Tozadenant (SYN115) in patients with Parkinson's disease who have motor fluctuations on levodopa: a phase 2b, double-blind, randomised trial

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Summary

Background Many patients with Parkinson's disease have motor fluctuations despite treatment with available drugs. Tozadenant (SYN115) is an oral, selective adenosine A_{2A} receptor antagonist that improves motor function in animal models of Parkinson's disease. We aimed to assess the safety and efficacy of tozadenant as an adjunct to levodopa in patients with Parkinson's disease who have motor fluctuations on levodopa.

Methods We did an international, multicentre, phase 2b, randomised, double-blind, placebo-controlled, parallel-group, dose-finding clinical trial of tozadenant in levodopa-treated patients with Parkinson's disease who had motor fluctuations (at least 2·5 h off-time per day). Eligible patients were randomly assigned via a computer-generated randomisation schedule to receive tozadenant 60, 120, 180, or 240 mg or matching placebo twice daily for 12 weeks. All study management, site personnel, and patients were masked to treatment assignment. The primary outcome was change from baseline to week 12 in hours per day spent in the off-state (assessed from Parkinson's disease diaries completed by patients). This study is registered at ClinicalTrials.gov, number NCT01283594.

Findings Of 420 randomised patients (mean age 63·3 [SD 8·3] years; mean duration of Parkinson's disease 8·7 [4·7] years), 403 provided post-baseline diary data and 337 completed study treatment. Compared with placebo, mean daily off-time was significantly reduced in the combined tozadenant 120 mg twice-daily and 180 mg twice-daily group (–1·1 h, 95% CI –1·8 to –0·5; p=0·0006), the tozadenant 120 mg twice-daily group (–1·1 h, –1·8 to –0·4; p=0·0039), and the tozadenant 180 mg twice-daily group (–1·2 h, –1·9 to –0·4; p=0·0039). The most common adverse events in these groups were dyskinesia (seven [8%] of 84 patients in the placebo group, 13 [16%] of 82 in the 120 mg twice-daily group, and 17 [20%] of 85 in the 180 mg twice-daily group), nausea (three [4%], 9 [11%], and ten [12%]), and dizziness (one [1%], four [5%], and 11 [13%]). Tozadenant 60 mg twice daily was not associated with a significant reduction in off-time, and tozadenant 240 mg twice daily was associated with an increased rate of discontinuation because of adverse events (17 [20%] of 84 patients).

Interpretation Tozadenant at 120 or 180 mg twice daily was generally well tolerated and was effective at reducing off-time. Further investigation of tozadenant treatment in phase 3 trials is warranted.

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Introduction

Levodopa remains the gold standard for symptomatic treatment of Parkinson's disease. However, long-term treatment is associated with the development of motor fluctuations and dyskinesias. In advanced disease, drugs are needed that can maintain robust benefit throughout the day or that can be added to levodopa to smooth the response without exacerbating dyskinesias.

Adenosine A_{2A} receptors are highly localised to enkephalinergic striatopallidal γ-aminobutyric acid (GABA)-containing neurons that form part of the indirect basal ganglia pathway.[1] Stimulatory A_{2A} and inhibitory D_2 dopamine receptors are colocalised on these neurons and modulate indirect pathway activity. Results of phase 2 clinical trials in patients with Parkinson's disease who have motor fluctuations on levodopa showed that the addition of the A_{2A} antagonists istradefylline[2–4] or preladenant[5] reduced off-time and did not significantly increase troublesome dyskinesia. However, preladenant was not effective in phase 3 clinical trials,[6] and istradefylline produced mixed results.[7,8] Although istradefylline was not approved by the US Food and Drug Administration in 2008, it was approved as an adjunct to levodopa in Japan in 2013.

Tozadenant (SYN115) is an A_{2A} antagonist that was assessed in a phase 2a study[9] that used a 2×2 crossover design in which patients with mild Parkinson's disease were randomly assigned either to 1 week of tozadenant, 1 week of washout, and 1 week of placebo, or to the reverse order. The results showed that tapping speed was faster on tozadenant 60 mg twice daily than on placebo both before (5%, p=0·03) and during a levodopa intravenous infusion (6%, p=0·02). Perfusion MRI showed that tozadenant induced highly significant decreases in regional cerebral blood flow, with the most significant decreases occurring in bilateral thalami.

Quantitative analyses suggested that higher doses than were tested in the trial might be more effective.[9]

See Online for appendix

In this phase 2b trial, we aimed to assess the safety and efficacy of various twice-daily doses of tozadenant in levodopa-treated patients with Parkinson's disease who have fluctuations.

Methods

Study design and participants

In this international, multicentre, phase 2b, randomised, double-blind, placebo-controlled, parallel-group trial, we compared several different doses of tozadenant and placebo in patients with Parkinson's disease. The study took place at 76 centres in six countries (Argentina, Canada, Chile, Romania, Ukraine, and USA). Eligible patients were aged 30–80 years, had a diagnosis of Parkinson's disease consistent with the UK Parkinson's Disease Society Brain Bank Criteria, were at Hoehn and Yahr stage 3 or lower in the on-state and stage 2–4 in the off-state, had been on a stable regimen of Parkinson's disease drugs for at least 4 weeks before screening, had been taking levodopa for at least 12 months and were currently taking levodopa at least four times per day with a good response, but were experiencing wearing-off motor fluctuations with at least 2·5 h of off-time per day. Concomitant treatment with dopamine agonists, catechol-*O*-methyl transferase (COMT) inhibitors, monoamine oxidase-B (MAOB) inhibitors, amantadine, and anticholinergic drugs at stable doses was permitted. The complete list of inclusion and exclusion criteria is provided in the appendix. An independent panel of experts confirmed that participants met the enrolment criteria before they were randomly assigned.

The study was done in accordance with International Harmonisation Conference guidelines on Good Clinical Practice. Before patient enrolment, the study's protocol, protocol amendments, and consent forms were approved by relevant institutional review boards and independent ethics committees, and all patients provided written informed consent.

Randomisation and masking

After patients successfully completed all screening and baseline assessments, they were randomly assigned (1:1:1:1:1) at baseline via a centralised, computer-based randomisation schedule to treatment with placebo or tozadenant 60, 120, 180, or 240 mg twice daily for 12 weeks. To implement the randomised allocation, authorised study staff assigned to each patient the next kit in the site's inventory (provided per the randomisation schedule) and entered the kit's randomisation number into the electronic case report forms. Bilcare (now Sharps, Phoenixville, PA, USA) generated the randomisation code. All study management, site personnel, and patients were masked to treatment assignment.

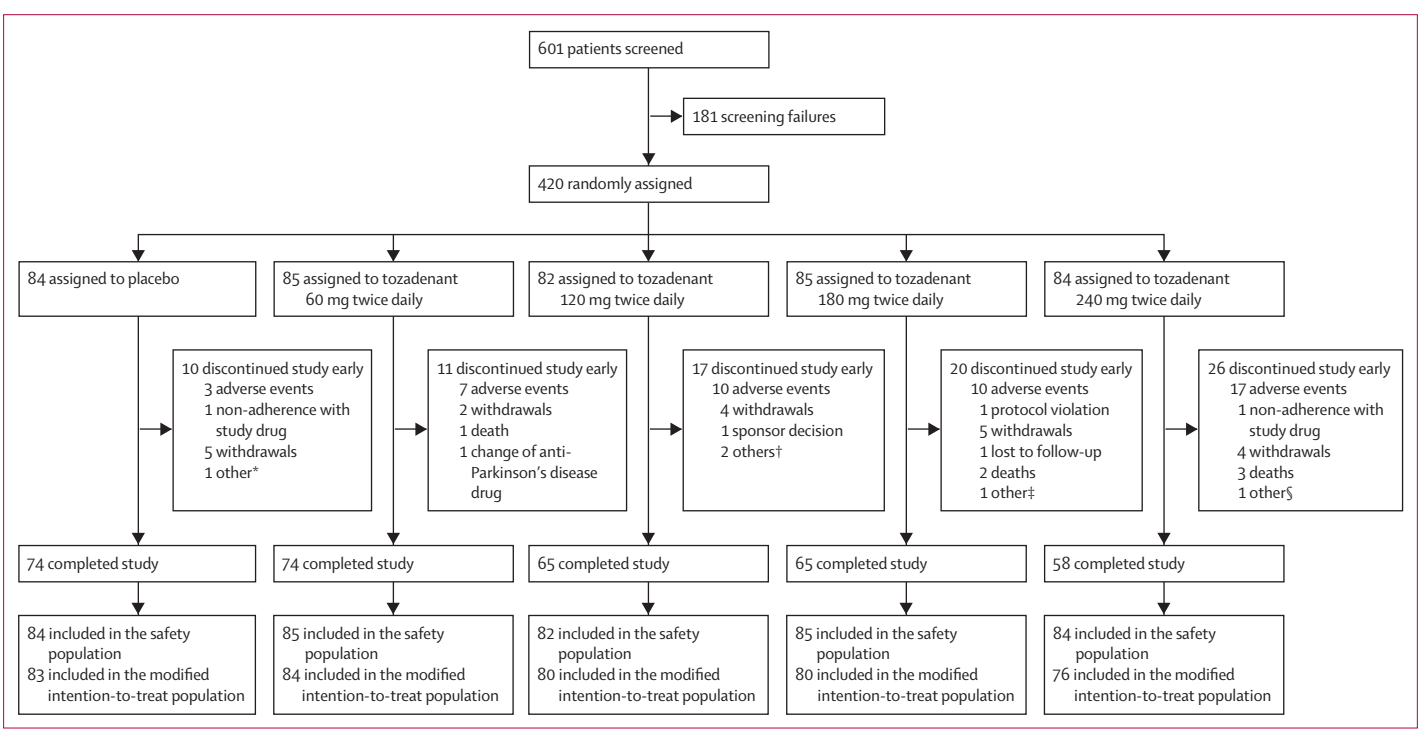

Figure 1: **Trial profile**

*Discontinued to proceed with deep-brain stimulation because of worsening Parkinson's disease symptoms. †One patient did not return for follow-up and one patient decided to stop taking the study drug because of adverse events (agitation, confusion, generalised weakness, insomnia, nausea, worsened anxiety, and worsened dyskinesias). ‡Stopped taking study drug for more than 2 weeks without informing study site investigators. §Decided to stop taking study drug because of an adverse event (double vision).

Procedures

For the assessment of efficacy, patients completed Parkinson's disease diaries[10] that indicated their predominant clinical status every half hour while awake for two consecutive 24 h periods (ie, 2 days) before study visits at baseline (treatment initiation) and weeks 2, 6, and 12 (end of treatment). An additional safety visit took place 2 weeks after each patient's last dose of study drug (ie, week 14). During the screening period, eligible patients had to successfully complete Parkinson's disease diary training and show valid diary completion. At the baseline visit, patients who returned valid baseline diaries that indicated at least 2·5 h of off-time on each of the 2 previous days and who met all other eligibility criteria were randomly assigned to treatment or matching placebo.

Study drugs were tozadenant 60 mg tablets (Biotie, South San Francisco, CA, USA) and matching placebo (identical in appearance and taste), packaged in blister cards within individual patient kits. The dosing schedule was four tablets in the morning and four tablets in the evening, ranging from all placebo tablets to all tozadenant tablets, dependent on assigned dose. Each dose was to be taken orally, before or at least 2 h after breakfast and dinner. Daily doses of other Parkinson's disease drugs could be reduced in response to clinically significant dopaminergic adverse events and could thereafter be increased back to the baseline dose; however, doses could not exceed those used at baseline.

For efficacy assessments, in addition to Parkinson's disease diaries, Unified Parkinson's Disease Rating Scale (UPDRS, parts I, II, III, and IV)[11] scores were obtained at screening, baseline, and weeks 2, 6, and 12. UPDRS part III (motor examination) assessments were made 2–3 h after the patient took a scheduled dose of levodopa (preferably the morning dose). Clinician Global Impression of Severity (CGI-S) was obtained at baseline and weeks 2, 6, and 12, and Patient Global Impression of Improvement (PGI-I) and Clinician Global Impression of Improvement (CGI-I) were obtained at weeks 2, 6, and 12. Scores for the 39-item Parkinson's Disease Questionnaire (PDQ-39),[12] the Beck Depression Inventory (BDI),[13] and the Beck Anxiety Inventory (BAI)[14] were obtained at baseline and weeks 6 and 12. Safety assessments included physical and neurological examinations, electrocardiography, laboratory tests, blood pressure recordings, assessment of treatment-emergent adverse events, modified Minnesota Impulsive Disorders Interview, the

	Placebo (n=84)	Tozadenant dose			
		60 mg twice daily (n=85)	120 mg twice daily (n=82)	180 mg twice daily (n=85)	240 mg twice daily (n=84)
Age (years)	63·5 (7·4)	64·2 (7·9)	62·6 (8·4)	62·6 (8·5)	63·3 (9·1)
Men	61 (73%)	57 (67%)	53 (65%)	59 (69%)	58 (69%)
Duration of Parkinson's disease (years)	8·7 (4·8)	8·4 (4·1)	8·4 (4·7)	9·5 (5·5)	8·3 (4·6)
Hoehn and Yahr stage in the on-state					
Stage 1 or 1.5	1 (1%)	5 (6%)	6 (7·3)	6 (7%)	10 (12%)
Stage 2	48 (57%)	49 (58%)	48 (59%)	44 (52%)	48 (57%)
Stage 2.5	25 (30%)	19 (22%)	11 (13%)	22 (26%)	20 (24%)
Stage 3	9 (11%)	11 (13%)	15 (18%)	12 (14%)	6 (7%)
Awake time in off-state (h)	6·07 (2·43)	5·98 (2·08)	5·89 (1·79)	6·16 (2·53)	6·16 (2·18)
UPDRS parts I–III combined score*	34·6	33·5	35·3	35·5	34·1
UPDRS part III score*	21·0	20·4	22·4	21·5	21·1
Antiparkinsonian drugs at baseline					
Levodopa or levodopa derivatives only	10 (12%)	10 (12%)	16 (20%)	19 (22%)	10 (12%)
Levodopa or levodopa derivatives plus one other antiparkinsonian drug	32 (38%)	31 (36%)	35 (43%)	26 (31%)	37 (44%)
Levodopa or levodopa derivatives plus two other antiparkinsonian drugs	30 (36%)	31 (36%)	23 (28%)	32 (38%)	29 (35%)
Levodopa or levodopa derivatives plus three or more other antiparkinsonian drugs	12 (14%)	13 (15%)	8 (10%)	8 (9%)	8 (10%)
Duration of levodopa use (years)	6·6	6·4	6·9	7·2	6·4
On dopamine agonists at baseline	57 (68%)	52 (61%)	51 (62%)	49 (58%)	53 (63%)
On COMT inhibitors	15 (18%)	16 (9%)	4 (5%)	6 (7%)	17 (20%)
On MAOB inhibitors at baseline	35 (42%)	34 (40%)	25 (30%)	30 (35%)	30 (36%)
Mini-Mental State Examination score	28·5	28·9	28·7	28·8	28·8

UPDRS=Unified Parkinson's Disease Rating Scale. COMT=catechol-*O*-methyl transferase. MAOB=monoamine oxidase type B. *Modified intention-to-treat population (part III score during on-state). Data are mean, mean (SD), or n (%).

Table 1: **Baseline demographic and clinical characteristics (intention-to-treat population)**

	Tozadenant	Placebo	Difference (tozadenant minus placebo)	Raw p value	Adjusted p value*
Patient Parkinson's disease diary					
Off-time while awake (h)†					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−1·887 (0·192)	−0·763 (0·268)	−1·124 (0·324)	0·0006	0·0006
Tozadenant 120 mg twice daily *vs* placebo	−1·857 (0·279)	−0·763 (0·268)	−1·094 (0·376)	0·0039	0·0039
Tozadenant 180 mg twice daily *vs* placebo	−1·916 (0·281)	−0·763 (0·268)	−1·154 (0·377)	0·0024	0·0039
Tozadenant 60 mg twice daily *vs* placebo	−1·392 (0·270)	−0·763 (0·268)	−0·629 (0·368)	0·0881	0·0881
Tozadenant 240 mg twice daily *vs* placebo	−1·627 (0·294)	−0·763 (0·268)	−0·864 (0·387)	0·0262	0·0881
On-time while awake (h)‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	1·773 (0·199)	0·832 (0·276)	0·941 (0·334)	0·0052	0·0052
Tozadenant 120 mg twice daily *vs* placebo	2·006 (0·289)	0·832 (0·276)	1·174 (0·389)	0·0027	0·0052
Tozadenant 180 mg twice daily *vs* placebo	1·540 (0·291)	0·832 (0·276)	0·708 (0·390)	0·0701	0·0701
Tozadenant 60 mg twice daily *vs* placebo	1·173 (0·278)	0·832 (0·276)	0·340 (0·380)	0·3708	0·3708
Tozadenant 240 mg twice daily *vs* placebo	1·644 (0·305)	0·832 (0·276)	0·812 (0·401)	0·0434	0·3708
Awake time in on-state without troublesome dyskinesia (defined as without dyskinesia or with non-troublesome dyskinesia; h)‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	1·547 (0·224)	0·860 (0·310)	0·688 (0·376)	0·0681	0·0681
Tozadenant 120 mg twice daily *vs* placebo	2·050 (0·323)	0·860 (0·310)	1·190 (0·437)	0·0068	0·0681
Tozadenant 180 mg twice daily *vs* placebo	1·045 (0·326)	0·860 (0·310)	0·186 (0·438)	0·6717	0·6717
Tozadenant 60 mg twice daily *vs* placebo	1·408 (0·312)	0·860 (0·310)	0·548 (0·427)	0·1994	0·6717
Tozadenant 240 mg twice daily *vs* placebo	1·415 (0·342)	0·860 (0·310)	0·555 (0·450)	0·2184	0·6717
Unified Parkinson's Disease Rating Scale					
Part I total score‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−0·200 (0·099)	−0·055 (0·136)	−0·145 (0·166)	0·3820	0·3820
Tozadenant 120 mg twice daily *vs* placebo	−0·235 (0·143)	−0·055 (0·136)	−0·180 (0·193)	0·3513	0·3820
Tozadenant 180 mg twice daily *vs* placebo	−0·165 (0·144)	−0·055 (0·136)	−0·110 (0·193)	0·5688	0·5688
Tozadenant 60 mg twice daily *vs* placebo	−0·146 (0·137)	−0·055 (0·136)	−0·091 (0·189)	0·6286	0·6286
Tozadenant 240 mg twice daily *vs* placebo	0·076 (0·151)	−0·055 (0·136)	0·130 (0·199)	0·5124	0·6286
Part II total score‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−1·649 (0·294)	−0·715 (0·410)	−0·935 (0·495)	0·0598	0·0598
Tozadenant 120 mg twice daily *vs* placebo	−1·576 (0·427)	−0·715 (0·410)	−0·861 (0·576)	0·1358	0·1358
Tozadenant 180 mg twice daily *vs* placebo	−1·723 (0·430)	−0·715 (0·410)	−1·009 (0·576)	0·0807	0·1358
Tozadenant 60 mg twice daily *vs* placebo	−1·971 (0·414)	−0·715 (0·410)	−1·256 (0·564)	0·0264	0·1358
Tozadenant 240 mg twice daily *vs* placebo	−1·964 (0·449)	−0·715 (0·410)	−1·249 (0·593)	0·0357	0·1358
Part III total score (during on-state)‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−3·353 (0·525)	−0·994 (0·733)	−2·358 (0·887)	0·0081	0·0081
Tozadenant 120 mg twice daily *vs* placebo	−3·204 (0·762)	−0·994 (0·733)	−2·210 (1·030)	0·0325	0·0325
Tozadenant 180 mg twice daily *vs* placebo	−3·501 (0·766)	−0·994 (0·733)	−2·507 (1·031)	0·0154	0·0325
Tozadenant 60 mg twice daily *vs* placebo	−2·815 (0·738)	−0·994 (0·733)	−1·821 (1·010)	0·0722	0·0722
Tozadenant 240 mg twice daily *vs* placebo	−3·845 (0·801)	−0·994 (0·733)	−2·851 (1·060)	0·0075	0·0722
Sum of parts I–III total scores‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−5·284 (0·721)	−1·936 (1·008)	−3·348 (1·219)	0·0063	0·0063
Tozadenant 120 mg twice daily *vs* placebo	−5·099 (1·046)	−1·936 (1·008)	−3·164 (1·416)	0·0260	0·0260
Tozadenant 180 mg twice daily *vs* placebo	−5·468 (1·053)	−1·936 (1·008)	−3·533 (1·417)	0·0130	0·0260
Tozadenant 60 mg twice daily *vs* placebo	−4·960 (1·015)	−1·936 (1·008)	−3·024 (1·389)	0·0301	0·0301
Tozadenant 240 mg twice daily *vs* placebo	−5·765 (1·101)	−1·936 (1·008)	−3·829 (1·458)	0·0090	0·0301
Clinician Global Impression of Severity score‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−0·240 (0·050)	0·028 (0·068)	−0·268 (0·083)	0·0014	0·0014
Tozadenant 120 mg twice daily *vs* placebo	−0·231 (0·072)	0·028 (0·068)	−0·259 (0·097)	0·0076	0·0076
Tozadenant 180 mg twice daily *vs* placebo	−0·249 (0·073)	0·028 (0·068)	−0·277 (0·097)	0·0045	0·0076
Tozadenant 60 mg twice daily *vs* placebo	−0·191 (0·069)	0·028 (0·068)	−0·219 (0·094)	0·0208	0·0208
Tozadenant 240 mg twice daily *vs* placebo	−0·210 (0·076)	0·028 (0·068)	−0·238 (0·100)	0·0175	0·0208

(Table 2 continues on next page)

	Tozadenant	Placebo	Difference (tozadenant minus placebo)	Raw p value	Adjusted p value*
(Continued from previous page)					
Clinician Global Impression of Improvement score‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	1·033 (0·082)	0·422 (0·113)	0·612 (0·137)	< 0·0001	< 0·0001
Tozadenant 120 mg twice daily *vs* placebo	1·062 (0·118)	0·422 (0·113)	0·641 (0·160)	< 0·0001	0·0001
Tozadenant 180 mg twice daily *vs* placebo	1·004 (0·119)	0·422 (0·113)	0·583 (0·160)	0·0003	0·0003
Tozadenant 60 mg twice daily *vs* placebo	0·847 (0·114)	0·422 (0·113)	0·426 (0·156)	0·0066	0·0066
Tozadenant 240 mg twice daily *vs* placebo	1·022 (0·125)	0·422 (0·113)	0·600 (0·165)	0·0003	0·0066
Patient Global Impression of Improvement score‡					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	1·089 (0·099)	0·741 (0·128)	0·349 (0·155)	0·0249	0·0249
Tozadenant 120 mg twice daily *vs* placebo	1·188 (0·133)	0·741 (0·128)	0·448 (0·180)	0·0134	0·0249
Tozadenant 180 mg twice daily *vs* placebo	0·991 (0·134)	0·741 (0·128)	0·250 (0·180)	0·1661	0·1661
Tozadenant 60 mg twice daily *vs* placebo	0·787(0·129)	0·741 (0·128)	0·046 (0·176)	0·7943	0·7943
Tozadenant 240 mg twice daily *vs* placebo	1·194 (0·141)	0·741 (0·128)	0·454 (0·186)	0·0149	0·7943
Beck Depression Inventory score§					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−1·327 (0·444)	−0·659 (0·623)	−0·669 (0·747)	0·3716	0·3716
Tozadenant 120 mg twice daily *vs* placebo	−2·036 (0·649)	−0·659 (0·623)	−1·377 (0·868)	0·1135	0·3716
Tozadenant 180 mg twice daily *vs* placebo	−0·618 (0·658)	−0·659 (0·623)	0·040 (0·870)	0·9631	0·9631
Tozadenant 60 mg twice daily *vs* placebo	−1·683 (0·635)	−0·659 (0·623)	−1·024 (0·853)	0·2309	0·9631
Tozadenant 240 mg twice daily *vs* placebo	−1·364 (0·683)	−0·659 (0·623)	−0·705 (0·895)	0·4313	0·9631
Beck Anxiety Inventory score§					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−0·919 (0·528)	−0·805 (0·738)	−0·114 (0·883)	0·8975	0·8975
Tozadenant 120 mg twice daily *vs* placebo	−1·106 (0·766)	−0·805 (0·738)	−0·301 (1·030)	0·7703	0·8975
Tozadenant 180 mg twice daily *vs* placebo	-0·732 (0·775)	−0·805 (0·738)	0·073 (1·029)	0·9434	0·9434
Tozadenant 60 mg twice daily *vs* placebo	−1·125 (0·740)	−0·805 (0·738)	−0·320 (1·003)	0·7496	0·9434
Tozadenant 240 mg twice daily *vs* placebo	−0·682 (0·815)	−0·805 (0·738)	0·123 (1·066)	0·9081	0·9434
PDQ-39 Single Index score§					
Tozadenant 120 mg twice-daily and 180 mg twice-daily groups combined *vs* placebo	−2·719 (0·783)	−4·043 (1·092)	1·325 (1·309)	0·3124	0·3124
Tozadenant 120 mg twice daily *vs* placebo	−2·372 (1·125)	−4·043 (1·092)	1·672 (1·525)	0·2739	0·3124
Tozadenant 180 mg twice daily *vs* placebo	−3·066 (1·153)	−4·043 (1·092)	0·977 (1·526)	0·5223	0·5223
Tozadenant 60 mg twice daily *vs* placebo	−3·299 (1·087)	−4·043 (1·092)	0·745 (1·488)	0·6170	0·6170
Tozadenant 240 mg twice daily *vs* placebo	−2·915 (1·217)	−4·043 (1·092)	1·128 (1·593)	0·4791	0·6170

Data are least squares mean change (SE) from baseline to week 12, unless otherwise indicated. PDQ=Parkinson's disease questionnaire. *The five comparisons were made by use of sequential testing with a fixed sequence to control the family-wise error for multiple comparisons at α=0·05 (two-tailed); each comparison was tested sequentially in the prespecified order; adjusted p values were calculated by taking the maximum of the raw p value from the comparison and the adjusted p value from the previous comparison in the sequence. †Primary efficacy endpoint. ‡Secondary efficacy endpoint. §Exploratory efficacy endpoint.

Table 2: **Efficacy results (modified intention-to-treat population)**

Epworth Sleepiness Scale, and the Columbia Suicide Severity Rating Scale. Additional details of the safety assessments are provided in the appendix. An independent data monitoring committee (masked to group assignment) reviewed all adverse events during the study, and an independent panel of experts reviewed these data after the study was complete and unblinded.

Outcomes

The primary efficacy outcome was the change from baseline to final visit (week 12 or the last available post-baseline value) in the number of hours spent in the off-state while awake, averaged over 2 consecutive days, in the modified intention-to-treat population. Secondary outcome measures were change from baseline to final visit in mean daily on hours and on hours with and without dyskinesia (troublesome and non-troublesome), UPDRS total score for parts I–III, UPDRS scores for individual parts (I, II, and III), and scores for CGI-S, CGI-I, and PGI-I. Exploratory outcome measures were change from baseline to final visit in BDI, BAI, and PDQ-39 scores.

Statistical analyses

The modified intention-to-treat population consisted of all randomised patients who took at least one dose of study drug and had valid diaries at baseline and at least one valid post-baseline diary. The primary analysis was a mixed-model repeated-measures ANCOVA that included terms for treatment group, geographical region (North

America [USA and Canada], South America [Argentina and Chile], or eastern Europe [Romania and Ukraine]), baseline number of hours of off-time per day, week of study, and the interaction between treatment group and week of study.

We did our initial test of the null hypothesis of the equality of the adjusted group means in the tozadenant and placebo groups for the combined tozadenant 120 mg twice-daily and 180 mg twice-daily dose groups first (the primary comparison of interest), using a significance level of 0·05 (two-tailed). Each individual tozadenant dose group was then tested the same way in this order: 120 mg twice daily, 180 mg twice daily, 60 mg twice daily, and 240 mg twice daily. If the p value for the first comparison was 0·05 or less, then the result would be regarded as significant and testing would proceed to the next comparison, and so on through the sequence.

We then derived adjusted p values by taking the greater of the raw p value from the statistical test and the adjusted p value from the previous test. The first comparison that yielded an adjusted p value greater than 0·05 and any comparison later in the sequence would be regarded as non-significant. This sequential step-down approach was implemented in a fixed order to control the family-wise error for multiple comparisons at an α of 0·05 (two-tailed). The two middle doses used in the study were combined in the first step of the sequential testing algorithm to increase the power of the study in the event that the SD used to calculate the power needed to differentiate individual tozadenant dose groups from placebo proved to be an underestimate. The testing order for the four individual dose groups was based on (unpublished) phase 1 data, findings from a phase 2 study,[9] and the anticipated likelihood of identifying a benefit compared with placebo. The 120 mg twice-daily dose was tested first because it was well tolerated in phase 1. The 240 mg twice-daily dose had a much higher frequency of adverse events, so it was placed last in the sequence, because a high withdrawal rate might reduce the power to detect efficacy. The 60 mg twice-daily dose was well tolerated, but seemed to be at the lower end of the efficacy range, so it was placed third in sequence. The 180 mg twice-daily dose had not previously been tested, but was hoped to be better tolerated than 240 mg twice daily and could potentially afford greater efficacy than 120 mg twice daily, so it was placed second in the sequence.

A review of findings from recent randomised trials[3–5] suggested that the SD of the primary efficacy outcome was about 2·5 h. A sample size of 80 patients per treatment group was planned to yield roughly 70 patients per treatment group in the modified intention-to-treat population, which would provide about 80% power to detect a difference in mean response between any active treatment group and the placebo group, with significance calculated by use of a *t* test, with an anticipated difference of 1·2 h and a significance level of 0·05 (two-tailed).

The study is registered with ClinicalTrials.gov, number NCT01283594.

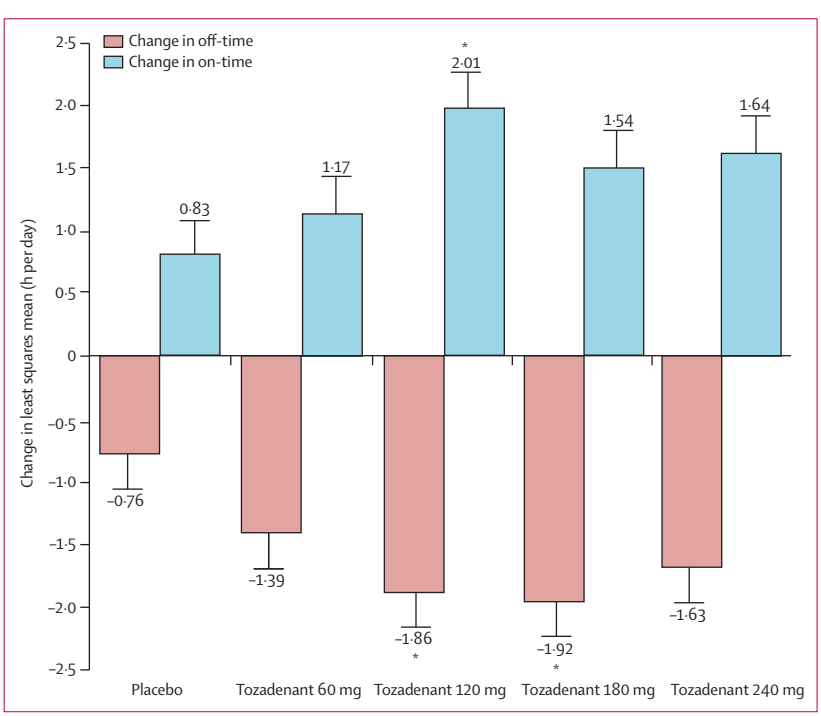

Figure 2: **Change in mean daily off-time and on-time**
Data are based on a 2-day average. *Adjusted p value versus placebo <0·01.

Role of the funding source

Data collection, analysis, and interpretation were coordinated by the funder and its designates (RAH, CWO, and KDK) who also contributed to the conduct of the study. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

The study took place from March 15, 2010, to Oct 17, 2012. 420 patients were randomly assigned and comprised the safety and intention-to-treat populations (figure 1). 403 (96%) of the randomised patients were included in the modified intention-to-treat population; 337 (80%) completed study treatment and 336 (80%) completed the study including the follow-up safety visit (figure 1). Baseline demographic and clinical characteristics were balanced across the treatment groups (table 1). Across all groups, randomised patients (n=420) had a mean age of 63·3 (SD 8·3) years and a Parkinson's disease duration of 8·7 (4·7) years. Mean daily off-time while awake at baseline in the modified intention-to-treat population was 6·06 (2·23) h.

Mean daily off-time compared with the placebo group was significantly reduced for the combined tozadenant 120 mg twice-daily and 180 mg twice-daily group, the tozadenant 120 mg twice-daily group, and the tozadenant 180 mg twice-daily group, but not the tozadenant 60 mg

twice-daily group or the tozadenant 240 mg twice-daily group (table 2, figure 2). Off-time reduction was at least 1 h per day in 40 (55%) of 73 patients in the tozadenant 60 mg twice-daily group, 42 (65%) of 65 in the 120 mg twice-daily group, 46 (72%) of 64 in the 180 mg twice-daily group, and 39 (68%) of 57 in the 240 mg twice-daily group, compared with 37 (51%) of 73 in the placebo group. Results of sensitivity analyses of the primary efficacy outcome with the last observation carried forward and multiple imputation methods were consistent with the primary analysis (appendix).

Mean daily total on-time compared with placebo was significantly increased in the combined tozadenant 120 and 180 mg twice-daily group and in the 120 mg twice-daily group (table 2). We did not note any significant increase in on-time without troublesome dyskinesia compared with placebo in the tozadenant 120 mg twice-daily group.

Total UPDRS scores for parts I–III combined were significantly improved in all tozadenant groups compared with placebo (table 2). UPDRS part III scores were significantly improved compared with placebo in the combined tozadenant 120 mg twice-daily and 180 mg twice-daily group, the 120 mg twice-daily group, and the 180 mg twice-daily group. UPDRS parts I and II scores were not significantly different for any tozadenant group compared with placebo. CGI-S and CGI-I scores were significantly improved compared with placebo in all tozadenant groups, and PGI-I scores were significantly improved compared with placebo in the combined tozadenant 120 mg twice-daily and 180 mg twice-daily group, and the 120 mg twice-daily group. Results for the exploratory outcomes (table 2) and post-hoc analyses are discussed in the appendix. Reductions in mean daily levodopa dose and mean daily levodopa dose equivalents were small in the placebo and all tozadenant dose groups (appendix).

The proportion of patients with treatment-emergent adverse events and the numbers of events were similar among the placebo and lower (60 mg twice-daily and 120 mg twice-daily) tozadenant dose groups and tended to increase with increasing tozadenant dose (table 3). Higher proportions of patients in the tozadenant groups discontinued study treatment early because of a treatment-emergent adverse event (table 3). The most common treatment-emergent adverse events leading to discontinuation in the placebo group (n=84) and tozadenant groups combined (n=336), respectively, were dyskinesia (one [1%] patient *vs* six [2%] patients),

	Placebo (n=84)	Tozadenant 60 mg (n=85)	Tozadenant 120 mg (n=82)	Tozadenant 180 mg (n=85)	Tozadenant 240 mg (n=84)
Total treatment-emergent adverse events	151	192	201	299	236
Patients with at least one treatment-emergent adverse event	55 (65%)	61 (72%)	61 (74%)	67 (79%)	69 (82%)
Patients who reported no treatment-emergent adverse events	29 (35%)	24 (28%)	21 (26%)	18 (21%)	15 (18%)
Patients with at least one treatment-emergent adverse event related to study drug	27 (32%)	37 (44%)	45 (55%)	47 (55%)	53 (63%)
Patients who discontinued because of a treatment-emergent adverse event (excluding death)	3 (4%)	7 (8%)	10 (12%)	10 (12%)	17 (20%)
Patients with at least one severe treatment-emergent adverse event*	4 (5%)	5 (6%)	10 (12%)	7 (8%)	8 (10%)
Patients with at least one serious treatment-emergent adverse event†	3 (4%)	1 (1%)	3 (4%)	2 (2%)	4 (5%)
Deaths	0	1 (1%)	0	2 (2%)	3 (4%)
Treatment-emergent adverse events reported by at least 5% of patients in any treatment group					
Dyskinesia	7 (8%)	12 (14%)	13 (16%)	17 (20%)	17 (20%)
Nausea	3 (4%)	5 (6%)	9 (11%)	10 (12%)	5 (6%)
Dizziness	1 (1%)	4 (5%)	4 (5%)	11 (13%)	8 (10%)
Constipation	0	8 (9%)	9 (11%)	3 (4%)	5 (6%)
Worsening Parkinson's disease	9 (11%)	4 (5%)	6 (7%)	8 (9%)	4 (5%)
Insomnia	2 (2%)	2 (2%)	7 (9%)	7 (8%)	5 (6%)
Fall	4 (5%)	4 (5%)	3 (4%)	7 (8%)	3 (4%)
Flushing	2 (2%)	2 (2%)	3 (4%)	6 (7%)	5 (6%)
Headache	1 (1%)	4 (5%)	4 (5%)	5 (6%)	3 (4%)
Blood creatine phosphokinase increased	2 (2%)	4 (5%)	2 (2%)	5 (6%)	3 (4%)
Urinary tract infection	4 (5%)	4 (5%)	5 (6%)	4 (5%)	1 (1%)
Sudden onset of sleep	5 (6%)	3 (4%)	2 (2%)	3 (4%)	4 (5%)
Back pain	4 (5%)	5 (6%)	1 (1%)	3 (4%)	2 (2%)

The first row is a count of all events, whereas the remaining rows are patient counts. Treatment-emergent adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0; for each MedDRA Preferred Term, patients are included only once, even if they had more than one event in that system organ class or preferred term category. *Severe adverse events were defined as causing inability to undertake usual activities and requiring close monitoring or intervention. †Serious adverse events were defined as fatal, life-threatening, requiring admission or prolonging hospital stay, or causing substantial disability.

Table 3: **Summary of treatment-emergent adverse events (safety population)**

insomnia (0 patients *vs* five patients [1%]), worsening Parkinson's disease (one [1%] patient *vs* four [1%] patients), headache (0 patients *vs* four [1%] patients), upper-abdominal pain (0 patients *vs* four [1%] patients), and nausea (0 patients *vs* four [1%] patients).

Serious treatment-emergent adverse events occurred in between 1% and 5% of patients in each group (table 3). Each of the serious treatment-emergent adverse events was reported in one patient, with the exception of acute myocardial infarction (reported by one patient each in the placebo and the tozadenant 240 mg twice-daily groups), acute renal failure (reported by two patients in the tozadenant 240 mg twice-daily group), and sepsis (reported by one patient each in the tozadenant 60, 180, and 240 mg twice-daily groups).

Six patients died during the study, all of whom were receiving tozadenant (table 3). The causes of death were disparate: sepsis in two patients (one each in the 60 and 180 mg twice-daily groups); pulmonary embolism in one patient (180 mg twice-daily group); sudden death associated with Pickwickian syndrome (obesity hypoventilation syndrome) in one patient (240 mg twice-daily group); multiorgan failure (subsequent to head injury and intracranial haemorrhage) in one patient (240 mg twice-daily group); and pneumonia, mesenteric ischaemia, sepsis, and acute renal failure in one patient with bowel perforation (240 mg twice-daily group). Two of the deaths were regarded as possibly related to the study drug, two were unlikely to be related, and two not related to the drug. The deaths showed no consistent pattern related to the administration of tozadenant. Neither the independent data monitoring committee nor the independent panel of experts who reviewed the data at the end of the study identified a relation between treatment with tozadenant and serious adverse events or deaths. Additional safety results are provided in the appendix.

Discussion

In this phase 2b study, tozadenant at doses of 120 mg twice daily and 180 mg twice daily (assessed together and separately) significantly reduced off-time compared with placebo and was well tolerated. Compared with placebo, tozadenant 120 mg twice daily reduced mean daily off-time by 1·1 h and tozadenant 180 mg twice daily by 1·2 h. These values exceed the reported minimum clinically important difference,[15] and both CGI-I and PGI-I scores were significantly improved in these dose groups. Additionally, mean daily total on-time compared with placebo was significantly increased in the combined tozadenant 120 mg twice-daily and 180 mg twice-daily group and the 120 mg twice-daily group, and UPDRS part III (motor) scores were significantly improved in both dose groups (120 mg and 180 mg twice daily), combined and individually.

The lowest tozadenant dose tested, 60 mg twice daily, was not associated with a significant reduction in off-time, and the highest dose tested, 240 mg twice daily, was associated with an increase in discontinuations because of adverse events (17 [20%] of 84 patients). Thus, the results of this phase 2b, dose-finding study suggest that 120 mg twice daily and 180 mg twice daily could define the clinically useful dose range for tozadenant. Since the tozadenant 180 mg twice-daily group showed an increase in troublesome dyskinesia, this dose might be at the top of the useful range, although this finding is only preliminary.

Our results are similar to those for other A_{2A} antagonists reported in phase 2 studies. For example, compared with placebo, istradefylline 40 mg per day reduced off-time by 1·2 h (p=0·005)[3] and, in another study,[4] 20 mg per day reduced off-time by 0·64 h (p=0·026) and 60 mg per day reduced off-time by 0·70 h (p=0·024). In a phase 2 trial of preladenant,[5] 5 mg twice daily reduced off-time by 1·0 h (p=0·0486) and 10 mg twice daily reduced off-time by 1·2 h (p=0·019). However, preladenant did not significantly reduce off-time in two phase 3 trials,[6] and istradefylline did not significantly reduce off-time at doses of 10, 20, or 40 mg per day in another phase 3 trial.[8] In a separate phase 3 trial, istradefylline 20 mg per day reduced off-time by 0·70 h (p=0·03).[7] Overall, these findings suggest that other A_{2A} antagonists might be effective at reducing off-time in patients with Parkinson's disease who have motor fluctuations on levodopa, but methodological issues in large phase 3 trials might obscure a trial's ability to identify this effect.

Investigators of a Cochrane systematic review[16] of the efficacy and safety of adjuvant treatment to levodopa in patients with Parkinson's disease who have motor complications[16] reported that MAOB inhibitors reduce off-time by about 0·93 h per day and COMT inhibitors reduce off-time by about 0·83 h per day. Thus, our findings from this phase 2b study of tozadenant suggest that it might be as good as or better than MAOB inhibitors and COMT inhibitors at reducing off-time. However, these findings must be interpreted cautiously and phase 3 results should be awaited.

There are reasons to hope that tozadenant might show better efficacy than preladenant and istradefylline in phase 3 trials. Both preladenant and tozadenant have been dosed twice daily in Parkinson's disease studies. However, a comparison of pharmacokinetic data suggests that the serum half-life of tozadenant (about 16 h) is more appropriate for twice-daily dosing than that of preladenant (about 2 h).[17] This difference is relevant at the receptor level; based on preliminary data from a primate study using PET, tozadenant engages the A_{2A} receptor much more consistently than preladenant throughout a 24 h period (unpublished data). Additionally, although comparisons across clinical studies can be problematic, the robustness of the efficacy data in this study is generally equivalent or superior to that of phase 2 and 3 data presented for istradefylline regarding the primary and several secondary endpoints used in the present study.

We noted a dose-related increase in dyskinesia in the trial. Such an increase has also been noted with other

Panel: Research in context

Systematic review

We searched PubMed for reports of clinical trials published in English up to March 31, 2014, using the terms "adenosine A_{2A}", istradefylline", "preladenant", "tozadenant", "SYN115", "vipadenant", "Parkinson's", and "Parkinson". We also searched press releases issued within the past 3 years from Merck and Kyowa Hakko Kirin, the manufacturers of preladenant and istradefylline, respectively. Results from three studies of preladenant showed that it was generally well tolerated in healthy adults[22] and in patients with Parkinson's disease who have motor fluctuations;[5,23] in a phase 2, 12-week trial,[5] higher doses (5 or 10 mg twice daily), but not lower doses (1 or 2 mg twice daily), significantly reduced mean daily off-time compared with placebo. However, a press release issued by Merck[6] in May, 2013, announced that phase 3 trials did not provide evidence of efficacy for preladenant compared with placebo, and that further development was being discontinued. Investigators of phase 2 trials[2–4] of istradefylline (20–60 mg per day) noted significant reductions in off-time compared with placebo, and results from a phase 3 trial[7] to assess istradefylline at 20 mg per day also showed a significant reduction in off-time. However, investigators of another phase 3 trial[8] that assessed istradefylline at 10, 20, and 40 mg per day did not identify significant reductions in off-time, and in February, 2008, the US Food and Drug Administration issued a Not Approvable letter.[24] A subsequent trial[25] done in Japan had positive results and led to regulatory approval in that country, and in November, 2013, Kyowa Hakko Kirin announced the launch of a global phase 3 clinical trial of istradefylline.[26]

Interpretation

Adenosine A_{2A} receptor antagonists have consistently shown effectiveness at reducing off-time in phase 2 studies,[2–5,23] but have either been ineffective (preladenant) or yielded mixed results (istradefylline) in phase 3 studies.[7,8,25] Such results probably reflect the present difficulties of doing studies that include large numbers of patients with Parkinson's disease with motor fluctuations at many study sites. Our phase 2b study is the first major clinical trial of tozadenant, and the results are consistent with previous findings showing that adenosine A_{2A} antagonists reduce off-time in patients with Parkinson's disease receiving concurrent levodopa treatment. These results will be useful in the design and implementation of phase 3 studies of tozadenant.

A_{2A} antagonists, and it seems likely that these drugs, when added to levodopa, could increase dyskinesia.[18] However, results from a proof-of-concept study[19] in which levodopa intravenous infusions were used suggested that, with the addition of an A_{2A} antagonist and lowering of the levodopa dose, anti-Parkinson's disease benefit can be maintained and dyskinesia can be decreased. The introduction of an A_{2A} antagonist in levodopa-treated patients before motor complications develop might also reduce the risk of dyskinesia.[20] To our knowledge, these possibilities have not been assessed in patients with Parkinson's disease, but these approaches hold great interest.

The main limitation of our study is that the primary outcome, reduction in off-time, was dependent on the ability of participants to understand the Parkinson's disease states and accurately complete the diaries. No objective or observer assessment of off-time was used. However, reductions in off-time as assessed by diaries were supported by improvements in observer-rated UPDRS motor scores. Another limitation is that our results might not be easily generalisable to other trial and clinical settings. As with most phase 2 trials, the study was done mainly at expert centres with selected patients who met stringent entry criteria and were deemed capable of completing Parkinson's disease diaries.

In summary, our results suggest that tozadenant might be useful as an adjunct to levodopa in patients with Parkinson's disease who have motor fluctuations. At 120 mg twice daily or 180 mg twice daily, tozadenant was generally well tolerated and was effective at reducing off-time. Although these results are from a large, international cohort of patients, this trial was a phase 2 study, and studies of A_{2A} antagonists have not consistently yielded positive phase 3 results.[6–8,21] Results from this phase 2 study will be useful in the design and implementation of phase 3 studies of tozadenant (panel).

Contributors

RAH contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting and editing the report, and he approved the final version for submission. CWO and KDK contributed to study design and analysis and interpretation of data, and they critically reviewed and revised the report. AN, CR, UM, and SB contributed to study design, endpoint selection, study conduct, the search of the scientific literature, and analysis and interpretation of data, and they critically reviewed and revised the report. EP, AD-A, ML, and OK enrolled patients during the study and critically reviewed and revised the report. CK contributed to the analysis and interpretation of data and critically reviewed and revised the report.

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Declaration of interests

RAH has received honoraria or payments for consulting, advisory services, or speaking services over the past 12 months from AbbVie, Allergan, AstraZeneca, Biotie Therapies, Ceregene, Chelsea Therapeutics, Cleveland Clinic, Eli Lilly, GE Healthcare, Impax Laboratories, Neurocrine, Indus, Ipsen Biopharmaceuticals, Lundbeck, Merck/MSD, Noven Pharmaceuticals, Pfizer, Straken Pharmaceuticals, Targacept, Teva Pharmaceuticals Industries, Teva Neuroscience, Upsher-Smith Laboratories, UCB, UCB Pharma SA, University of Houston, US World Meds, Xenoport, and Zambon Company. He has also received royalties in the past 12 months from the University of South Florida. His institution has received research support over the past 12 months from Abbot Laboratories, Addex Therapeutics, Allergan, AstraZeneca, Biotie Therapies, Chelsea Therapeutics, Civitas, GE Healthcare, Impax Laboratories, Ipsen Biopharmaceuticals, Merck/MSD, Merz, the Michael J Fox Foundation for Parkinson's Research, the US National Institute of Neurological Disorders (NINDS) and Stroke, Parkinson Study Group, Schering-Plough, Teva Neuroscience, UCB, and Vita-Pharm. CWO has served as consultant for Abbvie, AstraZeneca, Biotie, Cangene, Ceregene, Celgene, Civitas, CHDI Foundation, Heptares, Lundbeck, Medivation, Melior, Neuroderm, Neurophage, nLife, Norvartis, Orion, Otsuka, Pharm2B, Serina, Synagile, Synosia, Teva, Upsher Smith, UCB, and US WorldMed. He has served on the board of the Michael J Fox Foundation and the National Space Board Research Institute. KDK has received research grant support from the US National Institutes of Health (NIH), the Michael J Fox Foundation, Medivation, and Neurosearch, and serves as consultant to the US Food and Drug Administration, the Veteran's Administration, the NIH (NINDS), Abbvie, Acorda, Amgen, Aptiv, Astellas Pharma, AstraZeneca, Auspex, Biogen Idec, Biotie, Biovail, Boehringer Ingelheim, Bristol Myers Squibb, Cangene, Celgene, CHDI, Civitas, Clintrex, Cynapsus, Endo, Impax, INC Research, Intec, Ipsen, Isis, Knopp, Lilly, Lundbeck, LZ Therapeutics, Medavante, Medivation, Melior Discovery, Merck, Merz, Neotope/Elan Pharmaceutical, Neuroderm, Novartis, Omeros, Orion, Otsuka, Pharma2b, Phytopharm, Roche, Siena Biotech, Sofinnova, Synosia, Synagile, Teva, UCB Pharma, Upsher-Smith, US WorldMeds, Vaccinex, Vectura, Voyager, Xenoport, and Xeris. He has acted as a legal consultant to Thompson Hine. AN, CR, UM, SB, and CK are employees and stockholders of Biotie Therapies. EP, AD-A, ML, and OK declare no competing interests. All authors listed as study investigators were reimbursed for budgeted expenses related to this study by their respective institutions, which had negotiated a budget with Biotie Therapies; the institutions (not the investigators) were paid directly. No author was paid to write this report.

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References

1 Hettinger BD, Lee A, Linden J, Rosin DL. Ultrastructural localization of adenosine A_{2A} receptors suggests multiple cellular sites for modulation of GABAergic neurons in rat striatum. *J Comp Neurol* 2001; **431:** 331–46.

2 Hauser RA, Hubble JP, Truong DD, Istradefylline US-001 Study Group. Randomized trial of the adenosine A_{2A} receptor antagonist istradefylline in advanced PD. *Neurology* 2003; **61:** 297–303.

3 LeWitt PA, Guttman M, Tetrud JW, et al. Adenosine A_{2A} receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Ann Neurol* 2008; **63:** 295–302.

4 Stacy M, Silver D, Mendis T, et al. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. *Neurology* 2008; **70:** 2233–40.

5 Hauser RA, Cantillon M, Pourcher E, et al. Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial. *Lancet Neurol* 2011; **10:** 221–29.

6 Merck. Merck provides update on phase III clinical program for preladenant, the company's investigational Parkinson's disease medicine. May 23, 2013. http://www.businesswire.com/news/home/20130523006358/en/Merck-Update-Phase-III-Clinical-Program-Preladenant (accessed Feb 26, 2014).

7 Hauser RA, Shulman LM, Trugman JM, et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. *Mov Disord* 2008; **23:** 2177–85.

8 Pourcher E, Fernandez HH, Stacy M, Mori A, Ballerini R, Chaikin P. Istradefylline for Parkinson's disease patients experiencing motor fluctuations: results of the KW-6002-US-018 study. *Parkinsonism Relat Disord* 2012; **18:** 178–84.

9 Black KJ, Koller JM, Campbell MC, Gusnard DA, Bandak SI. Quantification of indirect pathway inhibition by the adenosine A_{2a} antagonist SYN115 in Parkinson disease. *J Neurosci* 2010; **30:** 16284–92.

10 Hauser RA, Friedlander J, Zesiewicz TA, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. *Clin Neuropharmacol* 2000; **23:** 75–81.

11 Fahn S, Elton RL, Members of the UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease. New York: Macmillan Healthcare Information, 1987: 153–63.

12 Peto V, Jenkinson C, Fitzpatrick R. PDQ39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *J Neurol* 1998; **245** (suppl 1): S10–14.

13 Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio: Psychological Corporation, 1996.

14 Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psych* 1988; **56:** 893–97.

15 Hauser RA, Auinger P, Parkinson Study Group. Determination of minimal clinically important change in early and advanced Parkinson's disease. *Mov Disord* 2011; **26:** 813–18.

16 Stowe R, Ives N, Clarke CE, et al. Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson's disease patients with motor complications. *Cochrane Database Syst Rev* 2010; **7:** CD007166.

17 Brooks DJ, Warrington S, Tendolkar A, Cutler DL, Hunter J. Positron emission tomography (PET) study of preladenant in healthy male subjects. *Mov Disord* 2009; **24** (suppl 1): S257.

18 Morelli M, Blandini F, Simola N, Hauser RA. A_{2A} receptor antagonism and dyskinesia in Parkinson's disease. *Parkinsons Dis* 2012; **2012:** 489853.

19 Bara-Jimenez W, Sherzai A, Dimitrova T, et al. Adenosine A_{2A} receptor antagonist treatment of Parkinson's disease. *Neurology* 2003; **61:** 293–96.

20 Bibbiani F, Oh JD, Petzer JP, et al. A_{2A} antagonist prevents dopamine agonist-induced motor complications in animal models of Parkinson's disease. *Exp Neurol* 2003; **184:** 285–94.

21 Chen W, Wang H, Wei H, Gu S, Wei H. Istradefylline, an adenosine A_{2A} receptor antagonist, for patients with Parkinson's disease: a meta-analysis. *J Neurol Sci* 2013; **324:** 21–8.

22 Cutler DL, Tendolkar A, Grachev ID. Safety, tolerability and pharmacokinetics after single and multiple doses of preladenant (SCH420814) administered in healthy subjects. *J Clin Pharm Ther* 2012; **37:** 578–87.

23 Factor SA, Wolski K, Togasaki DM, et al. Long-term safety and efficacy of preladenant in subjects with fluctuating Parkinson's disease. *Mov Disord* 2013; **28:** 817–20.

24 PR Newswire Services. Kyowa Hakko receives not approvable letter from FDA for istradefylline (KW-6002). Feb 27, 2008. http://www.prnewswire.com/news-releases/kyowa-hakko-receives-not-approvable-letter-from-fda-for-istradefylline-kw-6002-57334117.html (accessed March 21, 2014).

25 Mizuno Y, Hasegawa K, Kondo T, Kuno S, Yamamoto M. Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: a randomized, controlled study. *Mov Disord* 2010; **25:** 1437–43.

26 Kyowa Hakko Kirin. Kyowa Hakko Kirin initiates a global phase 3 trial of istradefylline (KW-6002) for Parkinson's disease. Nov 21, 2013. http://www.kyowa-kirin.com/news_releases/2013/e20131121_01.html (accessed March 19, 2014).