Monoacylglycerol Lipase Inhibition in Tourette Syndrome: A 12-Week, Randomized, Controlled Study

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ABSTRACT: Background: Modulation of the endocannabinoid system via monoacylglycerol lipase inhibition with Lu AG06466 (formerly known as ABX-1431) has previously been shown to reduce tics in patients with Tourette syndrome.

Objective: The aim of this study was to evaluate the efficacy and safety of Lu AG06466 in reducing tics, premonitory urges, and comorbidities in patients with Tourette syndrome.

Methods: This was a 12-week, multicenter, randomized, placebo-controlled, double-blind clinical trial of Lu AG06466 given at two dose levels in 49 adults with Tourette syndrome.

Results: Both treatment groups showed improvement on the Total Tic Score of the Yale Global Tic Severity Scale; the mean (95% CI) treatment difference at week 8 of 3.0 (0.1, 5.9) (P = 0.043) favored placebo. No significant differences were seen for other endpoints assessing changes in tic severity, premonitory urges, quality of life, and common psychiatric comorbidities. Treatment with Lu-AG06466 was generally safe.

Conclusions: There was no evidence that Lu AG06466 has efficacy in suppressing tics. © 2021 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: tics; Tourette syndrome; Lu AG06466; ABX-1431; endocannabinoid modulator

Tourette syndrome (TS) is a chronic, childhood-onset neurodevelopmental disorder characterized by motor and vocal tics often associated with a spectrum of psychiatric disorders. Although the neurobiological basis of TS remains unclear, most evidence supports an involvement of cortico-striato-thalamo-cortical circuits.1 In addition to dopaminergic dysfunction,2,3 several other neurotransmitters are likely involved, including the endocannabinoid system,4 which, in turn, has a complex functional interaction with the dopaminergic system.5 Hitherto, the role of the endocannabinoid system in TS has been supported by accumulating clinical evidence suggesting that cannabis-based medicines, including Δ9-tetrahydrocannabinol (THC), act as agonists at central cannabinoid CB1 receptors6 to reduce tics and comorbid symptoms.7-11 In addition, alterations of cerebrospinal fluid levels of the endogenous ligands (endocannabinoids) have been found.12

We have previously reported the results of a single-dose phase 1b study that indicated that the monoacylglycerol lipase (MAGL) inhibitor Lu AG06466 (previously known as ABX-1431) reduces tics and premonitory urges in adults with TS.13 MAGL inhibitors act by reducing the catabolism of the endocannabinoid 2-arachidonoylglycerol (2-AG) into arachidonic acid and glycerol, which further enhances endocannabinoid signaling by activation of cannabinoid receptors. This phase 2 study aimed to further evaluate the efficacy and safety of Lu AG06466 in reducing tics, premonitory urges, and comorbidities in patients with TS.

Patients and Methods

Study Design and Patients

This was a multicenter (n = 8 centers), phase 2 study (ClinicalTrials.gov: NCT03625453) consisting of an 8-week, double-blind, randomized, placebo-controlled phase at two target dose levels followed by an optional 4-week, open-label safety extension to determine the effects of Lu AG06466 in patients (18–64 years) with TS with moderate to severe tics as indicated by a Yale Global Tic Severity Scale14—Total Tic Score (YGTSS-
TSS) ≥ 22. The patient’s treatment for tics and comorbidities must have been stable for ≥30 days before entering the study. Cannabis-based medicines (including recreational cannabis) had to be discontinued ≥14 days before randomization. Behavioral intervention for tics had to be completed ≥30 days before entering the study. Patients with a history of psychotic disorders and any substance abuse disorder within the prior year were excluded.

The study was conducted between October 2018 and January 2020 in accordance with the Declaration of Helsinki; study protocols were approved by the ethics committee at each site, and all patients provided written informed consent.

TREATMENTS

In the double-blind phase, patients were randomized (1:1) using a computer-generated sequence (blocks of four) to receive 8 weeks of double-blind treatment with Lu AG06466 in escalating daily doses or matching placebo. Patients randomized to active treatment received 10 mg for the first 3 days, 20 mg on days 4–28, 30 mg on days 29–35, before the target dose of 40 mg was reached for 21 days until day 56. Dose escalation could be adjusted based on the investigator’s judgment of tolerability, but it should have been stable between days 14–28 and 42–56. After completing the double-blind phase, all patients could continue to the 4-week, open-label safety extension, in which all patients started at a Lu AG06466 dose of 10 mg and increased to the target dose of 20 mg after 3 days (4 weeks was considered too short to titrate patients previously randomly assigned to placebo to a higher target dose). An overview of the dosing schedule is provided in Appendix S1 (Fig. e1).

ASSESSMENTS

Data were collected at baseline; at weeks 2, 4, 6, and 8 of the double-blind phase; and at weeks 10 and 12 (open-label extension). The primary efficacy assessment was the change from baseline in YGTSS-TTS. Other efficacy measures included the clinician-rated Clinical Global Impression for Improvement (CGI-I) and Severity (CGI-S),15 self-rated Adult Tic Questionnaire (ATQ),16 Premoritory Urge for Tic Scale (PUTS, items 1–9),17 and Gilles de la Tourette Syndrome–Quality of Life Scale (GTS-QoL),18 and for psychiatric comorbidities, Yale Brown Obsessive Compulsive Scale,19 Conners’ Adult Attention Deficit and Hyperactivity Rating Scale (CAARS),20 Beck Anxiety Inventory (BAI),21 and Beck Depression Inventory (BDI-II).22 Safety and tolerability assessments included treatment-emergent adverse events (TEAEs), vital signs, laboratory tests, electrocardiogram, physical examinations, and Columbia-Suicide Severity Rating Scale (C-SSRS).23 Cognition was assessed using the Cogstate neuropsychological test battery.24

Statistical Analyses

Based on recent randomized controlled trials of THC in TS,10,11 a sample size of 48 patients was estimated to provide 80% power to declare significance at 5% alpha level for a one-sided test, assuming a standardized effect size of 0.73 on the YGTSS-TTS.

Efficacy endpoints were analyzed using a restricted maximum likelihood-based mixed model for repeated measurements, including treatment, visit, and site as covariates; baseline score as a continuous variable; and interaction terms for baseline score by visit and treatment by visit. To account for multiplicity, we applied a closed testing procedure to the double-blind phase, testing first the mean treatment difference at week 8, then at week 4, provided the former comparison favored the active treatment over placebo at a one-sided alpha level of 0.025. If not, all P values were considered nominal. CAARS data were analyzed only in patients with comorbid attention deficit hyperactivity disorder (ADHD). Open-label data are presented descriptively. Data were analyzed using SAS, Version 9.4.

RESULTS

Of 53 patients screened, 49 (93%) were randomized to double-blind treatment (Appendix S1, Fig. e2). Overall, 19 of 23 patients (83%) randomized to the Lu AG64066 group, and 25 of 26 (96%) patients randomized to the placebo group completed the double-blind phase; 41 patients (84%) were male, and the median (range) age was 31.0 (19–58) years; a total of 18 patients (37%) had comorbid ADHD and/or obsessive-compulsive disorder. Treatment groups were generally comparable, except the placebo group included a higher proportion of patients with obsessive-compulsive disorder (46% vs. 26%) and used concomitant central nervous system–active medications more often (73% vs. 52%) than the active group (Appendix S1, Table e1).

Efficacy

During the double-blind phase, YGTSS-TTS scores (mean ± SD) improved in both groups, from 30.4 ± 8.3 at baseline to 27.9 ± 7.8 at week 4 and 27.5 ± 8.8 at week 8 in the Lu AG64066 group and from 29.9 ± 7.2 at baseline to 26.7 ± 8.4 at week 4 and 24.0 ± 8.1 at week 8 in the placebo group (Appendix S1, Fig. e3). The mean (95% CI) treatment difference at week 8 of 3.0 (0.1, 5.9) (P = 0.043) favored placebo (Table 1), and thus the study did not meet its primary endpoint, and subsequent P values are considered nominal. At week 4, the mean (95% CI) treatment difference in YGTSS-TTS was 0.4 (−2.0, 2.7) (P = 0.746).
|                          | Lu AG06466 (n = 23) | Placebo (n = 26) | Lu AG06466 vs. Placebo, *P* Value |
|--------------------------|---------------------|-----------------|----------------------------------|
| **YGTSS-TTS (range, 0–50)** |                     |                 |                                  |
| Baseline (mean ± SD)     | 30.4 ± 8.3          | 29.9 ± 7.2      |                                  |
| CFB at week 4            | −2.5 (−4.2, −0.7)   | −2.9 (−4.5, −1.2) | 0.75                             |
| CFB at week 8            | −2.7 (−4.9, −0.6)   | −5.7 (−7.7, −3.7) | 0.04                             |
| **YGTSS–Impairment (range, 0–50)** |               |                 |                                  |
| Baseline (mean ± SD)     | 22.6 ± 11.4         | 25.8 ± 11.7     |                                  |
| CFB at week 4            | −3.4 (−7.9, 1.1)    | −5.0 (−9.2, −0.9) | 0.59                             |
| CFB at week 8            | −4.4 (−8.6, −0.3)   | −5.6 (−9.4, −1.8) | 0.67                             |
| **YGTSS–Global Score (range, 0–100)** |           |                 |                                  |
| Baseline (mean ± SD)     | 30.4 ± 8.3          | 29.9 ± 7.2      |                                  |
| CFB at week 4            | −5.3 (−10.8, 0.1)   | −8.2 (−13.3, −3.1) | 0.44                             |
| CFB at week 8            | −7.7 (−13.1, −2.3)  | −11.6 (−16.5, −6.6) | 0.29                             |
| **ATQ**                  |                     |                 |                                  |
| Baseline (mean ± SD)     | 7.7 ± 2.3           | 7.2 ± 3.3       |                                  |
| CFB at week 4            | −0.6 (−1.2, 0.0)    | −0.7 (−1.4, −0.1) | 0.73                             |
| CFB at week 8            | −1.0 (−1.8, −0.3)   | −1.3 (−2.0, −0.6) | 0.68                             |
| **PUTS**                 |                     |                 |                                  |
| Baseline (mean ± SD)     | 23.6 ± 5.7          | 21.5 ± 5.7      |                                  |
| CFB at week 4            | 0.2 (−1.8, 2.2)     | −0.7 (−2.6, 1.2) | 0.50                             |
| CFB at week 8            | −1.1 (−3.1, 0.8)    | −0.6 (−2.4, 1.2) | 0.67                             |
| **GTS-QoL**              |                     |                 |                                  |
| Baseline (mean ± SD)     | 23.9 ± 19.8         | 24.4 ± 15.8     |                                  |
| CFB at week 8            | −2.7 (−9.4, 4.0)    | −3.1 (−9.2, 2.9) | 0.45                             |
| **CGI-S**                |                     |                 |                                  |
| Baseline (mean ± SD)     | 4.5 ± 0.7           | 4.5 ± 0.8       |                                  |
| CFB at week 4            | −0.0 (−0.2, 0.2)    | −0.1 (−0.3, 0.1) | 0.62                             |
| CFB at week 8            | −0.3 (−0.6, 0.0)    | −0.4 (−0.6, −0.1) | 0.59                             |
| **CGI-I**                |                     |                 |                                  |
| Week 4                   | 3.6 (3.1, 4.0)      | 3.6 (3.2, 3.9)  | 0.70                             |
| Week 8                   | 3.5 (3.0, 3.9)      | 3.4 (2.9, 3.8)  | 0.79                             |
| **Y-BOCS**               |                     |                 |                                  |
| Baseline (mean ± SD)     | 8.2 ± 9.9           | 7.8 ± 7.6       |                                  |
| CFB at week 4            | −0.3 (−2.2, 1.5)    | −2.0 (−3.7, −0.3) | 0.19                             |
| CFB at week 8            | −1.5 (−23.3, 0.4)   | −2.4 (−4.1, −0.7) | 0.44                             |
| **BDI-II**               |                     |                 |                                  |
| Baseline (mean ± SD)     | 8.7 ± 11.0          | 7.9 ± 8.0       |                                  |
| CFB at week 4            | −0.2 (−2.8, 2.4)    | −0.2 (−2.6, 2.2) | 1.0                              |
| CFB at week 8            | −0.5 (−3.2, 2.1)    | 0.4 (−2.0, 2.8)  | 0.59                             |

(Continues)
No significant differences were noted between groups at weeks 4 and 8 for YGTSS impairment and global scores, ATQ, PUTS, GTS-QoL, CGI-I, and CGI-S. Although numerical differences on the CAARS were apparent for patients with ADHD (n = 5) (Appendix S1, Fig. e4), statistical significance was not reached. No significant differences were observed for any other scale assessing psychiatric comorbidities (Table 2). During the open-label extension period, YGTSS-TTS further decreased, with a mean ± SD change from the beginning of the open-label phase (week 8) to week 12 of −4.7 ± 13.1 points.

Safety

During the double-blind phase, all patients treated with Lu AG06466 reported a TEAE, compared with 92.3% in the placebo group (Table 2). TEAEs that were more commonly reported with Lu AG06466 than placebo were mild to moderate in severity and comprised fatigue, attention disturbance, nasopharyngitis, paresthesia, dizziness, vertigo, dry mouth, and hyperhidrosis. During the open-label extension, 29 patients (82.9%) reported TEAEs with Lu AG06466 treatment. Three patients in the Lu AG06466 group and none in the placebo group discontinued the double-blind phase because of a TEAE. Changes in dose as a result of TEAEs were required in 17 (74%) patients in the Lu AG06466 group versus 6 (23%) in the placebo group during the double-blind phase and in 12 (34%) patients during the open-label extension. Three patients reported four severe TEAEs (chills, confusional state, renal colic, and meniscus injury) with open-label treatment. There were no deaths or fatal events.

**Discussion**

In this phase 2 study, no effect on tics was seen with Lu AG06466 versus placebo at week 8 as assessed using the YGTSS-TTS, and hence the study did not meet its primary endpoint. We also could not demonstrate positive results for other endpoints assessing changes in tic severity, premonitory urges, global impairment, and quality of life, as well as common psychiatric comorbidities. Treatment with Lu AG06466 was generally safe, and there were no relevant safety signals.
Table 2: Summary of TEAEs During the Double-Blind and Open-Label Phases

|                                | Double-Blind, n (%) | Placebo (n = 26) | Open-Label, n (%) |
|--------------------------------|---------------------|------------------|-------------------|
| Patients with TEAEs            | 23 (100)            | 24 (92.3)        | 29 (82.9)         |
| Patients discontinuing because of AEs | 3 (13)             | 1 (3.8)          | 3 (8.6)           |
| Patients with AEs leading to dose reduction | 14 (60.9)        | 3 (11.5)         |                   |

TEAEs occurring in >10% in either group

- Fatigue: 8 (34.8), 4 (15.4), 5 (14.3)
- Disturbance in attention: 6 (26.1), 3 (11.5), 5 (14.3)
- Nasopharyngitis: 6 (26.1), 4 (15.4), 5 (14.3)
- Paresthesia: 5 (21.7), 0 (0), 2 (5.7)
- Dizziness: 4 (17.4), 2 (7.7), 6 (17.1)
- Feeling abnormal: 4 (17.4), 5 (19.2), 3 (8.6)
- Vertigo: 4 (17.4), 4 (15.4), 3 (8.6)
- Headache: 3 (13.0), 8 (30.8), 4 (11.4)
- Dry mouth: 3 (13.0), 0 (0), 0 (0)
- Hyperhidrosis: 3 (13.0), 0 (0), 0 (0)
- Diarrhea: 2 (8.7), 3 (11.5), 0 (0)
- Somnolence: 2 (8.7), 4 (15.4), 6 (17.1)
- Tourette’s syndrome: 2 (8.7), 3 (11.5), 3 (8.6)
- Sleep disorder: 1 (4.3), 4 (15.4), 2 (5.7)
- Pain in extremity: 0 (0), 3 (11.5), 0 (0)

AEs leading to discontinuation

- Disturbance in attention: 1 (4.3), 1 (3.8), 0 (0)
- Erythema: 1 (4.3), 0 (0), 0 (0)
- Fatigue: 1 (4.3), 0 (0), 0 (0)
- Reading disorder: 1 (4.3), 0 (0), 0 (0)
- Tachycardia: 1 (4.3), 0 (0), 0 (0)
- Headache: 0 (0), 1 (3.8), 0 (0)
- Palpitations: 0 (0), 0 (0), 1 (2.9)
- Chills: 0 (0), 0 (0), 1 (2.9)
- Dizziness: 0 (0), 0 (0), 1 (2.9)
- Somnolence: 0 (0), 0 (0), 1 (2.9)

No serious AEs or deaths occurred during the study.

TEAE, treatment-emergent adverse event; AE, adverse event.

Effect at 8 weeks favored placebo. Indeed, the mean reduction in YGTSS-TTS of 5.7 points in the placebo group was approaching current definitions of clinical relevance.26,27 Placebo effects of this magnitude are not uncommon in TS28 and, as in other movement disorders, have been attributed to expectation or bias regarding the putative effect of the therapy under scrutiny.29 Interestingly, only recently, other compounds such as deutetrabenazine and valbenazine have also shown positive results in small phase 1 studies30,31 but have failed in larger follow-up randomized controlled trials,32,33 showing the difficulties of scaling from exploratory studies conducted in expert sites to larger and possibly more heterogenous populations.

Finally, despite the lack of statistical significance because of the very small sample size, the apparently beneficial effect of Lu AG06466 on ADHD symptoms...
is promising, because there is also evidence that cannabis-based medicine may improve ADHD.34

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Data Sharing
The protocol and data are available upon reasonable request from the corresponding author.

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Supporting Data
Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.