Efficacy and Safety of Fenebrutinib, a Noncovalent, Reversible BTK Inhibitor, in MS: Primary Results of a Phase II Trial

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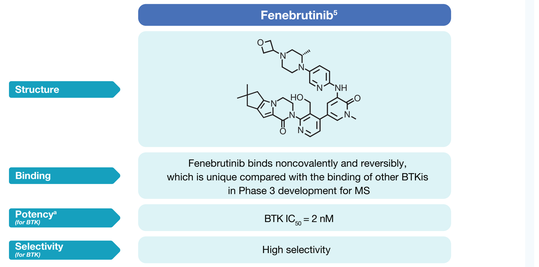
BACKGROUND

- Inflammation and secondary neurodegeneration processes begin early in multiple sclerosis (MS) and may drive progression of the disease[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]
- Fenebrutinib is a potent, highly selective, noncovalent, reversible BTK inhibitor under investigation for MS (**Figure 1**)

Figure 1. Molecular Properties of Fenebrutinib



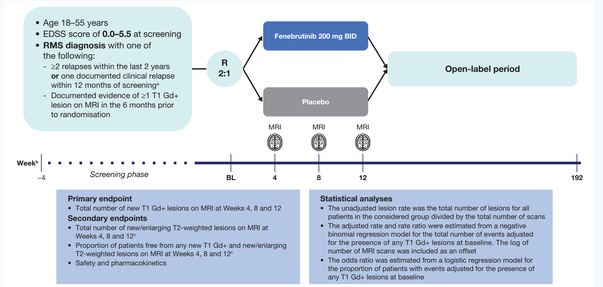
ATP, adenosine triphosphate; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; IC_{50}, half maximal inhibitory concentration; Km, Michaelis constant; MS, multiple sclerosis.
[a]BTK IC_{50} values determined in vitro using a kinase activity assay that monitors phosphorylation of a peptide substrate with ATP at its apparent Km.

OBJECTIVE

- The objective of FENopta, a randomised, double-blind, placebo-controlled, Phase II trial (NCT05119569), was to evaluate the efficacy and safety of fenebrutinib in relapsing MS (RMS) and the early impact of fenebrutuinib on MRI outcomes and soluble markers of disease activity and progression

METHODS

Figure 2. FENopta Study Design (NCT05119569)



BID, twice daily; BL, baseline; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis.
[a]But not within the 30 days prior to screening.
[b]Patients discontinuing at any time during the study will have the option to complete a 4-week safety follow-up.
[c]Prespecified analysis.

RESULTS

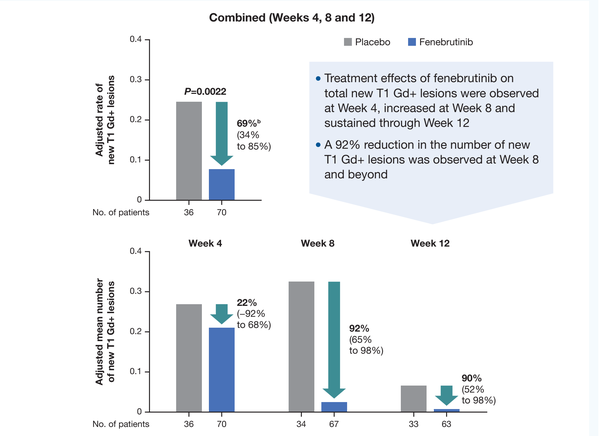
- Of the 109 patients randomised, 73 received fenebrutinib, and 36 received placebo (**Table 1**)
- There was no imbalance in number of T1 gadolinium-enhancing (Gd+) lesions at baseline between the fenebrutinib and placebo arms (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

	Fenebrutinib n=73	Placebo n=36	All patients N=109
Age, mean (SD), years	38.6 (8.5)	39.8 (7.7)	39.0 (8.2)
Female, n (%)	52 (71.2)	26 (72.2)	78 (71.6)
Time since diagnosis, mean (SD), years	4.9 (5.9)	5.9 (7.1)	5.2 (6.3)
Prior DMT use, n (%)	18 (24.7)	17 (47.2)	35 (32.1)
EDSS score, median (min–max)	2.5 (0.0–5.5)	3.0 (0.0–5.5)	2.5 (0.0–5.5)
No. of T1 Gd+ lesions, mean (SD)	0.74 (2.26)	0.72 (2.31)	0.73 (2.27)
Patients with T1 Gd+ lesions, n (%)	14 (19.2)	7 (19.4)	21 (19.3)
No. of T2 lesions, mean (SD)	45.03 (28.46)	52.22 (33.09)	47.40 (30.11)

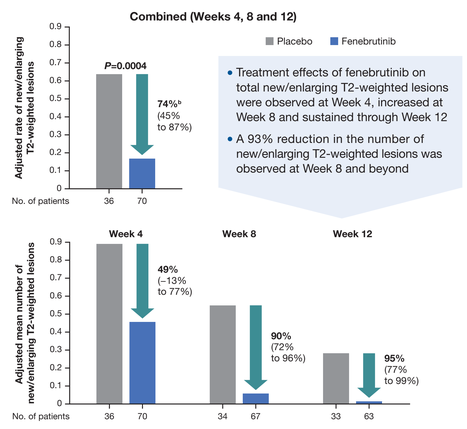
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing.

Figure 3. Total New T1 Gd+ Lesions Combined (Weeks 4, 8 and 12) and by Week[a]



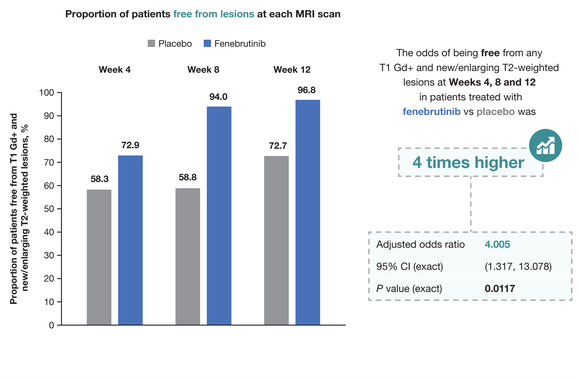
Gd+, gadolinium enhancing.
[a]Results were estimated from a negative binomial model controlling for baseline T1 Gd+ lesion status (presence or absence) and included log number of scans as an offset.
[b]Teal arrows indicate relative reduction (95% CI) of lesions.

Figure 4. Total New/Enlarging T2-Weighted Lesions Combined (Weeks 4, 8 and 12) and by Week[a]



Gd+, gadolinum enhancing.
[a]Results were estimated from a negative binomial model controlling for baseline T1 Gd+ lesion status (presence or absence) and included log number of scans as an offset.
[b]Teal arrows indicate relative reduction (95% CI) of lesions.

Figure 5. Proportion of Patients Free From Both New T1 Gd+ and New/Enlarging T2 Lesions[a]



Gd+, gadolinium enhancing.
[a]Results were estimated from a logistic regression controlling for baseline T1 Gd+ lesion status (presence or absence).

- No serious adverse events were reported (**Table 2**)
- There was no imbalance in infections between the fenebrutinib and placebo arms
- All adverse events (AEs) were Grade 1 or 2, except for two Grade 3 asymptomatic liver transaminase level elevations

Table 2. Safety Summary

	Fenebrutinib (n=73)	Placebo (n=36)
Patients with ≥1 AE, n (%)	28 (38.4)	12 (33.3)
Total no. of AEs	40	19
Patients with ≥1, n (%)		
AE with fatal outcome	0	0
SAE	0	0
AE leading to dose interruption	0	0
Related AE	10 (13.7)	2 (5.6)
Grade 3 AE	2 (2.7)[a]	0
Patients withdrawn from study due to an AE, n (%)	7 (9.6)[b]	0
Most common AEs, n (%)		
Abnormal hepatic enzyme levels	4 (5.5)	0
Urinary tract infection	4 (5.5)	2 (5.6)
Headache	3 (4.1)	1 (2.8)
Nasopharyngitis	2 (2.7)	0
Nausea	2 (2.7)	1 (2.8)
Pharyngitis	2 (2.7)	1 (2.8)
Upper abdominal pain	2 (2.7)	0

AE, adverse event; SAE, serious adverse event.
[a]Two Grade 3 AEs of abnormal hepatic enzyme levels (asymptomatic).
[b]AEs leading to withdrawal: 4 abnormal hepatic transaminase levels (discontinuation required by protocol); 1 upper abdominal pain, nausea and headache; 1 upper abdominal pain; and 1 hypersensitivity.

Conclusions

The efficacy results of FENopta in patients with RMS who received fenebrutinib were consistent with those seen with other high-efficacy disease--modifying therapies

- **Fenebrutinib reduced the number of new T1 Gd+ lesions**
  - **69%** reduction at Weeks 4, 8 and 12 combined
  - **92%** reduction at Week 8 and beyond
- **Fenebrutinib reduced the number of new/enlarging T2-weighted lesions**
  - **74%** reduction at Weeks 4, 8 and 12 combined
  - **93%** reduction at Week 8 and beyond
- **Patients who received fenebrutinib were 4 times more likely to be free from new T1 Gd+ and new/enlarging T2-weighted lesions at Week 12 compared with patients who received placebo**
- **No new safety concerns were identified**
  - No serious AEs or deaths were observed, and no new or serious safety concerns were identified in patients receiving fenebrutinib, a noncovalent , reversible BTK inhibitor
  - There was no imbalance in rate of infections between the fenebrutinib and placebo arms
  - No cases of Hy's Law[a] were observed, and the observed hepatic transaminase level elevations in fenebrutinib-treated patients were reversible and asymptomatic
- The FENopta open-label extension is ongoing, while Phase III studies are either currently recruiting patients with RMS (FENhance 1 and 2, NCT04586010/NCT04586023) or ongoing with patients with primary progressive MS (FENtrepid, NCT04544449)

[a]Hy's Law was defined as alanine transaminase >3x upper limit of normal (ULN) or aspartate aminotransferase >3x ULN; total bilirubin >2x ULN; no initial findings of cholestasis (alkaline phosphatase <2x ULN); and no other clinical reason (e.g., viral hepatitis) was found to explain the prior.

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DISCLOSURES

LHH has received personal fees for speaking, consulting and advisory board activities from Alexion, Bristol Myers Squibb, EMD Serono, Genentech, Genzyme, Greenwich Biosciences, Horizon and Novartis and research salary support paid to her institution from Biogen.

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HB has nothing to disclose.

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