

A Phase 2a study of KW-6356 in the Subjects with Parkinson's Disease

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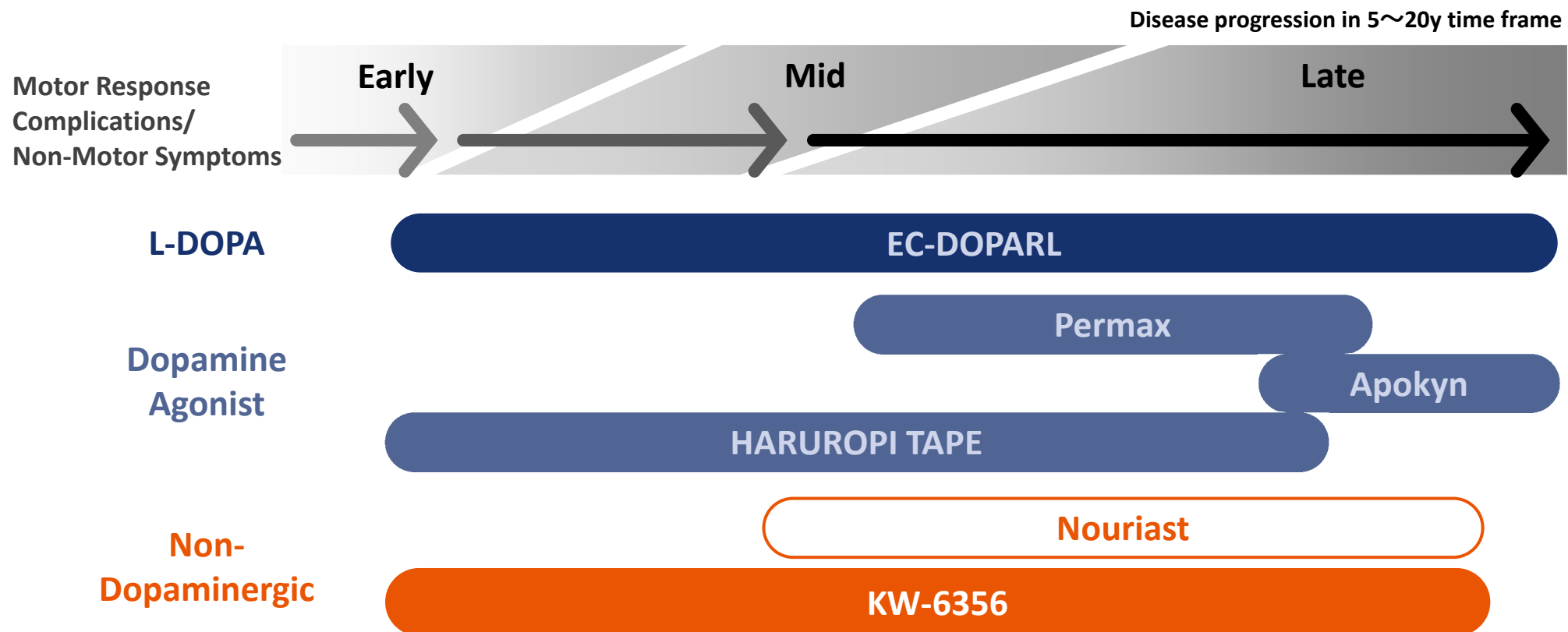
Background Information

- KW-6356 is a next generation of A_{2A} receptor antagonist. It was selected through Kyowa Kirin's drug discovery platform for Parkinson's disease (PD) therapy. This compound has many attractive and favorable profiles, leading expectation to bring much more clinical benefits through non-dopaminergic mode of action.
- KW-6356 showed good anti-parkinsonian activities in MPTP-treated common marmosets, either with or without adjunct L-DOPA treatment.
- In a Phase 1 study (6356-001), KW-6356 showed favorable safety and pharmacokinetics profiles in healthy Japanese subjects.
- A Phase 2a study (6356-002) with early PD patients as monotherapy has been completed with positive outcomes.
- We are conducting a dose finding study in PD patients under L-DOPA therapy (Phase 2b), and its future development plan will be also discussed.

Target Product Profile of KW-6356

KW-6356 is expected to bring new treatment options and clinical benefits

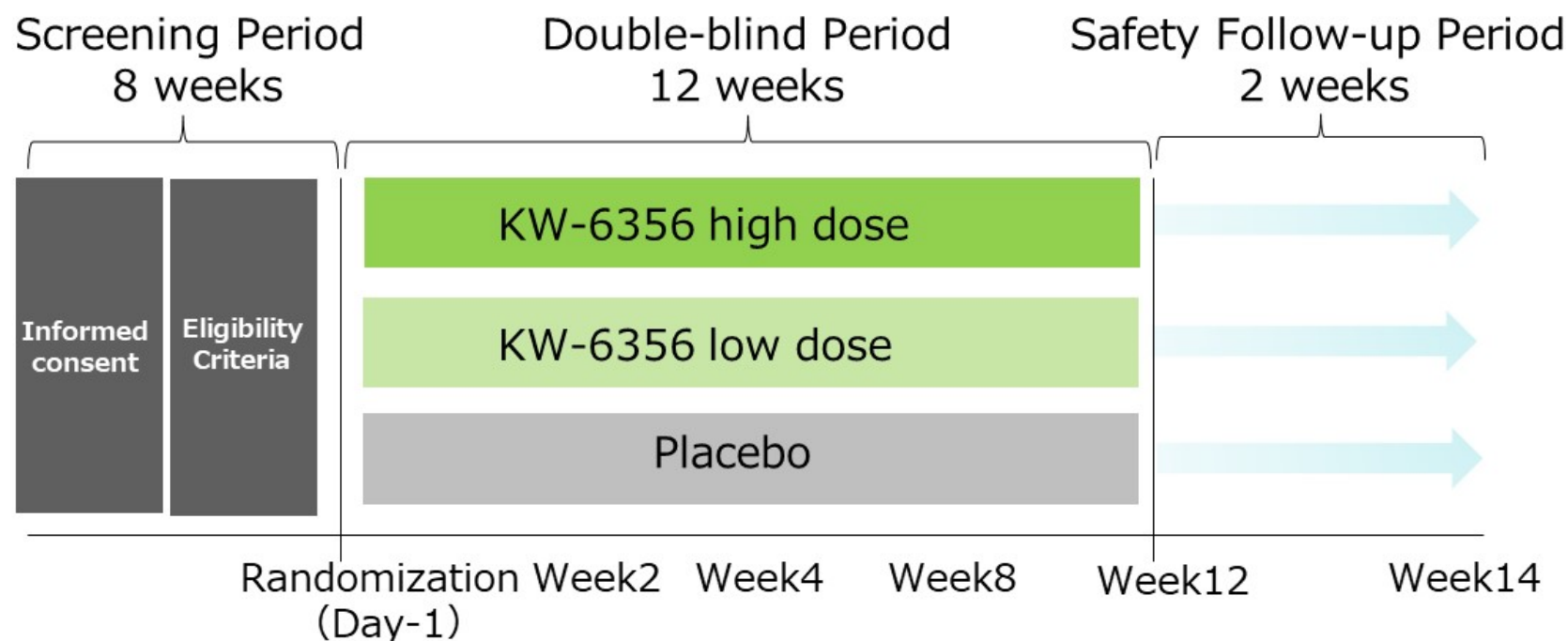
- to improve motor symptoms, and potentially non-motor symptoms and disease modification
- for broader target patients (from early to late stage as both monotherapy and adjunct therapy)
- with safer profile through non-dopaminergic mode of action



Phase 2a Study Design (6356-002)

NCT02939391

Study design	Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter study
Target	early Parkinson's disease patients
Treatment	KW-6356 Low dose, High dose or placebo for 12 weeks once a day, p.o. Planned 50 pts/arm, total 150 pts (Actual enrollment: 168 pts)
Primary endpoint	Change from baseline to Week 12 in the MDS-UPDRS part III score
Secondary endpoint	MDS-UPDRS part I ~ IV, CGI-I, PGI-I, PDQ-39



Subjects Inclusion/Exclusion Criteria

Key Inclusion Criteria

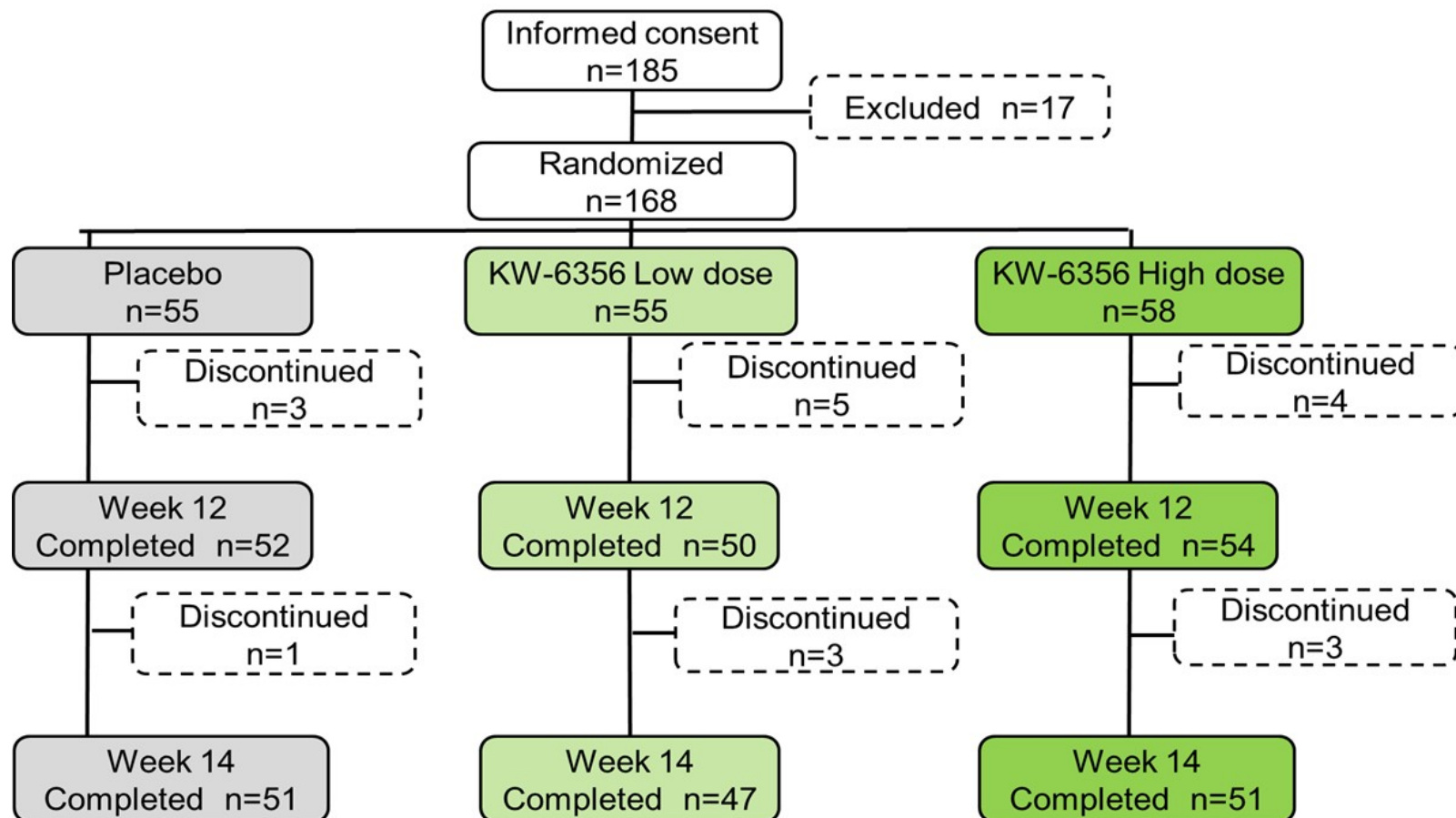
- Subject meets the UK Parkinson's Disease Society brain bank clinical diagnostic criteria
- PD stages 1 to 3 on the Modified Hoehn and Yahr Scale
- MDS-UPDRS part III score of ≥ 15

Key Exclusion Criteria

- Use of any CYP3A4/5-related drugs within 2 weeks prior to randomization (Day-1).
- Use of any of the specified anti-parkinsonian drugs and dopamine antagonists during the specified period.
- Treatment with levodopa/DCI at any time in the past for a period of 4 weeks or more.
- Neurosurgical operation for Parkinson's disease (stereotactic surgery, deep brain stimulation or gamma knife), or treatment by TMS.

Enrollment and Rates of Study Completion

- Of 185 subjects screened, 168 subjects were randomized; 55, 55, and 58 subjects were assigned to treatment with placebo, KW-6356 low dose, and KW-6356 high dose, respectively .
- Study completion rates were high (around 90%) across the treatment arms.



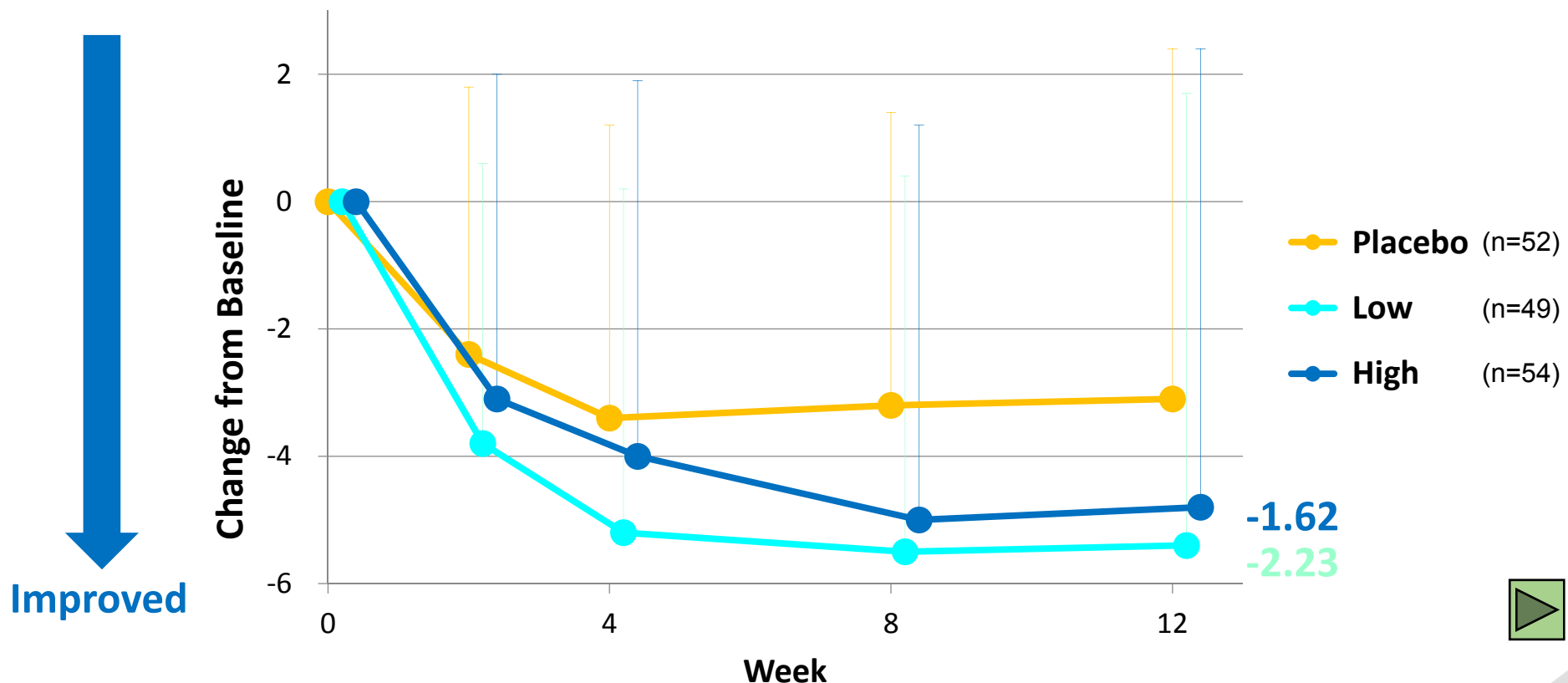
Baseline Characteristics

- The demographic and baseline characteristics of the subjects were generally well balanced among the three treatment groups.

	Placebo N = 55	KW-6356 low dose N = 55	KW-6356 high dose N = 58
Age, years; mean (SD)	66.6(8.0)	67.2(10.0)	65.9(9.2)
>=65 years, n (%)	40 (72.7)	38 (69.1)	40 (69.0)
Male gender, n (%)	34 (61.8)	29 (52.7)	26 (44.8)
Duration of PD, <=6, n (%)	46 (83.6)	47 (85.5)	46 (79.3)
Modified Hoehn and Yahr Scale; mean (SD)	2.17(0.46)	2.19(0.52)	2.11(0.51)
MDS-UPDRS Part I; mean (SD)	4.9(3.4)	5.6(3.9)	4.5(3.0)
MDS-UPDRS Part II; mean (SD)	6.6(4.4)	6.4(4.5)	5.5(4.7)
MDS-UPDRS Part III; mean (SD)	27.6(9.5)	29.7(9.7)	28.3(10.6)
PDQ-39 total score; mean (SD)	15.7(13.5)	19.0(18.7)	15.3(17.4)

Primary Outcomes: MDS-UPDRS part III

- The LS mean changes from baseline in MDS-UPDRS part III were -4.76 (95% CI, -6.55 to -2.96) for high dose, -5.37 (95% CI, -7.25 to -3.48) for low dose, and -3.14 (95% CI, -4.97 to -1.30) for placebo.
- Both of the KW-6356 groups showed a greater reduction in the primary outcome measure than placebo throughout 12-week study period.



Safety : KW-6356 was safe and well-tolerated

- Overall rate of TEAEs were similar across the study treatment groups.
- The most common TEAE was nasopharyngitis (7.3% for placebo, 7.3% for low dose, and 8.6% for high dose), none of which were considered to be related to the KW-6356.
- The incidences of drug-related TEAEs for placebo, KW-6356 low dose and KW-6356 high dose were 29.1%, 34.5%, and 27.6%, respectively.
- A total of three serious adverse events occurred in three subjects receiving KW-6356 low dose (three events; rhabdomyolysis ,cerebral hemorrhage and pneumonia, each occurred once). Of these events, causality of rhabdomyolysis and cerebral hemorrhage to KW-6356 was considered to be unknown, and pneumonia was judged not to be drug-related.
- No clinically meaningful changes in vital signs, body weight, laboratory results, or ECGs.

	Placebo N=55		Low dose N=55		High dose N=58	
Event	n	(%)	n	(%)	n	(%)
Subjects with any TEAE	24	(43.6%)	26	(47.3%)	29	(50.0%)
Nasopharyngitis	4	(7.3%)	4	(7.3%)	5	(8.6%)
Constipation	1	(1.8%)	4	(7.3%)	6	(10.3%)
Nausea	1	(1.8%)	0	(0.0%)	3	(5.2%)

TEAEs reported by 5% or more of subjects by preferred term — Safety Analysis Set

Summary of Phase 2a study

- KW-6356 was safe and well-tolerated during 12-week treatment.
- The clinical efficacy* of KW-6356 was confirmed in early Parkinson's disease as monotherapy.
- The results of this study suggest that KW-6356 improves motor symptoms in early Parkinson's disease.

*Patients under KW-6356 (low or high dose) treatment consistently showed the lower scores of MDS-UPDRS II, III, and II+III than placebo throughout the study period (12 weeks). Means for "Δ MDS-UPDRS II" and "Δ MDS-UPDRS II+III" of KW-6356 (low dose) and their 95% CI were - 1.32 (-2.57, -0.07) and -3.53 (-6.64, -0.43), respectively.

Future Direction

- Phase 2b study to evaluate efficacy and safety of KW-6356 as adjunctive therapy with L-DOPA is ongoing, in parallel with clinical pharmacology studies required for Phase 3 program.
- Options for global development are under evaluation, depending on outcomes from the ongoing studies.

NCT03703570

Objectives	To evaluate the efficacy of KW-6356 and confirm clinically recommended dosage for Parkinson's disease patients (with/without wearing off) being treated with levodopa by comparing the change in MDS-UPDRS Part III score to the placebo group.
# of patients	Total 486 pts (162 pts/arm)
Primary endpoint	Change from baseline in the MDS-UPDRS part III score
Key Secondary endpoint	Change from baseline in the total hours of awake time per day spent in the OFF state

**Screening
Period**
up to 8 weeks

Treatment Period 26 weeks

placebo,
KW-6356 low dose,
or KW-6356 high dose

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