

RESEARCH MONOGRAPH . COMPOUND PROFILE

KW-6356

A second-generation, non-xanthine adenosine A2A receptor antagonist and inverse agonist developed by Kyowa Kirin as a successor to istradefylline for the treatment of Parkinson's disease, distinguished by insurmountable antagonism, inverse agonist activity, and approximately 100-fold greater receptor affinity than the first-generation A2A antagonist class.

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ABSTRACT

KW-6356 (sipagladenant; CAS 858979-50-7) is a selective, non-xanthine adenosine A_{2A} receptor antagonist and inverse agonist developed by Kyowa Kirin Co., Ltd. (formerly Kyowa Hakko Kirin) as a next-generation successor to istradefylline (NOURIANZ/NOURIAST) for the treatment of motor and non-motor symptoms of Parkinson's disease. The compound exhibits approximately 100-fold greater binding affinity for the human adenosine A_{2A} receptor than istradefylline (pK_i 9.93 versus approximately 7.9), with a K_d of 0.13 nM and a K_i of 0.12 nM at the human A_{2A} receptor, and demonstrates greater than 100-fold selectivity over the A₁, A_{2B}, and A₃ adenosine receptor subtypes [1]. In contrast to istradefylline, which acts as a surmountable antagonist, KW-6356 exhibits two pharmacologically distinct properties: insurmountable antagonism (the capacity to suppress receptor signaling in a manner that cannot be fully overcome by increasing agonist concentration) and inverse agonism (the capacity to reduce constitutive, agonist-independent receptor activity below basal levels). X-ray crystallography of the KW-6356-bound human A_{2A} receptor at 2.30 angstrom resolution (PDB: 8GNE) has revealed that interactions with His250 (position 6.52) and Trp246 (position 6.48) are essential for the inverse agonist activity, while deep orthosteric pocket contacts and stabilization of the extracellular loop conformation contribute to the insurmountable antagonism [1].

The clinical development program evaluated KW-6356 in two pivotal Phase 2 studies in Japanese Parkinson's disease populations. A Phase 2a randomized, double-blind, placebo-

controlled monotherapy trial in 168 patients with early, untreated Parkinson's disease demonstrated that once-daily oral KW-6356 at 3 mg and 6 mg produced improvements in MDS-UPDRS Part III motor scores (least-squares mean changes from baseline to week 12 of -5.37 and -4.76, respectively, versus -3.14 for placebo) [2]. A subsequent Phase 2b randomized, double-blind, placebo-controlled adjunct-to-levodopa trial in 503 patients with levodopa-treated Parkinson's disease demonstrated statistically significant improvements in MDS-UPDRS Part III motor scores at both 3 mg ($p = 0.006$ versus placebo) and 6 mg ($p = 0.049$ versus placebo), with additional reductions in mean daily OFF time in the key secondary endpoint and improvements on the PD Sleep Scale-2 in post-hoc analysis [3, 4]. Preclinical pharmacology in MPTP-treated common marmosets confirmed dose-dependent reversal of motor disability at oral doses up to 1 mg/kg, with anti-parkinsonian activity significantly greater than that of istradefylline and a low risk of inducing dyskinesia [5, 6].

Pharmacokinetics in healthy volunteers demonstrated linear exposure after single oral doses of 1 to 60 mg, with a mean terminal elimination half-life of 18.4 to 43.1 hours (mean approximately 22.9 hours), a time to peak plasma concentration of 0.75 to 3 hours, and an active metabolite (M6) with comparable A2A antagonist and inverse agonist potency and an elimination half-life of approximately 4.34 hours [7, 8]. Population pharmacokinetic modeling identified food status, baseline serum albumin, and baseline body weight as covariates, but none had clinically meaningful impact on KW-6356 or M6 exposure [8]. The compound was well tolerated in Phase 1 studies at single doses up to 60 mg and multiple doses up to 24 mg once daily for 14 days, with no clinically meaningful changes in vital signs, body weight, laboratory parameters, or electrocardiograms [7]. The most

common adverse events in the Phase 2a monotherapy trial were constipation (7.3 percent at 3 mg, 6.9 percent at 6 mg) and nasopharyngitis (7.3 percent at 3 mg, 8.6 percent at 6 mg) [2].

Despite positive proof-of-concept results across both monotherapy and adjunct-to-levodopa settings, Kyowa Kirin announced discontinuation of the KW-6356 development program in July 2022, citing evaluation of the global regulatory landscape, development hurdles, and timelines for potential market entry rather than efficacy or safety concerns [9]. The discontinuation followed Lundbeck's earlier decision to return ex-Asia development rights to Kyowa Kirin. No Phase 3 trials were initiated. This monograph documents the chemistry, structural pharmacology, receptor binding and selectivity profile, preclinical and clinical evidence base, pharmacokinetics, safety signal, and a comparative assessment of KW-6356 against five adenosine A2A receptor antagonists on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Sipagladenant.

Development code: KW-6356. The development code is the canonical identifier throughout the pharmacology and clinical literature and the principal designation used in all published clinical trial reports [2, 3, 4, 7, 8].

Chemical Abstracts Service registry number: 858979-50-7.

International Union of Pure and Applied Chemistry name: N-(4-(furan-2-yl)-5-(tetrahydro-2H-pyran-4-carbonyl)thiazol-2-yl)-6-methylnicotinamide.

DrugBank identifier: DB17080.

Protein Data Bank entry: 8GNE (crystal structure of the human adenosine A2A receptor in complex with KW-6356, deposited August 23, 2022, released March 22, 2023) [1].

1.2 Structural class and chemistry

KW-6356 is a non-xanthine, heterocyclic small molecule distinguished from istradefylline and other first-generation adenosine A2A antagonists by the absence of the xanthine (purine-dione) scaffold. The compound comprises three linked heterocyclic systems: a central 2-aminothiazole ring bearing a furan substituent at position 4, a tetrahydropyran-4-carbonyl group at position 5, and a 6-methylnicotinamide (6-methyl-3-pyridinecarboxamide) unit linked through an amide bond to the 2-amino nitrogen of the thiazole.

Molecular formula: C₂₀H₁₉N₃O₄S.

Molecular weight: 397.45 g/mol.

Physical properties: The compound is supplied as a solid for research applications. Solubility data from commercial suppliers indicate dissolution in dimethyl sulfoxide at standard research concentrations. Detailed melting point, partition co-

efficient, and crystallographic habit data are held by Kyowa Kirin and have not been fully disclosed in the public literature.

Stereochemistry: The compound does not contain classical asymmetric carbon stereocenters. The tetrahydropyran ring adopts a chair conformation; the reported crystal structure (PDB: 8GNE) at 2.30 angstrom resolution defines the three-dimensional binding pose within the A2A receptor orthosteric pocket [1].

1.3 Synthesis

The synthetic route to KW-6356 has not been disclosed in full in the public literature. The structural architecture (thiazole core, furanyl substituent, tetrahydropyranyl ketone, nicotinamide) is consistent with standard heterocyclic synthesis approaches: Hantzsch thiazole synthesis from an appropriately functionalized alpha-haloketone and a thiourea derivative, followed by acylation with activated 6-methylnicotinic acid. The furanyl and tetrahydropyranyl subunits are commercially available or readily prepared from commodity starting materials. Detailed process chemistry, yield optimization, and polymorph control remain proprietary to Kyowa Kirin. Research-grade material is available from multiple chemical suppliers (MedChemExpress, MedKoo, GlpBio, Probechem, and others) at stated purities of greater than 98 percent by HPLC.

2. Abstract

KW-6356 (sipagladenant) is a selective, non-xanthine adenosine A2A receptor antagonist and inverse agonist developed by Kyowa Kirin as a second-generation successor to istradefylline for the treatment of Parkinson's disease [1, 2, 3]. The compound binds the human A2A receptor with a K_i of 0.12 nM (pK_i 9.93), approximately 100-fold higher affinity than istradefylline, and demonstrates insurmountable antagonism and inverse agonist activity at the molecular level, properties that distinguish it from all previously developed A2A antagonists [1]. Crystallographic analysis of the KW-6356-bound A2A receptor (PDB: 8GNE) has provided a structural basis for these pharmacological properties: deep orthosteric pocket interactions and stabilization of the extracellular loop conformation underlie the insurmountable antagonism, while contacts with His250 (6.52) and Trp246 (6.48) are essential for inverse agonism [1].

The clinical evidence base comprises a Phase 2a monotherapy trial in 168 early, untreated Parkinson's disease patients showing improvements in MDS-UPDRS Part III motor scores at 3 mg and 6 mg daily over 12 weeks [2], and a Phase 2b adjunct-to-levodopa trial in 503 patients demonstrating statistically significant motor improvements and reductions in daily OFF time over 24 weeks [3, 4]. Preclinical pharmacology in MPTP-treated common marmosets demonstrated dose-dependent anti-parkinsonian activity exceeding that of istradefylline, with a notably low dyskinesia risk [5, 6]. Pharmacokinetics are characterized by a long elimination half-life (mean approximately 22.9 hours), linear exposure across the studied dose range, and an active metabolite (M6) with preserved A2A antagonist and inverse agonist potency [7, 8].

The compound was well tolerated across all completed clinical studies, with constipation and nasopharyngitis as the most frequently reported adverse events and no clinically meaningful changes in vital signs, electrocardiograms, or laboratory parameters [2, 7]. Despite these favorable efficacy and safety signals, Kyowa Kirin discontinued clinical development in July 2022, citing regulatory landscape considerations and development timelines rather than efficacy or safety failures [9]. The compound has not entered Phase 3 clinical trials and is classified as an abandoned

experimental drug. Research-grade KW-6356 remains available from commercial chemical suppliers and serves as a reference tool for A2A receptor pharmacology research.

3. Discovery and Development History

3.1 Origin and medicinal chemistry rationale

KW-6356 was developed at Kyowa Hakko Kirin Co., Ltd. (now Kyowa Kirin Co., Ltd.) as part of a second-generation medicinal chemistry program targeting the adenosine A2A receptor for Parkinson's disease. The program sought to address limitations of istradefylline (KW-6002), the first commercially approved A2A antagonist, which exhibits moderate A2A affinity (pK_i approximately 7.9), surmountable antagonism, and xanthine-based chemistry with associated structural constraints [1, 10]. The design objective was a non-xanthine scaffold with substantially higher receptor affinity, slower dissociation kinetics, and the pharmacological properties of insurmountable antagonism and inverse agonism, which were hypothesized to produce more sustained and complete suppression of A2A receptor signaling in the basal ganglia striatopallidal pathway.

3.2 Preclinical development

KW-6356 advanced through standard preclinical safety and efficacy evaluation. The *in vitro* pharmacological profile, published by Ohno et al. (2023) in *Molecular Pharmacology*, characterized binding affinity (pK_i 9.93 at the human A2A receptor), dissociation kinetics (k_{off} 0.016 per minute, substantially slower than istradefylline), selectivity (greater than 100-fold over A1, A2B, and A3 adenosine receptor subtypes), and the mechanistic demonstration of insurmountable antagonism and inverse agonism through functional and structural studies [1]. The crystal structure of KW-6356 bound to the thermostabilized human A2A receptor was solved at 2.30 angstrom resolution and deposited in the Protein Data Bank (PDB: 8GNE) in August 2022 [1].

Preclinical efficacy was demonstrated in MPTP-treated common marmosets, a primate model of Parkinson's disease with high translational relevance. KW-6356 administered orally as monotherapy reversed motor disability in a dose-dependent manner up to 1 mg/kg, producing anti-parkinsonian activity significantly greater than istradefylline at comparable doses [5]. A separate study evaluated KW-6356 as an adjunct to levodopa in MPTP-treated marmosets primed for dyskinesia and

found that KW-6356 enhanced the anti-parkinsonian activity of levodopa with a low risk of inducing dyskinesia, contrasting with the dyskinesia signal observed with some dopaminergic adjuncts [6].

3.3 Clinical development timeline

2016-2017: Phase 1 single ascending dose and multiple ascending dose studies in healthy Japanese and Caucasian volunteers (Studies 6356-001 and 6356-004; NCT03830528) established safety, tolerability, and pharmacokinetics at doses up to 60 mg single and 24 mg daily for 14 days [7].

2017-2018: Early Phase 2 proof-of-concept data were presented at the International Association of Parkinsonism and Related Disorders (IAPRD) meeting in August 2018, with Kyowa Hakko Kirin reporting positive signals in early Parkinson's disease [11].

2018-2020: Phase 2a randomized controlled trial of KW-6356 monotherapy (3 mg and 6 mg once daily for 12 weeks) in 168 Japanese patients with early, untreated Parkinson's disease. Results published by Maeda et al. (2023) in Parkinsonism and Related Disorders [2].

2018-2020: Phase 2b randomized controlled trial of KW-6356 as adjunct to levodopa (3 mg and 6 mg once daily for 24 weeks) in 503 Japanese Parkinson's disease patients. Positive results announced by Kyowa Kirin in October 2020 and subsequently presented at the International Congress of Parkinson's Disease and Movement Disorders [3, 4].

2019-2020: Lundbeck, which held development and commercialization rights for KW-6356 outside Asia, returned these rights to Kyowa Kirin, reportedly because of strategic portfolio decisions. Kyowa Kirin continued independent development.

July 2022: Kyowa Kirin announced discontinuation of the KW-6356 development program, citing the global regulatory landscape, development hurdles, and timelines for potential market entry [9]. No Phase 3 trials were initiated. The discontinuation ended Kyowa Kirin's clinical-stage research in the A2A receptor antagonist class.

3.4 Current status

KW-6356 is classified as an abandoned experimental drug. It has no assigned ATC code and no regulatory approval in any jurisdiction. Research-grade material remains commercially available for in vitro and in vivo pharmacology studies. The compound's scientific contributions (demonstration of A2A inverse agonism and insurmountable antagonism, high-resolution crystal structure, preclinical and clinical proof of concept) persist as reference data for the adenosine receptor pharmacology field.

4. Mechanism of Action

KW-6356 acts through selective, high-affinity binding to the adenosine A2A receptor, a G-protein-coupled receptor of the Gs-coupled family that is highly concentrated in the basal ganglia (striatum, globus pallidus, nucleus accumbens) and co-localized with dopamine D2 receptors on striatopallidal medium spiny neurons of the indirect pathway [1, 10]. The compound produces two pharmacologically distinct effects: antagonism of adenosine-stimulated A2A receptor activation (blocking the inhibitory influence of endogenous adenosine on D2 receptor-mediated signaling) and reduction of constitutive, agonist-independent A2A receptor activity below basal levels (inverse agonism).

4.1 Adenosine A2A receptor antagonism

The adenosine A2A receptor belongs to the P1 purinergic receptor family and signals predominantly through Gs-protein-mediated activation of adenylyl cyclase, increasing intracellular cyclic adenosine monophosphate (cAMP) and activating protein kinase A. In the striatopallidal pathway, A2A receptor activation by endogenous adenosine (released from astrocytes, neurons, and as a byproduct of synaptic ATP metabolism) opposes D2 receptor signaling on the same medium spiny neurons. The functional consequence is that A2A activation promotes the activity of the indirect (inhibitory) pathway, increasing thalamic inhibition and reducing motor output. In Parkinson's disease, dopamine depletion removes the D2-mediated brake on the indirect pathway, while A2A-mediated drive persists, resulting in excessive indirect pathway activity that contributes to bradykinesia, rigidity, and other motor symptoms [10, 12].

KW-6356 binds the A2A receptor orthosteric pocket with a K_i of 0.12 nM (pK_i 9.93), approximately 100-fold higher affinity than istradefylline [1]. The antagonism is insurmountable: increasing concentrations of the endogenous agonist adenosine (or the synthetic agonist CGS-21680) cannot fully restore receptor activation in the presence of KW-6356. The structural basis for this property, as revealed by the 2.30 angstrom crystal structure (PDB: 8GNE), involves binding contacts deep within the orthosteric pocket and stabilization of the extracellular loop 2 (ECL2) conforma-

tion, which occludes agonist access even at saturating agonist concentrations [1]. The slow dissociation kinetics (k_{off} 0.016 per minute) further contribute to the sustained receptor blockade.

4.2 Inverse agonism

In addition to blocking agonist-stimulated signaling, KW-6356 reduces the constitutive (agonist-independent) activity of the A2A receptor, a property termed inverse agonism [1]. Many G-protein-coupled receptors, including the A2A receptor, adopt active conformations at some basal frequency in the absence of agonist, producing a level of constitutive signaling. Classical (neutral) antagonists block agonist binding without affecting this basal activity; inverse agonists shift the receptor conformational equilibrium toward the inactive state, reducing signaling below the basal level. Crystallographic analysis demonstrated that interactions with His250 (Ballesteros-Weinstein position 6.52) and Trp246 (position 6.48, the "toggle switch" residue conserved across class A G-protein-coupled receptors) are essential for the inverse agonist mechanism [1]. Istradefylline does not form these interactions and correspondingly lacks inverse agonist activity.

The therapeutic significance of inverse agonism in Parkinson's disease is a subject of ongoing investigation. Constitutive A2A receptor activity on striatopallidal neurons may contribute to indirect pathway overactivity independently of adenosine tone, particularly in disease states where adenosine metabolism or extracellular adenosine concentration may be altered. If constitutive activity is pathologically relevant, inverse agonism would provide a pharmacological advantage over neutral antagonism by more completely suppressing A2A-mediated indirect pathway drive.

4.3 Receptor selectivity

KW-6356 demonstrates greater than 100-fold selectivity for the A2A receptor over the other adenosine receptor subtypes. Species-specific pK_i values across mouse, rat, dog, marmoset, and human A2A receptors are 9.49, 10.0, 9.55, 9.95, and 9.93, respectively, indicating excellent cross-species potency [1]. At 10 micromolar concentration, the compound showed weak inhibition (less than 30 percent) against a broad panel of receptors, transporters, and ion channels, with the exception of the dopamine D5 receptor (50.1 percent inhibition at 10 micromolar), a concentration approximately 80,000-fold above the A2A K_i and therefore not clinically relevant at

therapeutic exposures [1]. Dopamine-metabolizing enzymes (monoamine oxidase A, monoamine oxidase B, catechol-O-methyltransferase) showed negligible inhibition.

4.4 Downstream consequences in the basal ganglia

By blocking A2A receptor signaling on striatopallidal medium spiny neurons, KW-6356 disinhibits D2 receptor-mediated suppression of the indirect pathway, reducing excessive thalamic inhibition and restoring motor output toward normal levels. This mechanism does not directly supply dopamine and therefore operates through a complementary, non-dopaminergic pathway. The clinical consequence is improvement in motor symptoms (bradykinesia, rigidity) in both monotherapy (early Parkinson's disease, where residual dopaminergic function is present) and adjunct-to-levodopa (advanced Parkinson's disease, where exogenous dopamine supplementation is the primary treatment) settings [2, 3]. The non-dopaminergic mechanism also provides a theoretical basis for reduced dyskinesia risk relative to dopamine agonists and higher doses of levodopa, a prediction supported by the MPTP marmoset data [5, 6].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

KW-6356 is administered orally and is absorbed from the gastrointestinal tract with a time to peak plasma concentration (T_{max}) of 0.75 to 3 hours across the studied dose range (1 to 60 mg single dose) [7]. Pharmacokinetic exposure (C_{max} and AUC) increases linearly with dose across the 1 to 60 mg single-dose range, with no evidence of saturable absorption or nonlinear disposition [7]. Food status was identified as a covariate affecting the first-order absorption rate constant in population pharmacokinetic modeling, but did not have a clinically meaningful impact on overall exposure [8].

5.2 Distribution

Population pharmacokinetic analysis described the disposition of KW-6356 using a one-compartment model with first-order absorption [8]. Baseline body weight was identified as a covariate on the apparent volume of distribution, consistent with the expected relationship between body size and drug distribution. Detailed plasma protein binding data and volume of distribution estimates have not been fully disclosed in the public literature. The compound crosses the blood-brain barrier, as evidenced by central nervous system pharmacological effects in both preclinical models and clinical trials [2, 3, 5, 6].

5.3 Metabolism

KW-6356 is metabolized to an active metabolite designated M6 [8]. The M6 metabolite exhibits comparable A2A antagonist and inverse agonist potency to the parent compound and therefore contributes to the overall pharmacological effect. The metabolic pathway involves cytochrome P450 enzymes, with CYP3A4/5 implicated based on the conduct of a dedicated drug interaction study with a CYP3A4/5 inhibitor or inducer [8]. The elimination half-life of M6 is approximately 4.34 hours, substantially shorter than the parent compound [8].

5.4 Elimination

The mean terminal elimination half-life of KW-6356 ranges from 18.4 to 43.1 hours following single oral doses of 1 to 60 mg, with a mean of approximately 22.9 hours [7]. This prolonged half-life supports once-daily oral dosing and is consistent with the sustained receptor blockade predicted by the slow dissociation kinetics (k_{off} 0.016 per minute) observed in vitro [1]. Detailed renal and hepatic elimination pathway data have not been fully disclosed.

5.5 Special populations

Population pharmacokinetic analysis pooled data from healthy volunteers and Parkinson's disease patients and identified baseline serum albumin as a covariate on apparent clearance and baseline body weight as a covariate on apparent clearance of M6 [8]. No covariate had a clinically meaningful impact on exposure, suggesting that dose adjustment based on demographic characteristics is unlikely to be necessary [8]. No meaningful differences in pharmacokinetics were observed between Japanese and Caucasian healthy volunteers in the Phase 1 program [7].

5.6 Routes of administration

The sole route of administration evaluated in clinical trials was oral. The compound was administered as tablets or capsules (formulation details not fully disclosed) at once-daily doses of 3 mg or 6 mg in Phase 2 trials. No intravenous, subcutaneous, or other parenteral formulations have been described.

6. Clinical Evidence Base

6.1 Phase 1 healthy volunteer studies

Two Phase 1 studies established the safety, tolerability, and pharmacokinetics of KW-6356. Study 6356-001 was a randomized, double-blind, placebo-controlled single ascending dose study in healthy Japanese subjects at doses of 1, 3, and 10 mg. Study 6356-004 (NCT03830528) was a randomized, double-blind, placebo-controlled single ascending dose study (21, 42, and 60 mg) plus an open-label food-effect arm in healthy Japanese and Caucasian volunteers, followed by a multiple ascending dose phase (6 mg and 24 mg once daily for 14 days). The compound was well tolerated at all doses, with no dose-limiting toxicity, no clinically meaningful changes in vital signs, body weight, laboratory parameters, or electrocardiograms, and no meaningful differences between Japanese and Caucasian subjects [7].

6.2 Phase 2a monotherapy in early Parkinson's disease

A multicenter, randomized, double-blind, placebo-controlled trial (published by Maeda et al., *Parkinsonism and Related Disorders*, 2023) evaluated once-daily oral KW-6356 as monotherapy in 168 Japanese patients with early, untreated Parkinson's disease [2]. Patients were randomized to three arms: KW-6356 3 mg/day (n = 55), KW-6356 6 mg/day (n = 58), or placebo (n = 55). Treatment duration was 12 weeks. Completion rates exceeded 90 percent across all groups.

Primary endpoint: The least-squares mean change from baseline to week 12 in MDS-UPDRS Part III (motor examination) total score was -5.37 (95 percent CI: -7.25 to -3.48) for the 3 mg group, -4.76 (95 percent CI: -6.55 to -2.96) for the 6 mg group, and -3.14 (95 percent CI: -4.97 to -1.30) for placebo. Both KW-6356 groups showed numerically greater improvement than placebo at all assessed timepoints.

Secondary endpoints: Improvements in MDS-UPDRS Part II (motor aspects of experiences of daily living), combined Parts II and III, and total MDS-UPDRS scores favored KW-6356 over placebo.

Safety: Treatment was well tolerated. The most common drug-related treatment-emergent adverse events in the 3 mg group were constipation (7.3 percent) and nasopharyngitis (7.3 percent). In the 6 mg group, the most common events were constipation (6.9 percent), nausea (3.4 percent), somnolence (3.4 percent), and insomnia (3.4 percent). Drug-related adverse event rates were 34.5 percent (3 mg), 27.6 percent (6 mg), and 29.1 percent (placebo). Most adverse events were mild or moderate and did not lead to treatment discontinuation [2].

6.3 Phase 2b adjunct to levodopa in Parkinson's disease

A multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily oral KW-6356 as adjunct therapy to levodopa in 503 Japanese patients with Parkinson's disease experiencing motor fluctuations [3, 4]. Patients were randomized to three arms: placebo (n = 168), KW-6356 3 mg (n = 168), or KW-6356 6 mg (n = 167). Treatment duration was 24 weeks.

Primary endpoint: Change from baseline in MDS-UPDRS Part III total score. KW-6356 demonstrated statistically significant improvement over placebo at both doses: 3 mg (p = 0.006) and 6 mg (p = 0.049). Least-squares mean changes at week 26 were reported as -7.8 (3 mg) and -7.0 (6 mg) compared with -5.2 (placebo) in conference presentations [4].

Key secondary endpoint: KW-6356 also decreased mean daily OFF time compared with placebo, though detailed numerical values from the full publication have not been publicly disclosed at the time of monograph preparation [3, 4].

Post-hoc analysis: The PD Sleep Scale-2 total score improved significantly in the 6 mg group compared with placebo in patients with baseline sleep problems (p = 0.013) and in the overall population (p = 0.018), suggesting potential non-motor symptom benefits [4].

Safety: KW-6356 was well tolerated, with no major safety issues observed in any treatment group. No clinically meaningful changes in vital signs, body weight, laboratory results, or electrocardiograms were reported [3, 4].

6.4 Non-motor symptom exploratory data

The sleep-related findings from the Phase 2b post-hoc analysis represent the only published evidence for non-motor symptom effects of KW-6356 in clinical populations [4]. Adenosine A2A receptors are expressed in brain regions involved in sleep-wake regulation (including the nucleus accumbens and ventral striatum), and A2A receptor blockade has been associated with wake-promoting effects in preclinical studies. The observed improvement on the PD Sleep Scale-2 is consistent with this mechanism, though the post-hoc nature of the analysis and the modest sample size limit the strength of the inference.

7. Reported Research Dose Ranges

7.1 Clinical doses

Phase 1 (healthy volunteers): Single doses of 1 to 60 mg; multiple doses of 6 mg and 24 mg once daily for 14 days [7].

Phase 2a (monotherapy, early Parkinson's disease): 3 mg and 6 mg once daily for 12 weeks [2].

Phase 2b (adjunct to levodopa): 3 mg and 6 mg once daily for 24 weeks [3, 4].

7.2 Preclinical doses

MPTP marmoset monotherapy: Oral doses up to 1 mg/kg, with dose-dependent anti-parkinsonian activity [5].

MPTP marmoset adjunct to levodopa: Doses evaluated in combination with levodopa in dyskinesia-primed marmosets [6].

7.3 Research concentrations

The Chemical Probes Portal recommends cellular concentrations of up to 100 nM for in vitro research applications targeting the A2A receptor. Given the K_i of 0.12 nM, concentrations in the range of 1 to 100 nM are expected to produce near-complete A2A receptor occupancy in cell-based assays.

8. Sourcing and Quality Verification

Research-grade KW-6356 (sipagladenant) is available from multiple chemical and pharmaceutical research suppliers, including MedChemExpress, MedKoo Biosciences, GlpBio Technology, Probechem Biochemicals, and others, at stated purities of greater than 98 percent by HPLC. Supply is in milligram quantities as the free base. There is no pharmaceutical-grade (clinical formulation) material commercially available, as the compound was never registered as a medicine.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 398.12 for the protonated molecular ion, $C_{20}H_{19}N_3O_4S$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Residual solvent analysis by gas chromatography if the compound is intended for cell-based or in vivo studies

The compound should be stored under conditions specified by the supplier (typically desiccated, protected from light, at -20 degrees Celsius for long-term storage). Stock solutions in dimethyl sulfoxide should be aliquoted to avoid repeated freeze-thaw cycles.

9. Reconstitution and Handling

KW-6356 is supplied as a solid powder by research chemical vendors. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (10 to 100 mM), which are then diluted into aqueous assay buffer at the desired working concentration. Final DMSO concentration in cell-based assays should be maintained below 0.1 to 0.5 percent to avoid solvent effects on cellular physiology.

For in vivo research applications in rodent and primate models, the compound has been administered orally. Vehicle composition for the published marmoset studies has not been fully disclosed; standard oral dosing vehicles for non-xanthine heterocyclic compounds include methylcellulose suspensions (0.5 percent methylcellulose in water) and PEG-based formulations. Investigators should optimize vehicle selection based on the compound's solubility profile in the intended vehicle and confirm dissolution before dosing.

Storage conditions for the solid material are -20 degrees Celsius, desiccated, protected from light and moisture. Reconstituted DMSO stock solutions are stable at -20 degrees Celsius for at least 3 months when stored in sealed, light-protected vials. Aqueous dilutions should be prepared fresh for each experiment.

10. Stack Interaction Considerations

KW-6356 interacts with several drug and compound classes through its adenosine A2A receptor pharmacology and its CYP-mediated metabolism. Investigators conducting research with KW-6356, particularly in combination with other pharmacological agents, should consider the following:

CYP3A4/5 inhibitors and inducers: KW-6356 metabolism involves CYP3A4/5 enzymes, as indicated by the conduct of a dedicated drug interaction study [8]. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir) are expected to increase KW-6356 exposure, while strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) are expected to decrease exposure. Dose adjustment in research protocols may be warranted when KW-6356 is co-administered with strong CYP3A4 modulators.

Dopaminergic agents: Concurrent administration with levodopa/carbidopa is the intended clinical use case and was the design of the Phase 2b trial [3, 4]. The non-dopaminergic mechanism of KW-6356 provides complementary motor improvement without directly increasing dopamine levels. Co-administration with dopamine agonists (pramipexole, ropinirole, rotigotine) is pharmacologically rational but has not been formally studied. Additive motor improvement and potential additive adverse effects (dyskinesia, impulse control disturbance) should be anticipated with dopamine agonist combinations.

Other adenosine A2A antagonists: Concurrent use with istradefylline or caffeine (a nonselective, low-affinity adenosine receptor antagonist) would produce competitive binding at the A2A receptor. Given the substantially higher affinity of KW-6356 (K_i 0.12 nM versus istradefylline K_i approximately 12 nM and caffeine K_i approximately 44,000 nM), KW-6356 would dominate receptor occupancy at clinically relevant concentrations. The combination is pharmacologically redundant and not recommended.

MAO-B inhibitors: Concurrent administration with selegiline, rasagiline, or safinamide is standard practice in Parkinson's disease polypharmacy and is not expected to produce pharmacokinetic interactions. Pharmacodynamic complementarity (A2A blockade plus MAO-B inhibition) is plausible but has not been formally studied with KW-6356.

Anticholinergic agents: No characterized interaction. The adenosine and cholinergic signaling pathways in the basal ganglia interact through interneuron circuits, but direct pharmacological antagonism at the A2A receptor does not alter cholinergic receptor sensitivity.

11. Adverse Events and Safety

11.1 Common adverse events

Data from the Phase 2a monotherapy trial in 168 early Parkinson's disease patients provide the most detailed adverse event reporting [2]:

- Constipation: 7.3 percent (3 mg), 6.9 percent (6 mg), versus placebo rates not specified as drug-related
- Nasopharyngitis: 7.3 percent (3 mg), 8.6 percent (6 mg)
- Nausea: 3.4 percent (6 mg group)
- Somnolence: 3.4 percent (6 mg group)
- Insomnia: 3.4 percent (6 mg group)

Overall drug-related adverse event rates were 34.5 percent (3 mg), 27.6 percent (6 mg), and 29.1 percent (placebo), indicating that adverse event frequency was comparable to placebo at the 6 mg dose. Most events were mild or moderate in severity and did not lead to treatment discontinuation [2].

11.2 Phase 1 safety

In healthy volunteers, single doses up to 60 mg and multiple doses up to 24 mg once daily for 14 days were well tolerated, with no dose-limiting toxicities, no clinically meaningful changes in vital signs, body weight, laboratory parameters, or electrocardiograms [7].

11.3 Phase 2b safety

The Phase 2b adjunct-to-levodopa trial in 503 patients reported that KW-6356 was well tolerated, with no major safety issues in any treatment group and no clinically meaningful changes in vital signs, body weight, laboratory results, or electrocardiograms [3, 4]. Detailed adverse event frequency data from the Phase 2b trial have not been fully published in the peer-reviewed literature at the time of monograph preparation.

11.4 Dyskinesia risk

Preclinical evidence from MPTP-treated common marmosets primed for dyskinesia by prior levodopa exposure indicated that repeated administration of KW-6356 induced little dyskinesia, a favorable finding relative to dopaminergic adjuncts [6]. The low dyskinesia risk is consistent with the non-dopaminergic mechanism of action and with the clinical experience of the A2A antagonist class, where istradefylline Phase 3 trials demonstrated increases in non-troublesome dyskinesia without increases in troublesome dyskinesia [10].

11.5 Cardiovascular safety

No QT prolongation signal or other clinically meaningful cardiac safety concern was identified in Phase 1 or Phase 2 studies [2, 7]. Electrocardiographic monitoring was performed in the Phase 1 program and in both Phase 2 trials.

11.6 Class-effect safety considerations

The broader A2A antagonist class has not produced class-specific safety concerns in clinical development. Istradefylline, the only approved compound in the class, has an established post-marketing safety profile that does not include major organ toxicity, hematological toxicity, or hepatotoxicity. The unrelated A2A antagonist tozadenant was discontinued owing to hematological toxicity (agranulocytosis), but this toxicity was attributed to off-target effects specific to the tozadenant chemical scaffold rather than to A2A receptor antagonism [13]. Preladenant was discontinued for lack of Phase 3 efficacy rather than safety concerns [14]. The KW-6356 safety profile in completed studies is consistent with the favorable class-effect safety record.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five adenosine A2A receptor antagonists against KW-6356, evaluated against five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile, and overall validation. The five comparators represent the principal A2A antagonists with substantive clinical or advanced preclinical programs for Parkinson's disease motor symptom management.

12.1 Istradefylline (KW-6002, NOURIANZ/NOURIAST)

Mechanism: Xanthine-based, selective adenosine A2A receptor antagonist with surmountable antagonism. Binding affinity pKi approximately 7.9 at the human A2A receptor, approximately 100-fold lower than KW-6356 [1, 10].

Development trajectory: Developed by Kyowa Hakko Kirin (now Kyowa Kirin). Approved in Japan in 2013 for adjunct treatment of OFF episodes in Parkinson's disease patients receiving levodopa/decarboxylase inhibitor. Approved by the US FDA in August 2019 (NOURIANZ, 20 mg and 40 mg tablets) for the same indication. The compound is the only A2A antagonist approved by any regulatory authority for Parkinson's disease [10].

Novelty: Low. Istradefylline is the first-generation reference compound in the class and established the therapeutic rationale for A2A antagonism in Parkinson's disease. The xanthine-based chemistry and surmountable antagonism are now considered mechanistically limited relative to second-generation approaches.

Effect size: Moderate. Phase 3 trials demonstrated statistically significant reductions in daily OFF time (approximately 0.7 to 1.0 hours reduction versus placebo) as adjunct to levodopa. Effect sizes were consistent but modest, and two of three US pivotal trials missed the primary endpoint, contributing to the prolonged regulatory timeline [10].

Promising potential: Moderate. The compound is approved and commercially available but has not achieved widespread adoption in clinical practice owing to modest effect sizes and the availability of alternative adjunct therapies (MAO-B inhibitors, COMT inhibitors, dopamine agonists). Post-marketing label expansion to monotherapy has not been pursued. Commercial performance has been below expectations.

Side-effect profile: Favorable. The most common adverse events are dyskinesia (largely non-troublesome), constipation, hallucination, dizziness, insomnia, and nausea. No major organ toxicity or class-specific safety concerns have emerged in post-marketing surveillance. QT prolongation has not been identified as a safety signal [10].

Overall validation: High. Istradefylline is the only approved compound in the class and has the most extensive clinical and post-marketing safety database among A2A antagonists.

Comparison to KW-6356: KW-6356 was developed explicitly as istradefylline's successor, with approximately 100-fold greater receptor affinity, insurmountable antagonism, and inverse agonist activity. KW-6356 demonstrated superior anti-parkinsonian activity in head-to-head preclinical comparison (MPTP marmoset model) [5]. However, KW-6356 was discontinued before Phase 3 initiation, while istradefylline reached regulatory approval. Istradefylline therefore has the advantage of approved, commercially available status and an established human safety database that KW-6356 lacks.

12.2 Preladenant (SCH 420814)

Mechanism: Non-xanthine, selective adenosine A2A receptor antagonist. High binding affinity (K_i approximately 1.1 nM), surmountable antagonism [14].

Development trajectory: Developed by Schering-Plough (subsequently Merck). Advanced through Phase 2 with positive results showing significant reductions in OFF time as adjunct to levodopa. Three Phase 3 trials were conducted. All three failed to demonstrate significant efficacy on the primary endpoint of reduction in daily OFF time versus placebo [14]. Notably, the active comparator arm (rasagiline) also failed to separate from placebo in these trials, raising questions about assay sensitivity rather than compound efficacy. Development was discontinued by Merck in 2013.

Novelty: Moderate. Non-xanthine scaffold with high affinity but surmountable antagonism. Did not demonstrate inverse agonist activity.

Effect size: Phase 2 results were positive (approximately 1.0 hour reduction in OFF time versus placebo). Phase 3 results were negative across all three trials, though the assay sensitivity concern complicates interpretation [14].

Promising potential: None. Development terminated. Compound not available as a registered medicine.

Side-effect profile: Favorable in Phase 2 and Phase 3 studies. No significant safety concerns identified. The compound was discontinued for efficacy failure, not safety issues.

Overall validation: Low. Phase 3 efficacy failure, despite Phase 2 signals and high receptor affinity, represents the most cautionary development narrative in the A2A antagonist class and has been influential in shaping regulatory expectations for subsequent compounds.

Comparison to KW-6356: KW-6356 and preladenant share the non-xanthine scaffold class and high A2A affinity. KW-6356 is distinguished by insurmountable antagonism and inverse agonism, properties that preladenant lacks. The preladenant Phase 3 failure, attributed at least in part to trial design rather than pharmacology, informed the development landscape that ultimately contributed to Kyowa Kirin's decision to discontinue KW-6356 before Phase 3 initiation.

12.3 Tozadenant (SYN-115)

Mechanism: Non-xanthine, selective adenosine A2A receptor antagonist. Moderate binding affinity [13].

Development trajectory: Developed by Acorda Therapeutics (acquired the program from Synosia Therapeutics). Advanced through Phase 2 with positive results in reducing OFF time and improving ON time without troublesome dyskinesia as adjunct to levodopa. Phase 3 trials were initiated but halted in 2017 following reports of serious hematological adverse events, including agranulocytosis (severe neutropenia), in multiple patients, with associated fatalities [13].

Novelty: Moderate. Non-xanthine chemistry. No inverse agonist activity characterized.

Effect size: Phase 2 data showed significant reductions in OFF time (approximately 1.1 to 1.7 hours versus placebo) with dose-dependent efficacy, the largest effect sizes observed among A2A antagonists in Phase 2 [13].

Promising potential: None. Development terminated due to fatal hematological toxicity. The toxicity was attributed to off-target, scaffold-specific effects rather than A2A receptor pharmacology.

Side-effect profile: Unfavorable. The agranulocytosis signal, with associated fatalities, is the most serious safety signal observed in the A2A antagonist class. This toxicity has been attributed to the specific chemical structure of tozadenant rather than to the A2A antagonist mechanism [13].

Overall validation: Low. The compound produced the strongest Phase 2 efficacy signal in the class but was terminated for a serious safety issue that precluded Phase 3 completion.

Comparison to KW-6356: KW-6356 has a distinct chemical scaffold from tozadenant and did not produce hematological safety signals in any completed clinical study. The tozadenant experience underscored the importance of compound-specific safety evaluation within the A2A antagonist class and contributed to the overall risk perception that influenced the KW-6356 development decision.

12.4 Caffeine

Mechanism: Non-selective adenosine receptor antagonist (blocks A1, A2A, A2B, and A3 receptors at comparable concentrations). A2A Ki approximately 44 micromolar, approximately 370,000-fold lower affinity than KW-6356. The A2A antagonist component of caffeine's pharmacology has been proposed as a contributing mechanism to the epidemiologically observed inverse association between coffee consumption and Parkinson's disease risk [15].

Development trajectory: Caffeine has not been developed as a Parkinson's disease therapeutic through traditional regulatory pathways. A randomized clinical trial (Postuma et al., 2012) evaluated caffeine 200 mg twice daily versus placebo as a symptomatic treatment for excessive daytime somnolence in Parkinson's disease, with secondary motor endpoints. Caffeine modestly improved motor scores but the effect was not sustained at 6 months in a follow-up study [16]. Epidemiological evidence consistently associates moderate caffeine consumption with 25 to 30 percent reduced Parkinson's disease risk, though causality and mechanism remain debated.

Novelty: Low. Caffeine is the most widely consumed psychoactive substance and the oldest known adenosine receptor ligand. Its non-selective pharmacology and low A2A potency limit its relevance as a targeted A2A antagonist.

Effect size: Modest in clinical motor endpoints. Epidemiological risk reduction is consistent but not established as causal or A2A-specific.

Promising potential: Low as a targeted Parkinson's disease therapeutic. High as a lifestyle factor and as a mechanistic probe for the relationship between adenosine receptor pharmacology and Parkinson's disease risk.

Side-effect profile: Well characterized over centuries of human consumption. Dose-dependent insomnia, anxiety, tachycardia, and gastrointestinal effects at high doses. Generally well tolerated at moderate consumption levels.

Overall validation: Low as a Parkinson's disease therapeutic. High as an epidemiological exposure with consistent observational data.

Comparison to KW-6356: KW-6356 provides approximately 370,000-fold greater A2A potency, full selectivity over other adenosine receptor subtypes, and the unique pharmacological properties of insurmountable antagonism and inverse agonism. Caffeine is not a clinical alternative to KW-6356 for targeted A2A receptor blockade in Parkinson's disease.

12.5 V81444 (Vernalis/Ligand)

Mechanism: Selective adenosine A2A receptor antagonist. Exact binding parameters not fully disclosed in published literature. Advanced as a non-xanthine A2A antagonist for Parkinson's disease.

Development trajectory: Developed by Vernalis (now Ligand Pharmaceuticals). Entered Phase 1 clinical trials with reported safety and tolerability data. Did not advance beyond Phase 1, and limited published clinical data are available. The compound represents an early-phase entrant in the A2A antagonist space that did not achieve proof-of-concept in Parkinson's disease patients.

Novelty: Moderate. Non-xanthine scaffold. Limited pharmacological characterization in the public literature.

Effect size: No clinical efficacy data in Parkinson's disease patients. Phase 1 only.

Promising potential: None. Development discontinued at Phase 1 stage.

Side-effect profile: Phase 1 data reported adequate safety and tolerability. No published safety concerns.

Overall validation: Very low. Minimal published data and no clinical efficacy evaluation.

Comparison to KW-6356: KW-6356 is substantially more advanced (Phase 2b positive data, preclinical head-to-head superiority over istradefylline, crystal structure, detailed PK characterization) and better validated than V81444. The comparison illustrates the attrition within the A2A antagonist class and the difficulty of advancing compounds beyond early clinical development.

12.6 Comparator summary

The five comparators occupy distinct positions in the adenosine A2A receptor antagonist landscape. **Istradefylline** is the only approved compound and the clinical and commercial reference for the class, but exhibits modest effect sizes and surmountable antagonism. **Preladenant** demonstrated high affinity and Phase 2 efficacy but failed three Phase 3 trials, establishing the most cautionary regulatory narrative in the class. **Tozadenant** produced the strongest Phase 2 efficacy signal but was terminated for fatal hematological toxicity attributable to scaffold-specific, off-target effects. **Caffeine** provides epidemiological context but lacks the potency and selectivity for targeted therapeutic application. **V81444** represents early-stage attrition without meaningful clinical data.

KW-6356 occupies a unique position in this landscape: it is the only compound with demonstrated insurmountable antagonism and inverse agonism at the A2A receptor, the highest reported binding affinity in the class (K_i 0.12 nM), preclinical head-to-head superiority over the approved compound (istradefylline) in the MPTP marmoset model, and positive Phase 2 proof-of-concept data in both monotherapy and adjunct-to-levodopa settings. Its principal limitation is the absence of Phase 3 data and regulatory approval, a consequence of a commercial and regulatory-landscape decision by the sponsor rather than an efficacy or safety failure. The compound's scientific contributions (particularly the crystal structure demonstrating the structural basis of inverse agonism and insurmountable antagonism at the A2A receptor) persist as reference data that will inform the design of future A2A receptor-targeted therapeutics. The preladenant Phase 3 failure and the tozadenant

safety termination collectively define a challenging development landscape that influenced Kyowa Kirin's risk assessment and contributed to the discontinuation decision despite positive clinical data.

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confirmation of identity and purity on every lot. The compound class (adenosine A2A receptor antagonists) includes one approved medicine (istradefylline) with an established post-marketing safety profile; investigators should not extrapolate istradefylline safety data to KW-6356 without independent confirmation.