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P0235

Safety of the Bruton's tyrosine kinase inhibitor evobrutinib in relapsing multiple sclerosis during an open-label extension to a phase II study

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Disclosures

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- 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 (a business of Merck KGaA, Darmstadt, Germany), Genzyme, Immunic, Medday, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS

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Jerry Wolinsky

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Background and objective

Background

- In a Phase II randomized study (NCT02975349) in patients with relapsing MS, evobrutinib 75 mg BID reduced total T1 Gd+ lesions (the primary endpoint) and ARR over 24 weeks versus placebo, with efficacy maintained through Week 108[1]
- Evobrutinib was generally well tolerated. The most commonly observed adverse events were nasopharyngitis and increases in levels of alanine aminotransferase, aspartate aminotransferase, and lipase. Patients with elevations in aminotransferase levels were asymptomatic, and the elevations were reversible[1]

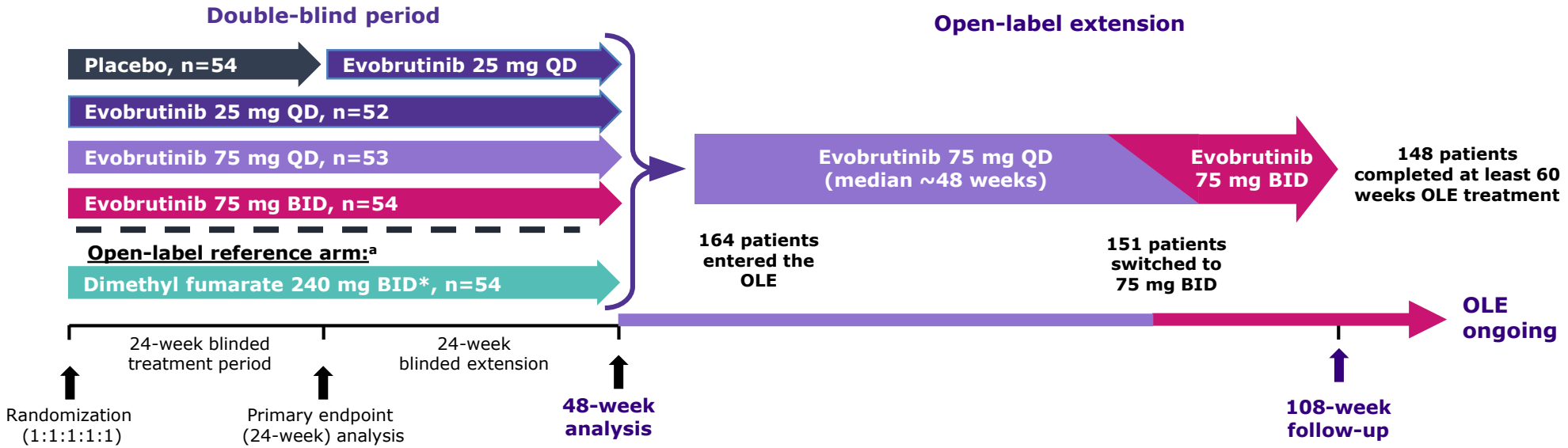
Objective

- To describe the safety profile of evobrutinib in the long-term treatment of MS by reporting detailed safety data from the study's ongoing OLE when all patients had been treated for at least 60 weeks of OLE (or discontinued)

ARR, annualized relapse rate; **BID**, twice daily; **MS**, multiple sclerosis; **OLE**, open-label extension; **QR**, qualified relapse

1. Montalban X, et al. *N Engl J Med* 2019;380:2406–2417

Study design: Phase II/open-label extension



- In the 48-week DBP, patients received evobrutinib 25 mg once-daily (QD) or 75 mg QD, 75 mg BID, or placebo for the first 24 weeks
- All arms continued with the original treatment assignment until Week 48, except placebo patients who were switched to evobrutinib 25 mg QD
- 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
- Safety was assessed throughout the OLE, by assessment of the nature, severity, and occurrence of TEAEs using NCI-CTCAE v4.03 criteria, as well as vital signs, ECGs, and clinical laboratory safety parameters

[a]Only patients treated with evobrutinib are included in the current analysis
*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; **ECG**, echocardiogram; **NCI-CTCAE v4.03,** National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03; **OLE**, open-label extension; **QD**, once daily; **TEAEs**, treatment-emergent adverse events

Overall TEAEs were mild/moderate in the OLE period

- **Of 213 patients who received evobrutinib during the DBP, 164 (77%) entered the ongoing OLE (safety analysis population)**
- **In this analysis, 148 (90%) of OLE participants had completed at least 60 weeks of treatment[a]**

Patients, n (%)	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib			Total safety analysis population (n=164)
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)	
Any TEAE	27 (69.2)	22 (56.4)	31 (73.8)	27 (61.4)	107 (65.2)
Any Grade 3 TEAE*	3 (7.7)	2 (5.1)	2 (4.8)	3 (6.8)	10 (6.1)
Any Grade 4 TEAE*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any serious TEAE	5 (12.8)	5 (12.8)	2 (4.8)	1 (2.3)	13 (7.9)
Any TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- **107/164 (65.2%) patients had a TEAE, the majority of which were mild (47.6%) or moderate (36.0%), and none led to death**
- **Thirteen patients (7.9%) reported a serious TEAE, most frequently related to infections (6 patients, not treatment-related)**

[a]Includes all safety data from the OLE using a data cut-off of 31 Dec 2019
*According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03
BID, twice daily; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily; **TEAEs**, treatment-emergent adverse events

TEAEs (occurring in ≥5% of patients) were balanced across previous DBP treatment groups

Values are: Patients, n (% of treatment group)	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib			Total safety analysis population (n=164)
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)	
Lipase increase	3 (7.7)	3 (7.7)	3 (7.1)	4 (9.1)	13 (7.9)
Nasopharyngitis	2 (5.1)	3 (7.7)	4 (9.5)	4 (9.1)	13 (7.9)
Upper respiratory tract infection	3 (7.7)	2 (5.1)	3 (7.1)	2 (4.5)	10 (6.1)
Headache	1 (2.6)	2 (5.1)	2 (4.8)	3 (6.8)	8 (4.9)
Urinary tract infection	3 (7.7)	3 (7.7)	1 (2.4)	1 (2.3)	8 (4.9)
Fatigue	1 (2.6)	1 (2.6)	3 (7.1)	1 (2.3)	6 (3.7)
Amylase increase	1 (2.6)	2 (5.1)	1 (2.4)	1 (2.3)	5 (3.0)
Respiratory tract infection	1 (2.6)	0 (0.0)	3 (7.1)	1 (2.3)	5 (3.0)
Arthralgia	3 (7.7)	0 (0.0)	0 (0.0)	2 (4.5)	5 (3.0)
Lymphocyte count decrease	1 (2.6)	2 (5.1)	0 (0.0)	1 (2.3)	4 (2.4)
Head injury	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)
Nausea	2 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)
Pneumonia	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)	2 (1.2)

The most frequent TEAEs over the OLE period, including the dose-switch, were:

- **Increased lipase (7.9%, Grade 3 or less)**
- **Nasopharyngitis (7.9%, Grade 2 or less)**
- **Upper respiratory tract infection (6.1%, Grade 2 or less)**
- **Urinary tract infection (4.9%, Grade 2 or less)**
- **Headache (4.9%, Grade 2 or less)**

The incidence of infections in the OLE was similar to that observed in the DBP

BID, twice daily; **DBP**, double-blind period; **OLE**, open-label extension; **QD**, once daily; **TEAEs**, treatment-emergent adverse events

TEAEs analysed by exposure-adjusted incidence rate were balanced before and after patients switched to 75 mg BID

Incidence rate [95% CI] per 1000 subject-years

	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib		
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)
Incidence for patients with at least 1 event during the OLE	862 [592;1258]	605 [398;918]	961 [676;1367]	643 [441;938]
Before switch	985 [655;1482]	732.4 [47;113]	1009.0 [676;1505]	627 [405;972]
After switch	1042 [638;1701]	977 [579;1650]	801 [475;1353]	660 [391;1114]

Incidence rate [95% CI] per 1000 subject-years

Most common TEAEs during the OLE	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib			Total safety analysis population (n=164)
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)	
Lipase increase	55 [18;170]	57 [18;176]	51 [17;159]	62 [23;165]	56
Nasopharyngitis	36 [9;143]	55 [18;172]	72 [27;191]	62 [23;165]	56
Upper respiratory tract infection	55 [18;170]	36 [9;146]	51 [17;159]	30 [8;120]	43
Urinary tract infection	57 [19;178]	56 [18;173]	17 [2;118]	15 [2;106]	34
Headache	18 [3;127]	36 [9;144]	34 [8;134]	45 [15;140]	34

Exposure Adjusted Incidence Rates (EAIRs) are calculated as number of subjects with an AE divided by the sum of the individual times at risk for the first occurrence of an AE of all subjects in the safety analysis set from start of treatment during OLE to first onset of AE during OLE before switch (or end of OLE period if no switch), date of switch, end of OLE period or death, whichever occurs first. EAIR values have been rounded to nearest integer

AE, adverse event; **BID**, twice daily; **OLE**, open-label extension; **QD**, once daily; **TEAEs**, treatment-emergent adverse events

No new safety signals were identified during the OLE

Grade 3 TEAEs reported during the OLE

	Placebo + evobrutinib 25 mg QD (n=39)	Evobrutinib		
		25 mg QD (n=39)	75 mg QD (n=42)	75 mg BID (n=44)
Subjects with at least 1 Grade 3 event, n (% of group)	**3 (7.7)**	**2 (5.1)**	**2 (4.8)**	**3 (6.8)**
For individual TEAEs, values are number of events (evobrutinib-related events)				
ALT increase	1			
AST increase	1			
Amylase increase*	1 (1)			
Lipase increase*	2 (1)			3 (2)
Gastroenteritis		1		
Pneumonia		1		
Dementia Alzheimer's type			1	
Femur fracture			1 (1)	
Osteonecrosis			1 (1)	

TEAEs leading to treatment withdrawal

- Five patients (3.0%) had a TEAE during the OLE that led to treatment withdrawal
  - Four in the placebo + evobrutinib 25 mg QD cohort
  - One in the evobrutinib 25 mg QD cohort
- Of these, three were considered related to treatment (nausea, increased lipase, and concurrent increase in both amylase and lipase)

- **There was no apparent effect of evobrutinib dose received in the DBP on safety parameters in the OLE**
- **Transient elevated liver aminotransferases reported in the 48-week DBP, which were asymptomatic and reversible, were not observed in the OLE after prolonged treatment or after the switch to 75 mg BID**
- **No adverse ECG findings were noted across all evobrutinib groups**

*Asymptomatic
BID, twice daily; **ECG**, echocardiogram; **OLE**, open-label extension; **QD**, once daily; **TEAEs**, treatment-emergent adverse events

Conclusions

- **Analysis of data from the OLE period of a Phase II study when all participants had completed at least 60 weeks of treatment or discontinued, found that the safety of evobrutinib was similar to that seen in the 48-week DBP**
    - **Transient treatment-related elevated liver aminotransferases reported in the DBP, (which were asymptomatic and reversible), were not observed in the OLE after prolonged treatment or after the switch to evobrutinib 75 mg BID**
- **The majority of TEAEs were mild or moderate and no new safety concerns were observed**
- **TEAEs (occurring in ≥5% of patients) were balanced across previous DBP treatment groups**
- **TEAEs analysed by exposure-adjusted incidence rate were balanced before and after patients switched to evobrutinib 75 mg BID**
- **Evobrutinib 75 mg BID was not associated with an increased incidence of infections**
- **Overall, long-term evobrutinib treatment was generally well tolerated in patients with relapsing MS**

For more evobrutinib Phase II study information, please see other presentations at MS Virtual 2020: 8th Joint ACTRIMS–ECTRIMS Meeting

Efficacy of long-term evobrutinib in patients with MS – Poster P0197

Long-term effects of evobrutinib on immune cells and Ig levels – Poster P0070

BID, twice daily; **DBP**, double-blind period; **MS**, multiple sclerosis; **OLE**, open-label extension; **QD**, once daily; **TEAEs**, treatment-emergent adverse events

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