Endocannabinoid Modulation Using Monoacylglycerol Lipase Inhibition in Tourette Syndrome: A Phase 1 Randomized, Placebo-Controlled Study

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Key words
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Introduction
Tourette syndrome (TS) is a complex neurodevelopmental disorder characterized by chronic motor and vocal tics. While consistently effective treatment is lacking, evidence indicates that the modulation of endocannabinoid system is potentially beneficial. Lu AG06466 (previously ABX-1431) is a highly selective inhibitor of monoacylglycerol lipase, the primary enzyme responsible for the degradation of the endocannabinoid ligand 2-arachidonoylglycerol. This exploratory study aimed to determine the effect of Lu AG06466 versus placebo on tics and other symptoms in patients with TS.

Methods
In this phase 1b cross-over study, 20 adult patients with TS on standard-of-care medications were randomized to a single fasted dose of Lu AG06466 (40 mg) or placebo in period 1, followed by the other treatment in period 2. The effects on tics, premonitory urges, and psychiatric comorbidities were evaluated using a variety of scaled approaches at different time points before and after treatment.

Results
All scales showed an overall trend of tic reduction, with two out of three tic scales (including the Total Tic Score of the Yale Global Tic Severity Score) showing a significant effect of a single dose of Lu AG06466 versus placebo at various time points. Treatment with Lu AG06466 resulted in a significant reduction in premonitory urges versus placebo. Single doses of Lu AG06466 were generally well-tolerated, and the most common adverse events were headache, somnolence, and fatigue.

Conclusion
In this exploratory trial, a single dose of Lu AG06466 showed statistically significant positive effects on key measures of TS symptoms.
Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by rapid, recurrent, involuntary movements and vocalizations, manifesting in childhood and often persisting into adulthood [1]. Psychiatric comorbidities such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and depression are common [2,3]. Current treatments are moderately effective; both comprehensive behavioral intervention for tics (CBIT) and pharmacotherapy with atypical antipsychotics (e.g., aripiprazole and risperidone) result in an average tic reduction of 30–50% [4,5]. However, CBIT is hard to access and the atypical antipsychotics are associated with side effects such as sedation and weight gain [4]. Therefore, there is a need for a consistently effective medication that is well-tolerated and, ideally, also helps manage some of the common co-morbidities of TS.

The neurobiological basis of TS remains unclear. Basal ganglia involvement is assumed due to its well-known role in facilitating voluntary and inhibiting involuntary movements, including the control of routine behaviors and habits [6]. A role for the endocannabinoid system (ECS) in TS has, to date, been predominantly supported by clinical evidence indicating a beneficial effect of cannabis-based medicines. Several recent case series [7–9] and clinical studies [10,11] have reported that the use of cannabinoids such as tetrahydrocannabinol (THC) improve both tics and psychiatric comorbidities in adults with TS. THC and other exocannabinoids primarily exert their beneficial effects in TS possibly by acting as agonists at the cannabinoid receptor 1 (CB1) receptor which is highly expressed in the basal ganglia [12]. The principal endogenous ligands of the ECS are the lipid transmitters N-arachidonoylethanolamine (also known as anandamide) and 2-arachidonoylglycerol (2-AG), which act on presynaptic CB1 receptors to attenuate neurotransmission, serving an essential feedback function [13]. So, an alternative approach to stimulating central CB1 receptors is to inhibit the degradation of 2-AG into arachidonic acid and glycerol by inhibiting its main catalyzing enzyme monoacylglycerol lipase (MAGL) [14]. Under physiological conditions, 2-AG is released ‘on demand’ and acts as a retrograde messenger to suppress neurotransmitter release via CB1 receptor activation – in effect acting as a system ‘brake’. Thus, in contrast to exocannabinoids, which produce sustained activation of CB1 across all neuronal circuits, MAGL inhibitory results in sustained 2-AG signaling through CB1 receptors only in the active synapses.

Lu AG06466 (previously known as ABX-1431) is a highly selective inhibitor of MAGL and is currently under investigation for the treatment of various psychiatric and neurological diseases where modulation of the ECS has been suggested to be of benefit. Its primary active metabolite, Lu AG06988 has a comparable in vitro and in vivo pharmacodynamic profile to Lu AG06466. Lu AG06988 is also a potent and selective MAGL inhibitor and thus may contribute to the overall MAGL inhibitory effect. The primary objective of this exploratory study was to determine the effect of a single dose of Lu AG06466 on tics and comorbid psychiatric symptoms in adult patients with TS. Secondary objectives were to evaluate Lu AG06466 pharmacokinetics (under fasting [Part A] and fed [Part B] conditions), safety, and tolerability in this population.

Methods

Study conduct

This was a phase 1b, randomized, double-blind, placebo-controlled, single-dose, crossover study to evaluate the effects of Lu AG06466 on tics and psychiatric comorbidities in TS. The study was conducted in two parts: part A was a cross-over study conducted under fasting conditions. Part B was a pharmacokinetic extension, added with a protocol amendment, under fed conditions (following a high-fat breakfast) in those patients who tolerated treatment in part A and who agreed to participate within a pre-specified time frame (~Fig. 1). The study (Clinicaltrials.gov identifier NCT03058562, EudraCT-No 2016-004294-40) was carried out between February 6, 2017, and September 20, 2017, at the early-phase clinical trial unit at the Clinical Research Center (CRC), Hannover Medical School (MHH), Germany. The trial was conducted in accordance with Good Clinical Practice, following local laws and regulations, and was approved by the local ethics committee at MHH (no. 7285 M) and the Federal Institute for Drugs and Medical Devices (BfArM, no. 4041769). Patients provided written informed consent before entering either part of the study.

Patients

Twenty patients were recruited from the TS outpatient clinic at MHH and also via German TS advocacy groups. Adult (18–65 years) patients with TS according to DSM-5 and a Yale Global Tourette Severity Scale (YGTSS) -Total Tic Score (TTS) > 18 [range 0–50] [15] at screening were eligible for inclusion in the study. For ≥30 days before the screening visit, patients taking daily medications for tics or psychiatric comorbidities had to be on a stable dose (except cannabinoids, cannabis extracts, or medical products containing cannabinoids, which were stopped ≥4 days prior to study entry and during the study) and were expected to remain on a stable dose during the study. Key exclusion criteria were evidence of alcohol, drug, or chemical abuse (including recreational cannabis use) within one year before the screening, current or previous cannabis dependency, cannabis withdrawal symptoms, history of psychosis or schizophrenia or diagnosis of any unstable psychiatric disorder, or suicidal ideation within 12 months preceding screening; and treatment with potent cytochrome P450 3A4/5 inducers, or strong P450 3A4/5 inhibitors.

Treatment

In part A, patients were randomized by concealed, computer-generated assignment to either a single fasted dose of 40 mg of Lu AG06466 or placebo in Period 1 followed by a 1–3-week washout period and then the other study treatment in Period 2. In each treatment period, patients were hospitalized in the clinical trial unit for up to 48 h, from the night before the start of dosing to enforce abstinence with cannabinoids, fasting, and to allow a timely start in the morning and ending (at the earliest) on the morning after the treatment day. An independent staff member (not otherwise involved in the study) dispensed study medication of identical appearance following the randomized assignments. The investigators, patients, raters, and the sponsor were blinded to treatment during study conduct.

In part B (pharmacokinetic extension), patients were re-randomized to either a single dose of 20 mg of Lu AG06466 or placebo...
with a high-fat breakfast in period 3, with the other treatment in period 4. The dose with a meal was chosen based on the expectation of higher plasma exposure of the active moiety, Lu AG06466, and the MAGL-selective, CNS-penetrant, active metabolite Lu AG06988. The procedures in part B were the same as in part A, including a 1–3-week washout period between single-day treatments (from period 2–3 and from period 3–4). Patients continued their normal medications, except they discontinued cannabis/cannabinoïds for four days prior to each treatment period.

Efficacy and safety assessments
Efficacy was assessed by experts in tic assessment at baseline, 4-, and 8-h post-dose. Key endpoints were the video-based Modified Rush Video Scale (MRVS) [16], YGTSS-TTS, and the self-assessment Adult Tic Questionnaire (ATQ) [17], as well as effects on premonitory urges using items 1–9 of the Premoritory Urge for Tic Scale (PUTS) [18]. Standardized video recordings (MRVS) were rated by an independent clinician blinded to treatment, treatment date, and acquisition time relative to dose. The ATQ and PUTS were also assessed at 12 hours post-dose. In addition, YGTSS-MTS, vocal tic (YGTSS-VTS), and YGTSS global scores (YGTSS-GS) were assessed at 4 h and 8 h. Psychiatric comorbidities were assessed using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [19] for OCD; the Conners’ Adult Attention Deficit and Hyperactivity Rating Scale (CAARS) [20] for ADHD; the Beck Anxiety Inventory (BAI) [21] for anxiety; the Beck Depression Inventory (BDI-II) [22] for depression. Effects on overall impairment and improvement were assessed using the Clinical Global Impression of Improvement (CGI-I) and the Clinical Global Impression of Severity (CGI-S) [23], and patients were asked to guess the treatment sequence they had received. Where needed, assessments were modified for a single-dose study which considered changes from baseline to 4, 8, and 12 h post-dose. Safety was assessed through an adverse event (AE) reporting by an investigator who was not involved in clinical assessments, and by assessments of vital signs, clinical laboratory tests, and ECG.

Pharmacokinetic and Pharmacodynamic assessments
The pharmacokinetic profiles of Lu AG06466 and its metabolite Lu AG06988 were measured by high-performance liquid chromato-
carbamazepine). Seven of the eight patients who agreed to continue study participation in part B completed the extended pharmacokinetic evaluation. One patient taking a placebo in period 3 discontinued due to AEs (headache, nausea, fatigue, vomiting, loss of appetite, and upper abdominal pain). Baseline characteristics for patients entering part A are provided in Table 1; patients were predominantly male (n = 16 out of 20) and the mean ± SD age was 34 ± 11 [18–54] years. The mean ± SD YGTSS-GS was 43.7 ± 14.4, with a mean YGTSS-TTS subscore of 27.2 ± 6.4, consistent with moderate-to-severe tics. Eleven of 20 patients (55.0 %) regularly used cannabis-based medicines to treat TS.

Efficacy analyses

Despite the small sample size, all scales showed an overall trend of tic reduction during part A of the trial. Placebo-adjusted reductions in tics and premonitory urges following treatment with Lu AG06466 during part A are shown in Table 2. Although the mean [90 % CI] TWA overall treatment effects versus placebo of −0.7 [−2.0, 0.5] for MRVS and −1.1 [−2.7, 0.5] for YGTSS-TTS failed to reach statistical significance, analysis of each time point revealed that the treatment effect on YGTSS-TTS was significant versus placebo at the 8 h time point (−3.0 [−5.4, −0.6], p = 0.04) and statistically significant mean placebo-adjusted reductions were also observed for YGTSS-MTS at 4 hours post-dose (−1.5 [−2.8, −0.3], p = 0.05). Patients treated with Lu AG06466 also showed a reduction of about 30 % in mean tic intensity, as self-assessed by the ATQ, with less robust effects on tic frequency. In addition, motor tic intensity was significantly decreased, relative to placebo, at 4 (−4.6 [−7.4, −1.8], p = 0.01), 8 (−4.5 [−7.1, −2.0]; p < 0.01), and 12 hours (−3.4

**Table 1** Baseline demographics of the patients included in the study.

| Characteristic              | N = 20 |
|-----------------------------|--------|
| Age (years); mean ± SD [range] | 33.7 ± 10.5 [18–54] |
| Sex (Male/Female); n (%)     | 16 (80 %)/4 (20 %) |
| Race (Caucasian); n (%)      | 20 (100 %) |
| Tics                        |        |
| Age at onset (mean, years)   | 6.7    |
| Severity                   |        |
| YGTSS-TTS (mean ± SD)       | 26.7 ± 6.2 |
| YGTSS-GS (mean ± SD)        | 43.6 ± 14.6 |
| MRVS (mean ± SD)            | 12.3 ± 3.8 |
| Premonitory urges           |        |
| PUTS (mean ± SD)            | 19.8 ± 5.6 |
| Comorbidities               |        |
| ADHD *; n (%)               | 4 (20 %) |
| OCD *; n (%)                | 5 (25 %) |
| Current treatment of TS     |        |
| Cannabis/cannabinoid drugs; n (%) | 11 (55 %) |
| Antipsychotics; n (%)       | 6 (30 %) |
| No pharmacological treatment| 4 (20 %) |

* Patients were assessed for obsessive compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD) at the screening, and were diagnosed according to clinical judgment. MRVS: Modified Rush Video Scale, PUTS: Premonitory Urge for Tic Scale; TS: Tourette Syndrome; YGTSS: Yale Global Tic Severity Scale; YGTSS-GS: Yale Global Tic Severity Scale – Global Score; YGTSS-TTS Yale Global Tic Severity Scale – Total Tic Score.
No significant effects were seen on confidence intervals crossed 0 for all other scale parameters and participants receiving Lu AG06466. Patients receiving placebo showed an adjusted mean baseline were observed on some scales with placebo, but not with Lu AG06466, compared to only two patients after treatment with placebo. There were no significant changes in ADHD, OCD, anxiety, and depression as assessed by CAARS, Y-BOCS, BAI, and BDI-II. Thirteen out of 18 patients guessed their treatment sequence correctly and one patient did not provide a guess.

In the pharmacokinetic extension (part B), tic reductions from baseline were observed on some scales with placebo, but not with Lu AG06466. Patients receiving placebo showed an adjusted mean [90% CI] reduction from baseline of −2.4 [−3.3 to −1.5] points on YGTSS-TTS (TWA), −2.3 [−3.6 to −1.1] points on ATQ number of tics, and 5.1 [−6.4 to −3.9] points on ATQ intensity, but 90% confidence intervals crossed 0 for all scale parameters and patients receiving Lu AG06466. No significant effects were seen on CGI or scales of psychiatric comorbidity.

### Adverse events

Overall, a single dose of Lu AG06466 was well-tolerated with full details of AEs during part A are presented in Table 3. In part A, more patients reported AEs after treatment with Lu AG06466, compared to placebo, with the most frequently cited being headache, somnolence, and fatigue. In general, AEs were transient and were resolved. No serious AEs occurred. There were no discontinuations due to Lu AG06466-related AEs. In part B, more AEs were reported after placebo (23 events reported by seven patients) compared to Lu AG06466 (three events reported by two patients).

### Pharmacokinetics and Pharmacodynamics

Evidence of systemic plasma exposure to Lu AG06466 was observed in all Lu AG06466-treated patients following single oral administrations in the fasted state (40 mg) or the fed state (20 mg). Under fasting conditions, plasma exposure of Lu AG06466 and its active metabolite Lu AG06988 measured over time, reached peak concentrations 2 to 4 h post-dose (Fig. 3a, Supplemental Table e1). Consistent with plasma exposures, MAGL activity was reduced by 80.5% following administration of Lu AG06466 by 4 hours, inhibition was maintained through 8 hours, and activity returned to near baseline levels by 24 hours post-dose (Fig. 3b). In part B, mean exposure values for Lu AG06466 were about 2-fold higher following a high-fat meal compared to the fasted state, although the Lu AG06466 dose administered was 2-fold lower (Supplemental Table e2). However, unlike the parent molecule, mean exposure values for the metabolite Lu AG06988 were lower in part B than in part A.

### Table 2

| Outcome | Placebo-adjusted change from baseline | Time weighted analysis (MMRM) |
|---------|--------------------------------------|--------------------------------|
| MRVS    | Time period post-dose (t-test)       |                                |
| 4h      | −1.1 [−3.0, 0.9]                     | N/A                            |
| 8h      | −1.4 [−3.9, 1.1]                     | −0.7 [−2.0, 0.5]                |
| 12h     | N/A                                 | −1.1 [−2.7, 0.5]                |
| YGTSS   | TTS                                 |                                |
|         | −2.0 [−4.3, 0.3]                     |                                |
|         | −3.0 [−5.4, −0.6] *                 |                                |
| MTS     | −1.5 [−2.8, −0.3] *                 | −1.3 [−2.3, −0.2]               |
| VTS     | −0.5 [−1.9, 0.9]                     | −1.4 [−3.1, 0.3]                |
| GS      | −5.7 [−11.9, 0.5]                   | −5.8 [−12.7, 1.1]               |
| ATQ     | Frequency                            |                                |
|         | MT                                  |                                |
|         | −2.9 [−7.0, 1.3]                     | −5.1 [−9.0, −1.1] *            |
|         | −3.5 [−6.4, −0.6]                   | −1.7 [−4.0, 0.6]               |
|         | VT                                  |                                |
|         | −1.4 [−3.4, 0.5]                     | −1.6 [−3.2, 0.0]               |
|         | 1.1 [−2.2, 0.1]                     | −0.1 [−1.1, 0.8]               |
|         | Total                               |                                |
|         | −4.3 [−10.0, 1.4]                   | −6.6 [−11.8, 1.5] *            |
|         | −4.6 [−8.0, 1.2] *                  | −2.6 [−5.4, 0.3]               |
| Intensity| MT                                 |                                |
|         | −4.6 [−7.4, −1.8] *                 | −4.5 [−7.1, −2.0] *            |
|         | −3.4 [−5.0, −1.7] *                 | −3.0 [−4.3, −1.6] *            |
|         | VT                                  |                                |
|         | −1.4 [−2.4, −0.3] *                 | −1.1 [−2.1, 0.0]               |
|         | −1.0 [−2.0, 0.0]                    | −0.7 [−1.1, −0.3] *            |
|         | Total                               |                                |
|         | −5.9 [−9.5, −2.4] *                 | −5.6 [−8.9, −2.3] *            |
|         | −4.4 [−6.7, −2.0] *                 | −4.2 [−5.7, −2.6] *            |
| PUTS    | −1.9 [−3.4, −0.4] *                 | −0.7 [−2.1, 0.6]               |
|         | −1.3 [−2.2, −0.4] *                 | −0.8 [−1.5, 0.0]               |

All post-dose measurements were analyzed by mixed model repeated measures (MMRM) and summarized by time-weighted average (TWA). ∗ Statistical significance was declared by a one-sided p-value ≤ 0.05. ATQ: Adult Tic Questionnaire; GS: Global Score; MT: Motor Tics; MTS: Motor Tic Score; MRVS: Modified Rush Video Scale; PUTS: Premonitory Urge for Tic Scale; TS: Tourette Syndrome; TTS: Total Tic Score; VT: Vocal Tics; VTS: Vocal Tic Score; YGTSS: Yale Global Tic Severity Scale.

### Table 3

| AE (Preferred term) reported in > 2 patients | Placebo (N = 19) | 40 mg Lu AG06466 (N = 20) | Overall (N = 20) |
|--------------------------------------------|------------------|--------------------------|------------------|
| Any AEs                                    | 8 (42.1%)        | 13 (65.0%)                | 15 (75.0%)       |
| Dizziness                                  | 1 (5.3%)         | 2 (10.0%)                 | 3 (15.0%)        |
| Headache                                   | 2 (10.5%)        | 7 (35.0%)                 | 9 (45.0%)        |
| Somnolence                                 | 1 (5.3%)         | 5 (25.0%)                 | 5 (25.0%)        |
| Fatigue                                    | 1 (5.3%)         | 3 (15.0%)                 | 4 (20.0%)        |
part A. Following an administration of 20 mg in the fed state, mean MAGL activity was reduced by 87% at 8 h post-dose administration.

Discussion
This randomized, double-blind, placebo-controlled phase 1b trial indicates that modulation of the ECS with the highly selective MAGL inhibitor Lu AG06466 affects a relevant tic reduction, as assessed by the YGTSS-TTS and the self-assessment ATQ. A reduction in premonitory urges preceding the tics was also observed using the PUTS. Clinical global assessment of change supported a generally well-tolerated and positive impact of treatment with single-doses of Lu AG06466.

In this exploratory study, three different approaches to tic assessment were used to explore pharmacodynamic efficacy on tic severity. We decided on this multi-assessment approach, because (i) all tic severity rating scales suffer from limitations, (ii) tic self-assessment may differ from results obtained from examiner assessments, (iii) our study design required modifications of the YGTSS-TTS as the gold standard for tic assessment and the self-assessment ATQ, and (iv) the assumed advantage of the video-based assessment MRVS to capture short-term fluctuations of tics [26]. However, while the YGTSS-TTS and the ATQ demonstrated significant tic reductions, the MRVS did not reveal efficacy. This discrepancy in our findings might be explained by the fact that the MRVS, although theoretically the ideal instrument to capture short-term tic fluctuations, is also more vulnerable to other influences such as stress than the YGTSS-TTS and the ATQ. Correlation between the MRVS and the YGTSS is unclear since high as well as a poor correlation has been reported [27–30]. Therefore, while the YGTSS-TTS and the ATQ show a strong correlation with the YGTSS [32]; however, it has not yet been widely used and further validation is missing [26].

It is noteworthy that we also found a significant improvement of premonitory urges after treatment with Lu AG06466. This is in line with data obtained from recent studies using different exocan-
nabnoids also reporting improvement of premonitory urges [33]. This finding is of paramount importance since it is believed that premonitory urges may represent the key element of TS; accordingly, patients often describe that a tic is only performed to relieve this preceding sensation [34]. As such, the improvements of tics and premonitory urges demonstrated after a single oral dose of Lu AG06466 adds to the accumulating evidence supporting ECS involvement in the pathobiology of TS. However, this evidence is mainly based on data from open uncontrolled case series using different exocannabinoids, two small randomized, placebo-controlled studies using pure THC [7–11], and elevated cerebrospinal fluid levels of endocannabinoids in TS [35]. To the best of our knowledge, there is currently no medication for tics available with efficacy also on premonitory urges.

Part B was primarily designed as a pharmacokinetic extension to understand if there is a food effect on drug absorption with the tested formulation, although safety and efficacy measures were also included. Lu AG06466 has fast absorption and elimination kinetics with \( t_{\text{max}} \) in the range of 2–4 h and \( t_{\frac{1}{2}} \) in the range of 3–5 h. It was hypothesized that administration of 20 mg Lu AG06466 with a high-fat meal would increase the exposure of Lu AG06466 and the major active metabolite, Lu AG06988; the meal was also expected to reduce pharmacokinetic variability between patients. In reality, however, while administration with a high-fat meal increased the exposure to Lu AG06466, there was lower plasma exposure of the active metabolite. From a pharmacological point of view, levels of MAGL-inhibition were similar in part A and part B. While the part B extension was not designed to further assess efficacy (limiting any efficacy conclusions from this part), the lack of separation from placebo in terms of tic reduction may reflect a mix of factors including the small sample size and expectation bias (as all patients in part B had already completed tic outcomes, including the YGTSS-TTS, several times in part A). We also cannot rule out the effect of a slightly lower dose (and thus lower plasma exposure) in part B.

Single doses of Lu AG06466 were generally well-tolerated, with an AE profile similar to that seen in single-dose and multiple-dose studies in healthy volunteers [36]. There were no serious AEs and no patient discontinuations due to Lu AG06466–related AEs. The most commonly observed AEs were transient and included headache, somnolence, and fatigue. Since a single dose of 40 mg of Lu AG06466 was well-tolerated, it can be anticipated that maintenance treatment with Lu AG06466 will be even better tolerated when treatment is started with a lower dose – comparable to the general recommendation for cannabis-based medicines according to the principle “start low and go slow.”

This exploratory study has several limitations, most notably the single-dose design which is likely to have limited our ability to detect any impact on comorbid psychiatric symptoms including ADHD, OCD, depression, and anxiety. In addition, patients were hospitalized in an unfamiliar environment in the clinical trial unit for two nights, which might have an impact on overall well-being and may, therefore, have influenced tics and psychiatric symptoms. On the other hand, it is remarkable that we were able to demonstrate significant improvement of tics against this background since stress is regarded as the main environmental factor that worsens tics. While patients were generally representative of the adult TS target population, relatively few patients in this study suffered from typical comorbidities, and a large proportion had used cannabis or cannabis-based agents previously for their TS symptoms. Although cannabis-based medication had to be stopped only ≥ 4 days prior to study entry, we do not believe that results were influenced by cannabis withdrawal syndrome, since in the context of medicinal use, even abrupt withdrawal from long-term treatment causes only mild and transient disturbances in a minority of patients but no withdrawal syndrome [37]. Furthermore, the number of patients included was small (including only four females) and insufficient to look for potential age and sex differences suggested by other studies [38–40]. The per-protocol population (patients with complete data and no major protocol violations) was chosen as the most scientifically valid sample for evaluating the proof-of-concept hypotheses.

In summary, this single-dose trial elucidated the first clinical evidence for a positive pharmacodynamic effect of the selective MAGL inhibitor Lu AG06466 for the treatment of tics and premonitory urges in adult patients with TS. However, despite these promising results, efficacy was not replicated in a subsequent, larger phase II study [41].

Author Contributions
KMV, CB, and CS participated in the study design, research, and data collection and contributed to the first draft of the manuscript. KMV, CF, CB, JI, HL, and CS contributed to the analysis and interpretation of data, writing, review, and approval of the manuscript for its publication.

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Conflict of Interest
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