The Safety Profile of Fenebrutinib in Patients With Multiple Sclerosis Is Consistent With Those in Previously Studied Autoimmune Indications

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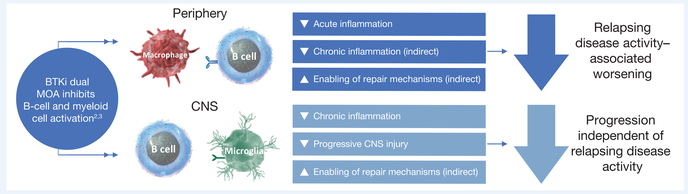
BACKGROUND

- Inflammatory and neurodegenerative processes begin early in multiple sclerosis (MS) and may drive progressive disease biology[1] (**Figure 1**)
- Bruton's tyrosine kinase (BTK) is implicated in peripheral and central nervous system inflammation in MS and is a therapeutic target for relapsing and progressive disease[2–4]

Figure 1. BTK Inhibitors May Treat MS via a Dual MOA



BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CNS, central nervous system; MOA, mechanism of action; MS, multiple sclerosis.

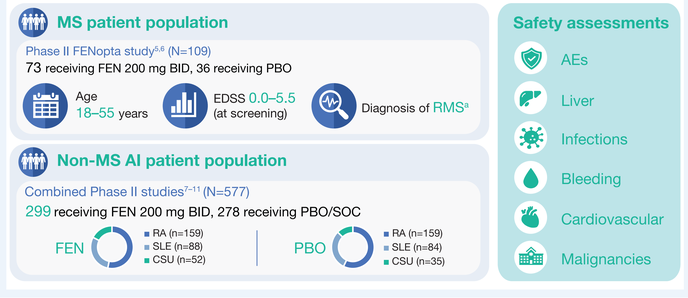
OBJECTIVE

- To compare the safety and tolerability of fenebrutinib in patients with MS vs in patients with non-MS autoimmune indications (AIs)

METHODS

- Fenebrutinib, a potent, highly selective, noncovalent, reversible BTK inhibitor under investigation for MS, has been studied extensively in other AIs, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and chronic spontaneous urticaria (CSU) (**Figure 2**)
  - Study duration for non-MS AIs ranged from 8 to 96 weeks

Figure 2. Pooled Safety Analysis of Fenebrutinib in MS vs Non-MS AIs



AE, adverse event; AI, autoimmune indication; BID, twice daily; CSU, chronic spontaneous urticaria; EDSS, Expanded Disability Status Scale; FEN, fenebrutinib; Gd, gadolinium; MS, multiple sclerosis; PBO, placebo; RA, rheumatoid arthritis; RMS, relapsing multiple sclerosis; SLE, systemic lupus erythematosus; SOC, standard of care.

[a]At least two relapses within the last 2 years **or** one documented clinical relapse within 12 months of screening (but not within the 30 days prior to screening) or documented evidence of at least one T1 Gd-enhancing lesion on MRI in the 6 months prior to randomization.

RESULTS

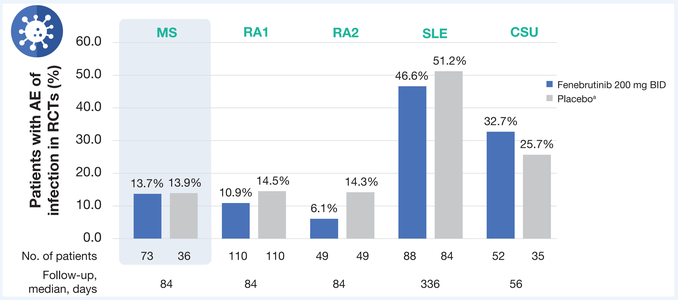
Table. Patients With MS or Non-MS AIs Had Mostly Nonserious AEs

	MS Fenebrutinib 200 mg BID (n=73)	MS Placebo (n=36)	Non-MS AI Fenebrutinib 200 mg BID (n=299)	Non-MS AI Placebo[a] (n=278)
Patients with ≥1 AE, n (%)	28 (38.4)	12 (33.3)	170 (56.9)	156 (56.1)
Total no. of AEs	38	19	507	431
Investigator-reported events in >5% of fenebrutinib-treated patients in RCTs, n (%)				
Abnormal hepatic enzyme levels[b]	5 (6.8)	0	13 (4.3)	4 (1.4)
Urinary tract infections	4 (5.5)	2 (5.6)	11 (3.7)	15 (5.4)
Headache	3 (4.1)	1 (2.8)	16 (5.4)	17 (6.1)
Nasopharyngitis	2 (2.7)	0	18 (6.0)	13 (4.7)
Nausea	2 (2.7)	1 (2.8)	17 (5.7)	12 (4.3)
Deaths, n (%)	0	0	1 (0.3)[c]	2 (0.7)
SAEs, n (%)	0	0	18 (6.0)	9 (3.2)
Treatment-related SAE	0	0	6 (2.0)	5 (1.8)
SAE leading to dose interruption	0	0	6 (2.0)	1 (0.4)
Treatment-related AEs, n (%)	10 (13.7)	2 (5.6)	77 (25.8)	60 (21.6)
AEs leading to treatment withdrawal n (%)	7 (9.6)[d]	0	32 (10.7)	13 (4.7)

AE, adverse event; AI, autoimmune indication; BID, twice daily; MS, multiple sclerosis; RCT, randomized clinical trial; SAE, serious adverse event.
[a]Placebo was used in addition to standard of care for each indication. [b]This includes any patient with report of any of the following AE terms: abnormal hepatic enzymes, increased alanine aminotransferase or increased aspartate aminotransferase. [c]The cause of death in the fenebrutinib arm was acute myocardial infarction deemed unrelated to fenebrutinib. [d]AEs leading to withdrawal: abnormal hepatic transaminase levels (n=4; discontinuation required by protocol); upper abdominal pain (n=1); nausea, headache and upper abdominal pain (n=1); and hypersensitivity (n=1).

- AEs reported in patients with MS were consistent with those reported in patients with non-MS AIs (**Table**)
- Low serious adverse event rates in all indications were reported

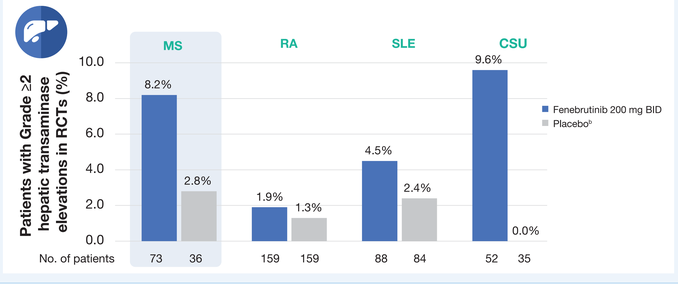
Figure 3. Infection Rates Were Similar Between Fenebrutinib and Control Arms Across Indications



AE, adverse event; BID, twice daily; CSU, chronic spontaneous urticaria; MS, multiple sclerosis; RA, rheumatoid arthritis; RCT, randomized clinical trial; SLE, systemic lupus erythematosus.
[a]Placebo was used in addition to standard of care for each disease studied.

- There was no imbalance in the pattern, duration, seriousness or severity of infections in patients with MS receiving fenebrutinib vs placebo, which was consistent with observations in other AIs, despite background immunosuppressant therapy use (eg, methotrexate, corticosteroids) in RA and SLE (**Figure 3**)
  - Six patients (2.0%) in the combined fenebrutinib arms and 5 (1.8%) in the combined placebo arms had serious infections

Figure 4. More Fenebrutinib- vs Placebo-Treated Patients Had Grade ≥2[a] Elevated Hepatic Transaminase Levels



ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CSU, chronic spontaneous urticaria, MS, multiple sclerosis; RA, rheumatoid arthritis; RCT, randomized clinical trial; SLE, systemic lupus erythematosus.
[a]Highest grade of ALT/AST was used for calculation; Common Terminology Criteria for Adverse Events v4 was used. [b]Placebo was used in addition to standard of care for each disease studied.

- No other signs of hepatic dysfunction were observed (**Figure 4**)
- Aminotransferase levels were asymptomatic and returned to baseline/normal with treatment cessation
- No additional treatment was required for elevated aminotransferase levels

Figure 5. Other Potential Class Effects Appeared Less Relevant to Fenebrutinib Due to Increased Selectivity for BTK

Bleeding or bruising[a]
- In patients with MS, 1.4% (n=1) in the fenebrutinib arm vs no events in the placebo arm
- In patients with AIs, 7.7% (n=23) in fenebrutinib arms vs 3.2% (n=9) in combined placebo[b] arms

Cardiovascular disease[c]
- No RCT patients had atrial fibrillations, flutters or other supraventricular tachyarrhythmias
- No QT prolongation was observed in FENopta

Malignancy
- No imbalance in malignancies between fenebrutinib and placebo arms
- One patient developed Stage 0 cervical carcinoma (fenebrutinib, RCT) vs no patients receiving placebo

AI, autoimmune indication; BTK, Bruton's tyrosine kinase; MS, multiple sclerosis; OLE, open-label extension; RA, rheumatoid arthritis; RCT, randomized clinical trial.
[a]One patient developed Grade 3 purpura in the RA placebo arm; 2 patients in RA OLE study developed Grade 3 vaginal hemorrhage. [b]Placebo was used in addition to standard of care for each disease studied. [c]One patient with RA receiving fenebrutinib experienced ventricular extrasystole; in OLEs, 2 patients (0.3%) developed atrial fibrillation, and 1 (0.1%) developed supraventricular tachycardia.

CONCLUSIONS

- The safety and tolerability profile of fenebrutinib in MS remains consistent with those in previously studied AIs (RA, SLE and CSU) and contributes to the current extensive safety database for fenebrutinib (>2500 patients)
- The Phase II MS FENopta safety data did not differ from what was observed in non-MS AIs, except for urinary tract infections, which were more common in MS
- Elevated hepatic transaminase levels remain an identified risk observed with fenebrutinib treatment in MS, but these cases were reversible and asymptomatic
- These data further support fenebrutinib's favorable safety profile in MS as well as its clinical development across the Phase III MS clinical program

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