twice daily; **CI**, confidence interval; **NE**, not estimable; **QD**, once daily; **QR**, qualifying relapse

- **The largest and most sustained reduction in ARR was achieved when BTK occupancy was >95%, observed in nearly all patients receiving 75 mg BID (Figure 4)**
- **95% BTK occupancy is necessary to reach maximum efficacy**

Figure 4. BTK occupancy according to evobrutinib dosage



[a]Based on 124 (35/46/43) pre-dose observations from 11–17 fasted patients per dose level at Weeks 4, 12, 24
ARR, annualized relapse rate; **BID**, twice daily; **BTK**, Bruton's tyrosine kinase; **BTKO**, Bruton's tyrosine kinase occupancy; **CI**, confidence interval; **QD**, once daily

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DISCLOSURES

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 Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Inc., Rockland, MA, USA, Genzyme, Immunic, MedDay Pharmaceuticals, Merck KGaA, Darmstadt, Germany, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceuticals, TG Therapeutics, Excemed, MSIF, and NMSS. DLA reports consultant fees and/or grants from Acorda, Adelphi, Alkermes, Biogen, Celgene, Frequency Therapeutics, Genentech, Genzyme, F. Hoffmann-La Roche, Immune Tolerance Network, Immunotec, MedDay Pharmaceuticals, EMD Serono, Inc., Rockland, MA, USA, Novartis, Pfizer, Receptos, and Sanofi-Aventis and an equity interest in NeuroNv Research. MSW has received travel funding and/or speaker honoraria from Biogen-Idec, EMD Serono, Inc., Rockland, MA, USA, Novartis, F. Hoffmann-La Roche, TEVA, Bayer, and Genzyme. ES has received travel funding, registration fees, and/or speaker honoraria from Sanofi-Genzyme, Ewopharma-Biogen, Shire, Gedeon-Richter, TEVA, Boehringer Ingelheim, Pfizer, Bayer, F. Hoffmann-La Roche, Mylan, Polpharma, Penumbra, Adapt, and EMD Serono, Inc., Rockland, MA, USA. KP-S has received travel funding and/or speaker honoraria from EMD Serono, Inc., Rockland, MA, USA, Sanofi-Aventis, Biogen Idec, TEVA, and F. Hoffmann-La Roche and has served on scientific advisory boards for Sanofi-Aventis and Biogen Idec.

JGW has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alkermes, Brainstorm Cell Therapeutics, EMD Serono, Inc., Rockland, MA, USA, GW Pharma, MedDay Pharmaceuticals, NervGen Pharma Corp., Novartis, Roche/Genentech, and Sanofi Genzyme. Royalties have been received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation. ECM, MM, and FD are employed by EMD Serono Research and Development Institute, Inc., Billerica, MA, USA.

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