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Characteristics and Outcomes of COVID-19 Cases from the Long-term Extension Study of Tolebrutinib in Patients with Relapsing MS

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OBJECTIVE

- **Describe characteristics and outcomes of COVID-19 cases reported in the tolebrutinib long-term extension study**

CONCLUSIONS

- **All COVID-19 cases were mild or moderate, and patients recovered and remained in the study**
- **Most patients continued receiving tolebrutinib without interruption during their COVID-19 infection**
- **These preliminary data do not indicate an increased risk of severe COVID-19 outcomes during tolebrutinib treatment**

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INTRODUCTION

- Bruton's tyrosine kinase (BTK) inhibitors are a new class of treatment for multiple sclerosis (MS) with immune modulatory characteristics
- Tolebrutinib is an oral, brain-penetrant BTK inhibitor modulating innate (microglia and macrophages) and adaptive (B cells) immunity in the periphery and central nervous system,[1] thereby resulting in the reduction of BTK-dependent inflammatory signalling in these major drivers of inflammation in MS[2]
- Inhibition of BTK by tolebrutinib results in modulation of B-cell function, rather than depletion[2-4], the difference is important for safety concerns regarding potential susceptibility to treatment-emergent infections
- In a phase 1 study, pharmacologically relevant levels of tolebrutinib in cerebrospinal fluid were demonstrated[2,5]
- In the phase 2b trial (NCT03889639), tolebrutinib was safe and well tolerated over 12 weeks with dose-dependent reduction in new gadolinium (Gd)-enhancing T1 and new/enlarging T2 lesions in patients with relapsing MS (RMS)[6]
- Upon completing the study, patients could enter an ongoing long-term extension study (NCT03996291) to further evaluate the safety and efficacy of tolebrutinib
- Given its novel mechanism of action, research is needed to understand the potential impact of tolebrutinib on outcomes of infections such as COVID-19 in patients with RMS

METHODS

- The long-term extension study consists of 2 parts:
  - **in Part A**, participants continued double-blind treatment with the same tolebrutinib dose as administered in the core dose-finding study (5, 15, 30 or 60 mg/day)
  - **in Part B**, participants receive open-label tolebrutinib treatment at 60 mg once daily, which is being tested in the phase 3 trials
- Reported COVID-19 cases in the long-term extension study were analyzed for demographics, severity, duration and outcomes, and vaccination status
- Descriptive statistics were used to analyze all variables

RESULTS

- Of 130 participants randomized in the phase 2b trial, 129 completed the core study and 125 enrolled in the long-term extension study
- 20 (16%) participants (mean age: 41 years ± 9; range: 25–57 years) reported COVID-19 infection as of September 6, 2021 (**Table 1**)
- 19 cases were confirmed with polymerase chain reaction (PCR) and 1 with antigen
- COVID-19 cases were mild (n=11) or moderate (n=9). Three of the moderate COVID-19 cases were considered serious, of which 2 were hospitalized (female aged 55 years and male aged 57 years). All patients recovered and all patients remained in the study (**Table 2**).
- There were no deaths reported in the study
- By investigator choice, tolebrutinib was interrupted temporarily in 4 patients while the remaining 16 patients continued tolebrutinib uninterrupted during COVID-19 infection. Only 1 fully vaccinated patient (female, aged 56 years) contracted COVID-19 (**Table 3**)

Table 1. Demographic Data

Case	Country	Age (Years)	Sex	Duration of Illness (Days)	Illness Severity	Drug Interruption	Hospitalization
1	Czech Republic	55	Female	21	Moderate	Yes	Yes
2	Czech Republic	47	Male	21	Mild	No	No
3	Czech Republic	35	Female	11	Mild	No	No
4	Czech Republic	53	Male	25	Mild	No	No
5	Czech Republic	50	Female	10	Mild	No	No
6	Czech Republic	50	Female	27	Mild	No	No
7	Estonia	36	Female	1	Mild	No	No
8	Estonia	56	Female	20	Moderate	No	No
9	Russian Federation	36	Male	28	Mild	No	No
10	Russian Federation	25	Female	23	Moderate	No	No
11	Russian Federation	30	Female	27	Mild	No	No
12	Russian Federation	43	Female	24	Mild	No	No
13	Russian Federation	57	Male	74	Moderate	Yes	Yes
14	Ukraine	30	Female	23	Mild	No	No
15	Ukraine	38	Female	18	Mild	No	No
16	Ukraine	34	Female	17	Moderate	No	No
17	Ukraine	45	Female	29	Moderate	Yes	No
18	Ukraine	32	Female	15	Moderate	No	No
19	United States	38	Female	27	Moderate	Yes	No
20	United States	36	Female	12	Moderate	No	No

Table 2. Patients with Serious COVID-19 Infections

	Age (Years)	Sex	Duration of Illness (Days)	Comments	Relevant previous medical history
Case 1	55	Female	21	• Hospitalized (16 days). COVID-19 pneumonia • Drug was temporarily interrupted for 15 days (interruption driven by the use of an anticoagulant, which is not permitted to be taken concomitantly with tolebrutinib in the study)	• Obesity (body mass index 38.9) • Hypothyroidism, aortic atherosclerosis status post stent, recurrent nephrolithiasis, complicated cholelithiasis status post cholecystectomy
Case 13	57	Male	74	• Hospitalized (12 days). COVID-19 pneumonia • Drug was temporarily interrupted for 69 days (interruption driven by the use of an anticoagulant, which is not permitted to be taken concomitantly with tolebrutinib in the study)	• Hypertension, aortic arteriosclerosis, autoimmune thyroiditis, enterocolitis, nephrolithiasis
Case 19	38	Female	27	• Not hospitalized. Patient recovered at home • PI reported the event as serious (other medically important event) as this occurred at the onset of the COVID-19 pandemic • Tolebrutinib was temporarily interrupted for 14 days	• None

Table 3. Vaccination Status in Patients with COVID-19

	Vaccination Status	Vaccine Type
Case 1	Not vaccinated	N/A
Case 2	Not vaccinated[a]	N/A
Case 3	Not vaccinated	N/A
Case 4	Not vaccinated	N/A
Case 5	Not vaccinated[a]	N/A
Case 6	Not vaccinated[a]	N/A
Case 7	Not vaccinated[a]	N/A
Case 8	Vaccinated	BNT162b2
Case 9	Not vaccinated	N/A
Case 10	Not vaccinated	N/A
Case 11	Not vaccinated[b]	N/A
Case 12	Not vaccinated	N/A
Case 13	Not vaccinated	N/A
Case 14	Not vaccinated	N/A
Case 15	Not vaccinated	N/A
Case 16	Not vaccinated	N/A
Case 17	Not vaccinated	N/A
Case 18	Not vaccinated	N/A
Case 19	Not vaccinated[c]	N/A
Case 20	Not vaccinated	N/A

The BNT162b2 (Comirnaty) vaccine was developed and manufactured by Pfizer/BioNTech. The Gam-COVID-Vac (Sputnik V) vaccine was developed by the Gamaleya Research Institute of Epidemiology and Microbiology. The mRNA-1273 (Moderna COVID-19) vaccine was developed and manufactured by Moderna.
[a]Patients vaccinated with the BNT162b2 after COVID-19 infection
[b]Patient vaccinated with the Gam-COVID-Vac after COVID-19 infection
[c]Patient vaccinated with the mRNA 1273 after COVID-19 infection

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