Clinical pharmacology studies investigating novel formulations of dopaminergic drugs

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CHAPTER 2

A randomized trial assessing the safety, pharmacokinetics, and efficacy during morning *OFF* of AZ-009

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ABSTRACT

Background Inhalation of apomorphine could be a faster-acting and more user-friendly alternative to subcutaneous injection for treating *OFF* periods in PD.

Objectives To compare the safety and pharmacokinetics of inhaled apomorphine (AZ-009) with subcutaneous apomorphine (APO-go PEN) in healthy volunteers, and to examine the safety, pharmacokinetics, and efficacy of AZ-009 in PD patients.

Methods In part A of this study, 8 healthy volunteers received 1 mg AZ-009 and 2 mg subcutaneous apomorphine in a randomized crossover manner. In the subsequent single ascending dose parts in healthy volunteers (part B, n=16) and PD patients (part C, n=25), participants were randomized to placebo or AZ-009 up to 4 mg. In patients, after medication withdrawal, MDS-UPDRS III and *ON*/*OFF* states were assessed pre- and post-dose.

Results AZ-009 was rapidly absorbed with peak plasma concentrations at 2 minutes, as compared to 30 minutes for subcutaneous apomorphine. Adverse events for AZ-009 were comparable to subcutaneous apomorphine, except for mild and transient throat irritation. Adverse events limited AZ-009 dose escalation in healthy volunteers to 3 mg. Patients tolerated up to 4 mg. In PD patients, 2, 3, and 4 mg AZ-009 reduced mean MDS-UPDRS III score (standard deviation) by 10.7 (13.6), 12.8 (7.9) and 10.3 (3.7) points respectively, compared to 4.8 (4.9) after placebo at 10 minutes post-dose. The percentage of patients achieving full *ON* within 45 minutes post-dose increased dose-dependently: 0% (placebo), 17% (2 mg), 50% (3 mg), 83% (4 mg).

Conclusions AZ-009 appears to be a rapid-acting and reasonably well-tolerated formulation for treating *OFF* periods.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting movement, cognition, emotion, and autonomic activity. PD patients are usually treated with dopaminergic drugs such as levodopa and/or a direct-acting dopamine agonist. Initial therapy is selected based upon a number of criteria including patient age, comorbid conditions, disease severity and degree of functional disability.[1–3] However, most patients eventually require levodopa therapy and a large proportion of patients develop motor complications within a few years of starting its use.[4–6] Complications consist of predictable end of dose *OFF* episodes ('wearing *OFF*'), prolonged latency to *ON*, inability to turn *ON*, sudden *ON*/*OFF* fluctuations and/or dyskinesia. These fluctuations in therapeutic effects can be predictable or unpredictable and do not only involve fluctuations in motor symptoms but also in non-motor symptoms such as anxiety/panic attacks, mood changes, slow thinking, and pain.[7]

A number of strategies have been investigated to increase *ON* time while reducing disabling *OFF* time, e.g., dosing more often with a lower levodopa dose, adding dopamine agonists, giving catechol-O-methyltransferase or monoamine oxidase B inhibitors, administering controlled- or sustained-release drug formulations, or following a protein redistribution diet.[2,8,9] However, despite optimal oral therapy, patients often continue to experience *OFF* periods that severely compromise quality of life and daily activities.[10] Subcutaneous apomorphine provides rapid and effective relief from such *OFF* periods and has been indicated for use in advanced PD for approximately two decades. Often reported side effects include injection site reactions, hallucinations, sedation, somnolence, dizziness, yawning, nausea and vomiting. In addition, there is an increased risk of orthostatic hypotension in the elderly population especially during initiation of therapy.[11] To diminish the risk of nausea, vomiting, and (orthostatic) hypotension, patients are usually pretreated with domperidone or another antiemetic for at least 2 days prior to initiation of apomorphine.[11–13] Although the subcutaneous formulation of apomorphine is efficacious, it has disadvantages such as difficulty self-administering

a subcutaneous injection while *OFF* and a high incidence of injection site reactions.[14] A more user-friendly formulation would allow for a broader use of apomorphine. This unmet medical need is recognized by the medical community, and research has been focused on finding more suitable formulations.[14,15] Recently, sublingual apomorphine has been approved by the FDA, providing a more user-friendly formulation, albeit still requiring a film strip under the tongue for up to 3 minutes.[16] It is expected that apomorphine inhalation will not only be more user-friendly, but also result in an even faster action.

AZ-009, also called Staccato® apomorphine, is a single-use, disposable, breath-actuated drug-device combination product for oral inhalation. It has been developed to deliver apomorphine hydrochloride as a thermally generated, condensation aerosol to the deep lung for rapid systemic exposure. We performed a 3-part phase 1 trial to evaluate the pharmacokinetics (PK) of AZ-009 and compare it with a registered subcutaneous apomorphine injection (part A), and to study the safety and PK of single ascending doses of AZ-009 in healthy volunteers (HVs) (part B) and PD patients (part C). The last study part also evaluated AZ-009's efficacy during an induced morning *OFF* state.

METHODS

The study was conducted in accordance with European Medicines Agency guidelines for Good Clinical Practice and registered in ClinicalTrials.gov (NCT03822364). The protocol was approved by the Independent Ethics Committee of Foundation Beoordeling Ethiek Biomedisch Onderzoek. Prior to any study-related activity, all participants provided written informed consent. The study was conducted at the Centre for Human Drug Research between October 2018 and May 2019.

Study design

This study was divided into three parts: part A, B and C. Refer to Supplemental Figure 1 for a schematic overview of the study designs.

The randomization code was generated separately for each part using SAS version 9.4 by a study-independent CHDR statistician. No formal sample size calculations were performed. Part A of the study was a randomized, open-label crossover study assessing single doses of AZ-009 (1 mg) and subcutaneous apomorphine (2 mg) in 8 HVs. The washout between the two study periods was at least three days (apomorphine half-life is approximately 30-50 minutes).[17,18] Safety data were examined during a dose level evaluation meeting before proceeding to study part B. Part B was a randomized, double-blind, placebo-controlled, single-ascending dose study of AZ-009 with planned doses of 2, 3, and 4 mg in HVs. The 4 mg cohort was cancelled due to incidence of adverse events (AEs) in the 3 mg cohort. Each cohort was composed of 8 HVs of which 6 were randomized to receive active treatment and 2 to receive placebo. Before advancing to the next cohort, safety data were evaluated. Part C had the same study design as part B, but was performed in PD patients after overnight anti-Parkinson medication withdrawal. Patients were dosed the next morning only when they were in an *OFF* state as assessed by a physician.

The study consisted of:

- a screening visit;
- at-home pretreatment with an antiemetic (domperidone) three times daily (TID);
- a single stay of 7, 3, or 2 days (part A, B and C respectively) at the clinical research unit;
- and a follow-up telephone call.

In part A, participants received 10 mg domperidone TID from 3 days prior to dosing until after last dose. In part B, domperidone dose was increased to 20 mg on the evening and morning prior to dosing. At other time points domperidone intake remained 10 mg as in part A. In part C, participants received 20 mg domperidone TID from 2 days prior to dosing until after dosing.

Participants

In study parts A and B, healthy non-smoking men and women aged 18-60 years with a body mass index of 18–32 kg/m^2 were eligible

to participate. In study part C, non-smoking PD patients with recognizable *OFF* periods aged 30-85 years with Hoehn and Yahr stage I-IV were eligible for participation. Patients were excluded if their systolic blood pressure (BP) was below 100 mmHg at screening or baseline, they had symptomatic clinically relevant and medically uncontrolled orthostatic hypotension, or a history of long QT syndrome and/or a QTcF of >470 ms (male) or >480 ms (female).

Investigational drugs

AZ-009 was available in two dose strengths (1 and 2 mg apomorphine hydrochloride). A dose of 3 mg was delivered by 3 consecutive oral inhalations of 1 mg, and a dose of 4 mg by 2 consecutive inhalations of 2 mg. Matching Staccato placebo (including number of devices inhaled) was identical to AZ-009, but without a coated apomorphine film. AZ-009 and matching placebo were manufactured by Alexza Pharmaceuticals, Inc. Participants were instructed to inhale through the mouthpiece with a steady deep breath and to hold their breath for as long as possible, up to 10 seconds.

Inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free apomorphine to form a thermally generated drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung, i.e., with a mass median aerodynamic diameter in the range of 0.5 to 3.5 µm.

In study part A, apomorphine was also administered subcutaneously with the APO-go PEN. APO-go was provided as the commercially available product with the appropriate country-specific labeling by the Leiden University Medical Centre pharmacy. A volume of 0.2 mL (2 mg) was injected in the thigh.

Safety

For all study parts, a medical screening was performed to assess eligibility based on medical history, concomitant medications, ECG, vital signs, routine hematology, chemistry and urinalysis, and physical examination. Electrolytes and QTcF were assessed at screening (prior to domperidone initiation) and again at baseline (after domperidone initiation and prior to apomorphine administration). During the study, safety was evaluated by monitoring of AEs (classified by Medical Dictionary for Regulatory Activities (MedDRA) version 20.1), vital signs, ECGs, physical examination, and clinical laboratory tests. Orthostatic hypotension was defined as a systolic BP drop of ≥20 mmHg or a diastolic BP drop ≥10 mmHg upon standing. Postural dizziness was defined as dizziness upon standing that was not accompanied by a drop in BP (at the scheduled measurement time) as defined for orthostatic hypotension.

Pharmacokinetics

Blood samples for PK analysis were obtained pre-dose and 1, 2, 5, 10, 20, 30, and 45 minutes, and 1, 2, 4, 8 and 24 hours post-dose in parts A/B. In part C, samples were obtained pre-dose and 2, 5, 15, 30, and 45 minutes, and 1, 1.5, 4 and 5 hours post-dose. A lower sampling frequency and shorter sampling duration were chosen in part C to allow time for efficacy measurements and to reduce patient burden. Plasma samples were analyzed for apomorphine using a validated liquid chromatography–tandem mass spectrometry method.

Plasma concentrations of apomorphine were analyzed using non-compartmental analysis in Phoenix™ WinNonlin® version 8.1. PK parameters that were calculated include maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), apparent terminal elimination half-life ($T_{½}$) and area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$).

For part A, the comparison of the dose-normalized log-transformed PK parameters C_{max} and $AUC_{0\text{-}inf}$ for apomorphine across treatments (1 mg AZ-009 inhalation vs. 2 mg subcutaneous apomorphine) was performed using an analysis of variance (ANOVA) model and the two one-sided t-tests procedure. The ANOVA model included factors for sequence, subject within sequence, treatment, and period. Point estimates and 90% confidence intervals for the geometric mean ratios (AZ-009/subcutaneous apomorphine) were calculated for PK parameters by back transformation to the original scale.

For parts A-C combined, C_{max} and $AUC_{0\text{-}inf}$ for apomorphine were compared across dose levels (1-4 mg) to assess dose proportionality. Statistical analyses were conducted using a power model with mixed effects.[19]

Efficacy

Motor function was assessed using part III of the licensed Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Physicians administering the scale were trained and certified in its use. To the degree feasible, the same physician evaluated a patient at Day -1 (day before dosing) and Day 1 pre-dose and 10-, 30- and 60-minutes post-dose. Mean change from baseline (CFB) MDS-UPDRS III total score was calculated and presented graphically.

The disease state of a patient was assessed by a physician pre-dose and 2, 10, 20 and 45 minutes post-dose. Possible categories were *ON* with disabling dyskinesia, *ON* with non-disabling dyskinesia, *ON* with no dyskinesia and normal motor function, partial *ON* and *OFF*. The first 3 categories were combined, classified as full *ON*, and presented graphically as percentage of patients turning full *ON*.

RESULTS

Demographics

See Supplemental Figure 2-4 for CONSORT flow diagrams providing an overview of number of participants screened, randomized, completed, and analyzed per study part. Table 1 outlines the demographics and disposition of all participants enrolled in the study. Eight HVs completed the comparative PK study part (part A), and two cohorts of eight HVs (6 AZ-009: 2 placebo) completed the single ascending dose study part (part B). Demographics of HVs in part A and B were comparable, only the median age was higher in part A compared to part B (40 and 26 years, respectively). In part C of the study, a total of 25 PD patients were included, divided over three cohorts receiving 2, 3, or 4 mg AZ-009, or placebo in a 6:2 ratio. The 2 mg AZ-009 group contained one additional patient due to a replacement in cohort 1 (see Supplemental Figure 4). The age of PD patients was higher than that of HVs. All groups contained males and females, except for the placebo group, which was composed of males only.

Pharmacokinetics

PART A: COMPARATIVE PK IN HVS

Apomorphine was rapidly absorbed into the systemic circulation following administration of AZ-009 and subcutaneous apomorphine in HVs (Figure 1). Descriptive statistics of the PK parameters are summarized in Supplemental Table 1. AZ-009 inhalation resulted in peak plasma apomorphine concentrations (C_{max}) 1-2 min after dosing and showed a bi-exponential elimination phase. In contrast, apomorphine concentrations after subcutaneous apomorphine injection increased over time with a median T_{max} of 30 minutes. When normalized for dose, the C_{max} and $AUC_{0\text{-}inf}$ geometric mean ratios (90% confidence interval) of AZ-009/subcutaneous apomorphine were 2.9 (1.6-5.4) and 0.8 (0.5-1.2) respectively. Mean apomorphine $T_{½}$ ± standard deviation (SD) of AZ-009 was shorter (39 ± 7 min) than that of subcutaneous apomorphine (55 ± 22 min). Inter-subject variability (CV%) in apomorphine C_{max} and $AUC_{0\text{-}inf}$ was higher for AZ-009 (53.7% and 47.2%) than for subcutaneous apomorphine (36.4% and 22.7%).

PARTS B AND C: SINGLE ASCENDING DOSES IN HVS AND PD PATIENTS

AZ-009 was rapidly systemically absorbed in HVs (Figure 2A), as well as in PD patients (Figure 2B). Median T_{max} in HVs was similar as in part A, i.e., 1 minute. The first PK sample in PD patients was taken at 2 minutes post-dose. Median T_{max} in PD patients was 2 or 3 minutes depending on the dose group (Supplemental Table 2). C_{max} and $AUC_{0\text{-}inf}$ after 2 and 3 mg AZ-009 were similar for HVs and PD patients. $T_{½}$ in both HVs and PD patients was similar as was reported for 1 mg AZ-009 in part A. In PD patients, $AUC_{0\text{-}inf}$ increased from 2 to 3 mg, but not from 3 to 4 mg, i.e., mean (SD) $AUC_{0\text{-}inf}$ was 5.1 (1.5), 12.6 (4.5) and 11.3 (5.1) h·ng/mL for 2, 3 and 4 mg AZ-009 respectively.

Dose proportionality was assessed on the combined data of part A-C. The estimated exponent (90% confidence interval) was 0.57 (0.15-1.00) for the C_{max} and 0.77 (0.41-1.13) for the $AUC_{0\text{-}inf}$.

Safety and tolerability

The incidence of moderate AEs was 62.5% after AZ-009 and 100% after subcutaneous apomorphine treatment (Table 2). The most frequently reported TEAEs were nausea and presyncope (despite pretreatment with 10 mg domperidone TID), and somnolence and headache. Participants who received subcutaneous apomorphine reported the first AEs around 20 minutes post-dose, whereas for AZ-009 this was after 2-3 minutes (data not shown).

In part B, the domperidone dose was increased to 20 mg on the evening and morning prior to dosing in HVs. At other time points, domperidone intake remained 10 mg. A dose of 2 mg AZ-009 combined with this higher domperidone dose was better tolerated than 1 mg AZ-009 combined with a lower dose of domperidone (Table 2). The most frequently reported TEAEs were somnolence and yawning. The number of TEAEs, and in particular the frequency of moderate TEAEs, increased from 2 to 3 mg AZ-009. Nausea, orthostatic hypotension, somnolence, and yawning were reported most often in the 3 mg group. Standing BPs as low as 70/34 mmHg were measured and 5 out of 6 participants in the 3 mg group needed to lie down until symptoms subsided. Due to the dose-dependent increase in incidence of TEAEs, it was decided not to escalate to 4 mg in HVs and to increase the domperidone dose to 20 mg TID from 2 days prior to dosing in part C of the study in PD patients[12,13].

AZ-009 was relatively well tolerated by PD patients at 2, 3, and 4 mg with mostly mild TEAEs (Table 2). The most frequently reported TEAEs in the AZ-009-treated groups were throat irritation, orthostatic hypotension, and yawning. Orthostatic hypotension was mostly asymptomatic and was also reported in the placebo group. Some patients reported an increase in their PD symptoms in the days after the overnight Parkinson's medication withdrawal and dosing with placebo or AZ-009. No increase in incidence and severity of TEAEs was observed with an increase in dose. Most TEAEs resolved without treatment, except for one case of severe hypotension in the 3 mg group which was treated with ephedrine, and two cases where the number of Parkinson's medication doses was increased for several days after study participation because of increased PD symptoms.

No consistent or clinically relevant QTcF prolongation or clinical laboratory changes were reported in any of the participants.

Efficacy

PD patients in part C were dosed during an *OFF* state after overnight medication withdrawal. All three AZ-009-treated dose groups showed a reduction from baseline in mean MDS-UPDRS part III total score at the first assessment 10 minutes post-dose (Figure 3A). The mean MDS-UPDRS III change from baseline (CFB) with SD at this time point was -10.7 (13.6) for the 2 mg group, -12.8 (7.9) for the 3 mg group, -10.3 (3.7) for the 4 mg group, and -4.8 (4.9) for the placebo group. The effect observed in the AZ-009-treated groups started to decrease at 30 minutes post-dose and further decreased at 1 hour post-dose to less than half of the maximum effect observed at 10 minutes post-dose. In contrast, the placebo group no longer showed a reduction compared to baseline at 1 hour post-dose.

All patients were assessed by a physician as being in an *OFF* state prior to dosing (Figure 3B). None of the placebo-treated patients achieved a full *ON* response at any of the time points. In contrast, the first patients converted to a full *ON* as early as 2 minutes after AZ-009 dosing. The highest percentage of patients in an *ON* state occurred 10 minutes post-dose for the 3 mg AZ-009 group and 20 minutes post-dose for the 2 and 4 mg AZ-009 groups. The percentage of patients achieving a full *ON* at any time point within 45 minutes post-dose increased with dose from 17% (2 mg) to 50% (3 mg) to 83% (4 mg). No patients presented with disabling dyskinesias.

DISCUSSION

Subcutaneous apomorphine injections have long been used by PD patients for the treatment of sudden or early morning *OFF* periods.

Even though subcutaneous apomorphine is efficacious, it can be painful and/or difficult to self-administer, and often results in injection site reactions.[11] Moreover, maximal motor improvements have been shown to occur only after about 20 to 40 minutes following subcutaneous apomorphine.[20-22] This formulation of inhalable apomorphine, AZ-009, could provide an easier and faster-acting formulation for the treatment of *OFF* periods. This 3-part study was designed to evaluate the PK of AZ-009 and compare it with the subcutaneous injection, and to examine the safety and PK of ascending doses of AZ-009 in HVs and PD patients. The last study part also aimed to evaluate AZ-009's efficacy in PD patients during an induced morning *OFF* state.

AZ-009 led to rapid systemic exposure with a median T_{max} of 2 minutes based on the combined data of HVs and PD patients. In contrast, the subcutaneous apomorphine injection resulted in a T_{max} of 30 minutes. AZ-009's PK profile makes it especially suitable for fast onset of action which is preferential in the treatment of sudden *OFF* periods. Dosing with 1 mg AZ-009 resulted in a mean (SD) C_{max} of 14.3 (7.7) ng/mL and 2 mg subcutaneous apomorphine in 8.6 (3.1) ng/mL. A difference in total exposure ($AUC_{0\text{-}inf}$) between inhalable and subcutaneous apomorphine could not be confirmed due to the relatively high variability and small sample size. Similarly, no definitive conclusions could be drawn on dose proportionality. Future larger trials will need to be conducted to gain more information on this.

Despite comparable PK, AZ-009 resulted in a less favorable safety profile in HVs than in PD patients. This was not unexpected since PD patients are likely to have developed tolerance because of daily dopaminergic medication use. Also, PD patients were administered a higher domperidone dose compared to HVs. The most frequently reported AEs in PD patients were throat irritation, orthostatic hypotension, and yawning. Throat irritation occurred immediately after dosing and usually resolved within minutes. Orthostatic hypotension was mostly asymptomatic and was observed in the placebo group as well. This can likely be partly explained by autonomic dysregulation in PD.

One PD patient receiving 3 mg AZ-009 presented with severe hypotension shortly after dosing that was treated with ephedrine. Hypotension is a known side effect of apomorphine[12,23] and moderate hypotension was also reported by one healthy volunteer receiving 2 mg subcutaneous apomorphine in study part A. All participants that presented with reduced blood pressure spontaneously recovered after lying down or lying in Trendelenburg position. However, in the context of patient comfort, ephedrine was more readily administered during the patient part of the study. Moreover, AZ-009 gives higher peak apomorphine concentrations than subcutaneous apomorphine and this patient was immediately given 3 mg AZ-009. In clinical practice, subcutaneous apomorphine is initiated under medical supervision at 2 mg and titrated up to a dose that is both tolerable and effective. The same should be done with AZ-009 when used in clinical practice. For some patients, AZ-009 might not be tolerable at effective doses, as is now also the case for some patients receiving subcutaneous injections.

During this trial a prototype of the inhalation device was used. Of 25 PD patients, 23 (92.0%) indicated they liked how the drug was delivered. Whether they also found the device easy to use could not be adequately evaluated due to the prototype being used. Future trials should therefore focus on ease of use of the commercial device in PD patients.

Treatment with 2, 3 and 4 mg AZ-009 showed promise in controlling morning *OFF* periods in PD patients after overnight medication withdrawal. At 10 minutes post-dose, all three AZ-009 dose groups showed a clear reduction (10.3-12.8 points) from baseline in mean MDS-UPDRS III score that was greater than for placebo (4.8 points). These reductions were larger than 3.25 points, which has been described as the minimal, but clinically relevant improvement.[24] Moreover, the difference in MDS-UPDRS III response between placebo and apomorphine was comparable to that reported in another apomorphine inhalation study (8.4 points (95% confidence interval: 1.2-15.5)).[25] MDS-UPDRS III improvement did not seem to correlate with AZ-009 dose. This is likely the result of inter-patient variability in exposure and MDS-UPDRS III response. From literature, it was already known that the minimally effective apomorphine concentration differs widely between patients,[26] and that the degree of response is (partly) dependent on disease

severity.[27] The fast onset of action and relatively short duration of action would make this formulation ideal for patients suffering from sudden and unpredictable *OFF* periods or from delayed *ON*. Findings on the MDS-UPDRS III were supported by the physician's *ON*/*OFF* state assessment. Whereas none of the placebo patients achieved a full *ON* response, the AZ-009-treated patients dose-dependently converted from *OFF* to full *ON*. For future studies, assessing *ON*/*OFF* states after 45 minutes is advised to determine duration of clinical effect. Since patients were randomized to their AZ-009 dose, it is likely that they did not reach their maximum possible improvement. In clinical practice, the dose of apomorphine is titrated to reach a dose with optimal efficacy and minimal side effects. Whereas this study demonstrates a beneficial effect of AZ-009 over placebo, future studies should further investigate the efficacy of AZ-009 at the patient's optimal dose.

Taken together, AZ-009 is reasonably well tolerated by PD patients pretreated with domperidone. AZ-009 is rapidly absorbed into the systemic circulation and can provide rapid relief from early morning *OFF* periods.

TABLE 1 **Demographics of participants in study parts A to C.**

	PART A	PART B			
Demographic variables for healthy volunteers	**All participants (N=8)**	**All participants (N=16)**	**2 mg AZ-009 (N=6)**	**3 mg AZ-009 (N=6)**	**Placebo (N=4)**
Age (years)					
Median (range)	40 (19-58)	26 (19-60)	29 (21-39)	24 (21-60)	40 (19-58)
BMI (kg/m^2)					
Median (range)	25 (20-31)	24 (19-30)	24 (19-28)	24 (21-27)	26 (24-30)
Sex (n/n (%/%))					
Female/Male	5/3 (62.5/37.5)	12/4 (75.0/25.0)	5/1 (83.3/16.7)	5/1 (83.3/16.7)	2/2 (50.0/50.0)
Race (n (%))					
Asian	0 (0)	2 (12.5)	1 (16.7)	1 (16.7)	0 (0)
Mixed	2 (25.0)	2 (12.5)	2 (33.3)	0 (0)	0 (0)
White	6 (75.0)	12 (75.0)	3 (50.0)	5 (83.3)	4 (100.0)
		PART C			
Demographic variables for patients with PD	**All participants (N=24)[a] (N=25)[b]**	**2 mg AZ-009 (N=6)[a] (N=7)[b]**	**3 mg AZ-009 (N=6)**	**4 mg AZ-009 (N=6)**	**Placebo (N=6)**
Age (years)					
Median (range)	62 (44-83)	63 (58-75)	55 (53-67)	67 (56-71)	58 (44-83)
BMI (kg/m^2)					
Median (range)	25 (20-31)[a] 25 (20-32)[b]	27 (20-30)[a] 27 (20-32)[b]	26 (22-29)	24 (22-27)	24 (22-31)
Sex (n/n (%/%))					
Female/Male	7/17 (29.2/70.8)[a] 7/18 (28.0/72.0)[b]	3/3 (50.0/50.0)[a] 3/4 (42.9/57.1)[b]	1/5 (16.7/83.3)	3/3 (50.0/50.0)	0/6 (0/100.0)
Race (n (%))					
Other[c]	1 (4.2[a], 4.0[b])	0 (0)	1 (16.7)	0 (0)	0 (0)
White	23 (95.8)[a] 24 (96.0)[b]	6 (100.0)[a] 7 (100.0)[b]	5 (83.3)	6 (100.0)	6 (100.0)
MMSE					
Median (range)	29 (25-30)	30 (27-30)	29 (27-30)	30 (25-30)	29 (26-30)

[continuation of Table 1]

Demographic variables for patients with PD	PART C				
	All participants (N=24)[a] (N=25)[b]	2 mg AZ-009 (N=6)[a] (N=7)[b]	3 mg AZ-009 (N=6)	4 mg AZ-009 (N=6)	Placebo (N=6)
Hoehn and Yahr stage at Day -1 (when using regular medication) (n (%))					
Stage 1	1 (4.2)	0 (0)	0 (0)	0 (0)	1 (16.7)
Stage 2	15 (62.5)	5 (83.3)	3 (50.0)	4 (66.7)	3 (50.0)
Stage 3	6 (25.0)	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)
Stage 4	2 (8.3)	0 (0)	1 (16.7)	0 (0)	1 (16.7)
MDS-UPDRS III total score at Day -1 (when using regular medication)					
Median (range)	33 (13-76)	30 (15-38)	36 (19-73)	30 (22-50)	32 (13-76)
Concomitant PD medication (n (%))					
Levodopa-containing agents	23 (95.8)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)
Dopamine agonists	16 (66.7)	5 (83.3)	5 (83.3)	2 (33.3)	4 (66.7)
COMT inhibitors	7 (29.2)	3 (50.0)	2 (33.3)	2 (33.3)	0 (0)
MAO-B inhibitors	3 (12.5)	2 (33.3)	1 (16.7)	0 (0)	0 (0)
Amantadine	4 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	0 (0)

In part C, when the pharmacodynamics population differed from the pharmacokinetics/safety population in age, BMI, sex, and/or race, information is provided for both; remaining variables are presented for the pharmacodynamics population only.
a. Information given for pharmacodynamics analysis population. / b. Information given for pharmacokinetics and safety analysis population. / c. North African.
BMI, body mass index; MMSE, Mini Mental State Examination; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease, COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase B.

TABLE 2 Summary of the number of TEAEs and the number and percentage of participants (n (%)) with any, mild, moderate and severe TEAEs and with a specific TEAE as indicated per treatment group and study part.

	PART A Crossover study in HVs		PART B SAD study in HVs			PART C SAD study in PD patients			
	2 mg sc apo (N=8)	1 mg AZ-009 (N=8)	2 mg AZ-009 (N=6)	3 mg AZ-009 (N=6)	Placebo (N=4)	2 mg AZ-009 (N=7)	3 mg AZ-009 (N=6)	4 mg AZ-009 (N=6)	Placebo (N=6)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
#TEAEs[a]	43	35	13	43	0	23	24	24	10
Any TEAEs	8 (100.0)	7 (87.5)	6 (100.0)	6 (100.0)	-	6 (85.7)	5 (83.3)	6 (100.0)	5 (83.3)
Mild TEAEs	7 (87.5)	7 (87.5)	5 (83.3)	6 (100.0)	-	6 (85.7)	5 (83.3)	6 (100.0)	4 (66.7)
Moderate TEAEs	8 (100.0)	5 (62.5)	3 (50.0)	5 (83.3)	-	3 (42.9)	1 (16.7)	2 (33.3)	1 (16.7)
Severe TEAEs	-	-	-	-	-	-	1 (16.7)	-	-
Most common TEAEs[b]									
Lacrimation increased	-	-	1 (16.7)	2 (33.3)	-	1 (14.3)	-	1 (16.7)	-
Nausea	6 (75.0)	5 (62.5)	1 (16.7)	5 (83.3)	-	1 (14.3)	1 (16.7)	2 (33.3)	1 (16.7)
Vomiting	4 (50.0)	1 (12.5)	-	1 (16.7)	-	-	-	-	-
Throat irritation	-	-	1 (16.7)	2 (33.3)	-	2 (28.6)	2 (33.3)	5 (83.3)	-
Fatigue	2 (25.0)	1 (12.5)	1 (16.7)	-	-	1 (14.3)	2 (33.3)	-	1 (16.7)
Feeling hot	3 (37.5)	2 (25.0)	-	1 (16.7)	-	1 (14.3)	2 (33.3)	-	-
Sluggishness	1 (12.5)	1 (12.5)	-	-	-	-	-	-	-
Dizziness	3 (37.5)	2 (25.0)	-	2 (33.3)	-	1 (14.3)	1 (16.7)	1 (16.7)	-
Headache	3 (37.5)	4 (50.0)	-	-	-	-	1 (16.7)	-	-
Orthostatic hypotension									
- Asymptomatic	1 (12.5)	-	-	-	-	2 (28.6)	2 (33.3)	2 (33.3)	4 (66.7)
- Symptomatic	2 (25.0)	-	-	4 (66.7)	-	1 (14.3)	-	-	-
Dizziness postural[c]	2 (25.0)	3 (37.5)	-	1 (16.7)	-	1 (14.3)	1 (16.7)	1 (16.7)	-
Increased PD symptoms	-	-	-	-	-	2 (28.6)	-	2 (33.3)	2 (33.3)
Presyncope	5 (62.5)	3 (37.5)	-	3 (50.0)	-	2 (28.6)	-	1 (16.7)	-
Somnolence	5 (62.5)	3 (37.5)	3 (50.0)	5 (83.3)	-	2 (28.6)	1 (16.7)	1 (16.7)	-
Syncope	1 (12.5)	1 (12.5)	-	-		-	1 (16.7)	-	-
Time perception altered	1 (12.5)	2 (25.0)	-	2 (33.3)	-	-	1 (16.7)	-	-
Yawning	-	1 (12.5)	2 (33.3)	4 (66.7)	-	2 (28.6)	2 (33.3)	1 (16.7)	-

a. Not expressed as n (%). This parameter describes the total number of TEAEs reported, and hence is unitless. / b. TEAEs reported by at least two (part A/B) or three (part C) of the apomorphine-treated participants. / c. Dizziness on standing but no significant blood pressure decline measured at scheduled standing blood pressure measurement.
TEAE, treatment-emergent adverse event; sc apo, subcutaneous apomorphine; HV, healthy volunteer; SAD, single ascending dose; PD, Parkinson's disease.

FIGURE 1 Mean (standard deviation) apomorphine concentration time profiles after single-dose administrations of 1 mg AZ-009 and 2 mg subcutaneous (sc) apomorphine on semilogarithmic scale to healthy volunteers up to 8 hours (A) and 1 hour (B) postdose.

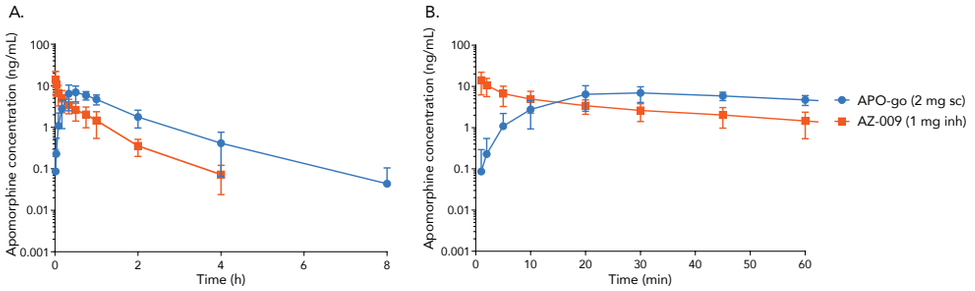


FIGURE 2 Mean (standard deviation) apomorphine concentration time profiles after single-dose administrations of 2 or 3 mg AZ-009 to healthy volunteers (part B) (A) and 2, 3, or 4 mg AZ-009 to patients with PD (part C) (B) on a semilogarithmic scale.

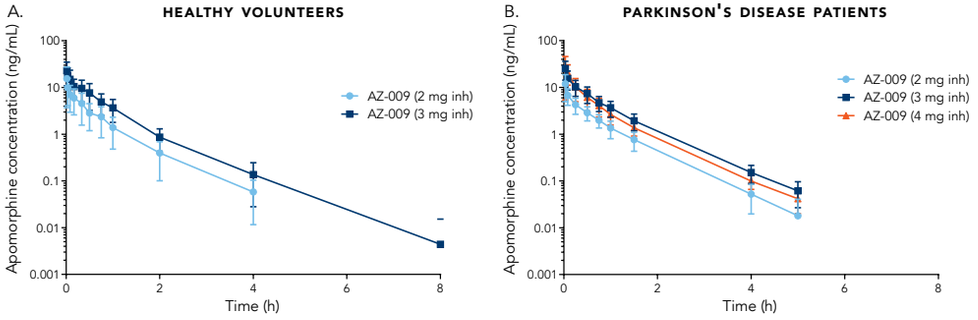
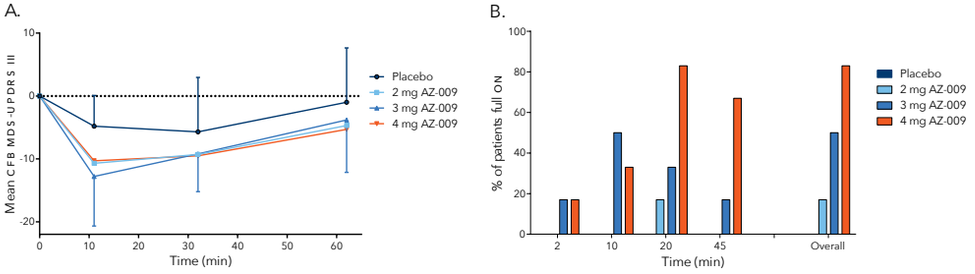


FIGURE 3 Mean change from baseline (CFB) Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III total score with standard deviation (A) and percentage (%) of patients achieving a full *ON* response (B) after the indicated treatment in patients with PD during an induced *OFF* state.



SUPPLEMENTARY MATERIAL

SUPPLEMENTAL TABLE 1 Pharmacokinetic parameters of apomorphine after single-dose administrations of 1 mg AZ-009 inhalation and 2 mg subcutaneous injection to healthy volunteers.

	2 mg sc apomorphine (N=8)	1 mg AZ-009 (N=8)
T_{max} (min)		
Median (range)	30 (20-60)	1 (1-2)
C_{max} (ng/mL)		
Mean (SD)	8.6 (3.1)	14.3 (7.7)
Median (range)	6.8 (5.2-12.9)	14.5 (3.7-23.7)
$AUC_{0\text{-}inf}$ (h·ng/ml)		
Mean (SD)	11.4 (2.6)	4.9 (2.3)
Median (range)	11.8 (7.6-14.6)	4.9 (2.3-9.1)
$T_{½}$ (min)		
Mean (SD)	55 (22)	39 (7)
Median (range)	49 (33-95)	39 (25-48)

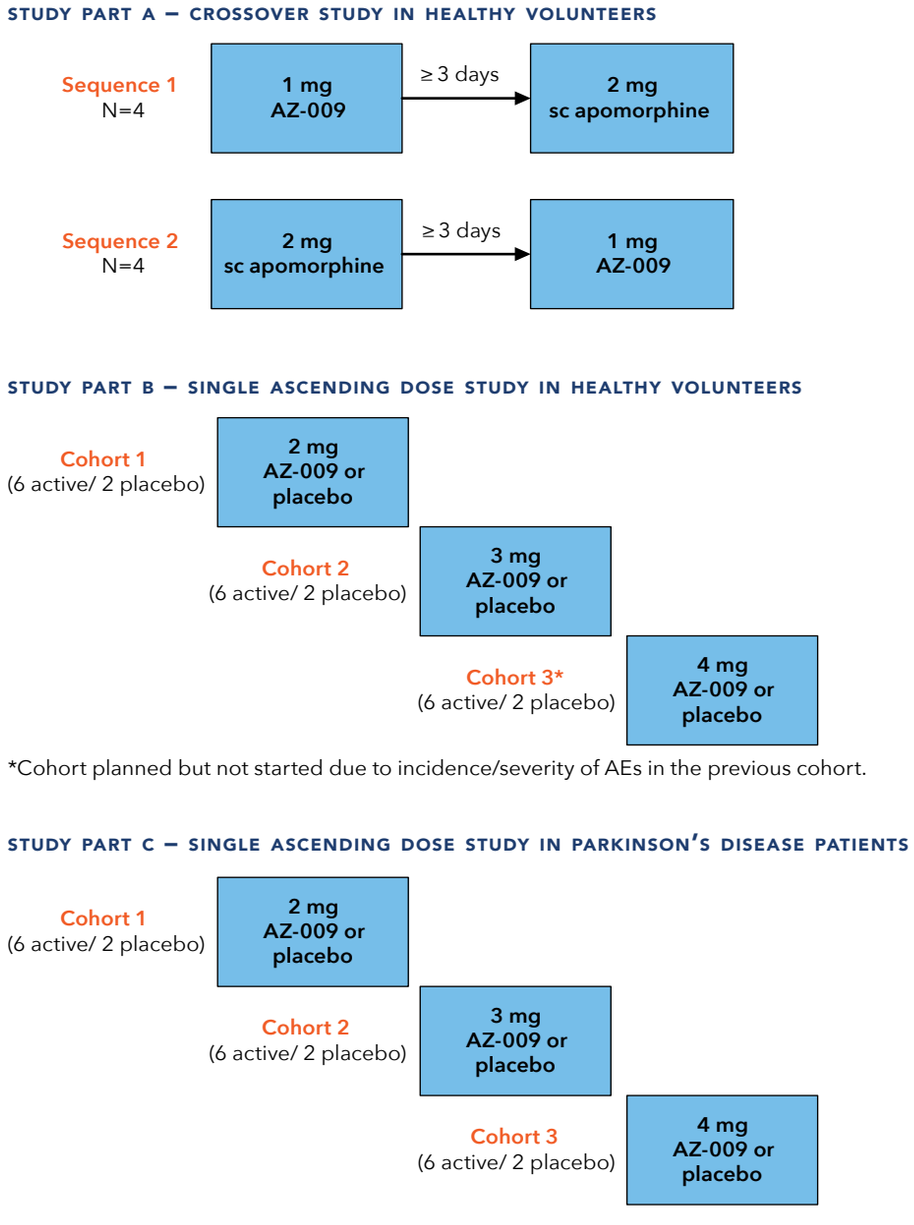
T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; SD, standard deviation; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from zero to infinity; $T_{½}$, apparent terminal elimination half-life; sc, subcutaneous.

SUPPLEMENTAL TABLE 2 **Pharmacokinetic parameters of apomorphine after single-dose administrations of 2 and 3 mg AZ-009 to healthy volunteers (part B) and 2, 3, and 4 mg AZ-009 to Parkinson's disease patients (part C).**

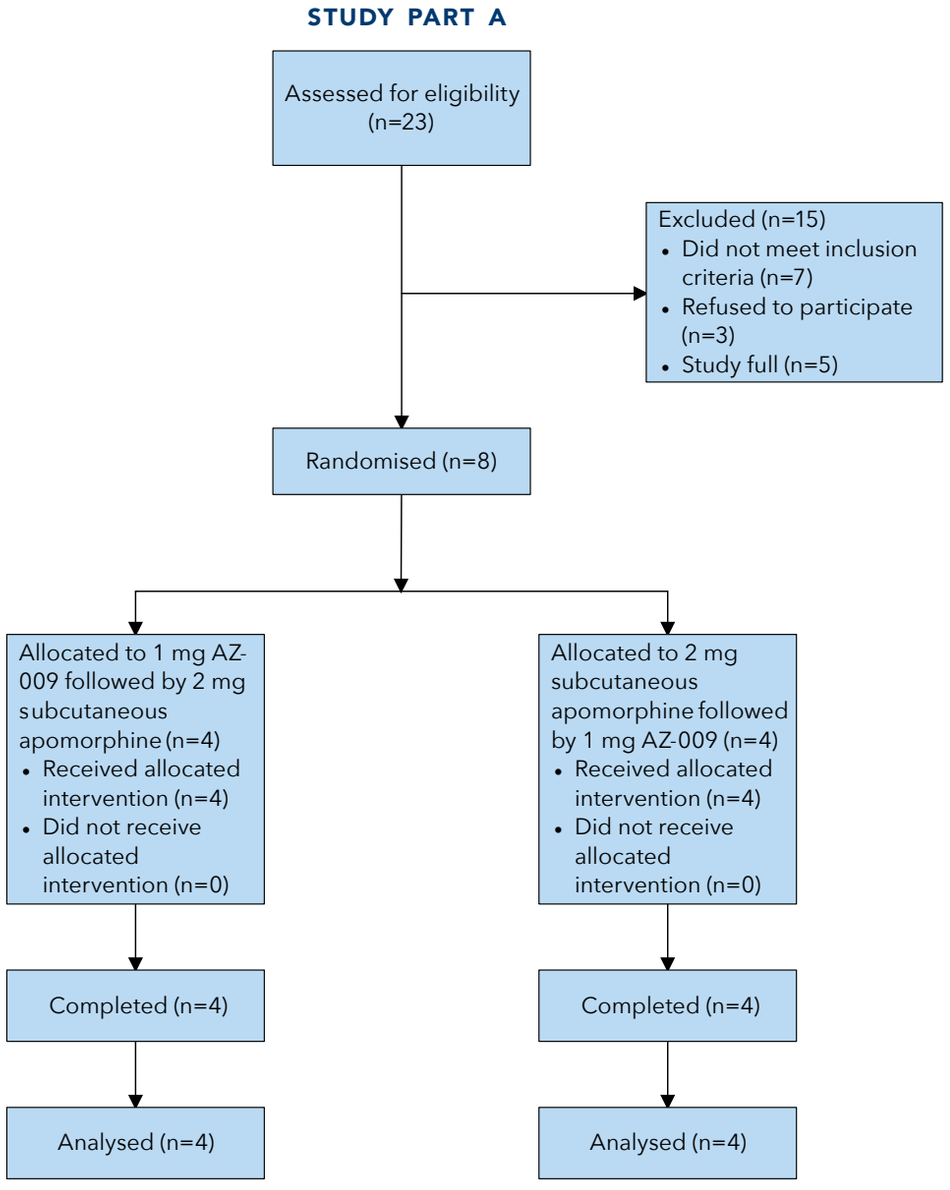
	Healthy volunteers (PART B)		Parkinson's disease patients (PART C)		
	2 mg AZ-009 (N=6)	3 mg AZ-009 (N=6)	2 mg AZ-009 (N=7)	3 mg AZ-009 (N=6)	4 mg AZ-009 (N=6)
T_{max} (min)					
Median (range)	1 (1-10)	1 (1-5)	2 (2-6)	2 (2-2)	3 (2-5)
C_{max} (ng/mL)					
Mean (SD)	16.2 (11.1)	25.0 (9.5)	12.0 (6.8)	25.3 (11.0)	26.5 (16.6)
Median (range)	15.2 (1.3-29.3)	26.6 (11.0-38.2)	10.4 (4.4-22.7)	29.4 (6.0-36.7)	23.6 (10.3-54.2)
AUC_{0-inf} (h·ng/mL)					
Mean (SD)	5.3 (3.1)	11.8 (5.4)	5.1 (1.5)	12.6 (4.5)	11.3 (5.1)
Median (range)	5.3 (0.7-9.9)	12.7 (2.5-17.6)	5.0 (3.3-7.1)	14.3 (3.7-15.6)	10.3 (6.5-20.6)
$T_{½}$ (min)					
Mean (SD)	38 (4)	40 (15)	38 (10)	42 (3)	40 (5)
Median (range)	39 (32-42)	35 (28-68)	38 (20-50)	42 (38-45)	39 (34-48)

T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; SD, standard deviation; AUC_{0-inf}, area under the plasma concentration-time curve from zero to infinity; $T_{½}$, apparent terminal elimination half-life.

SUPPLEMENTAL FIGURE 1 **Overview of study designs.**

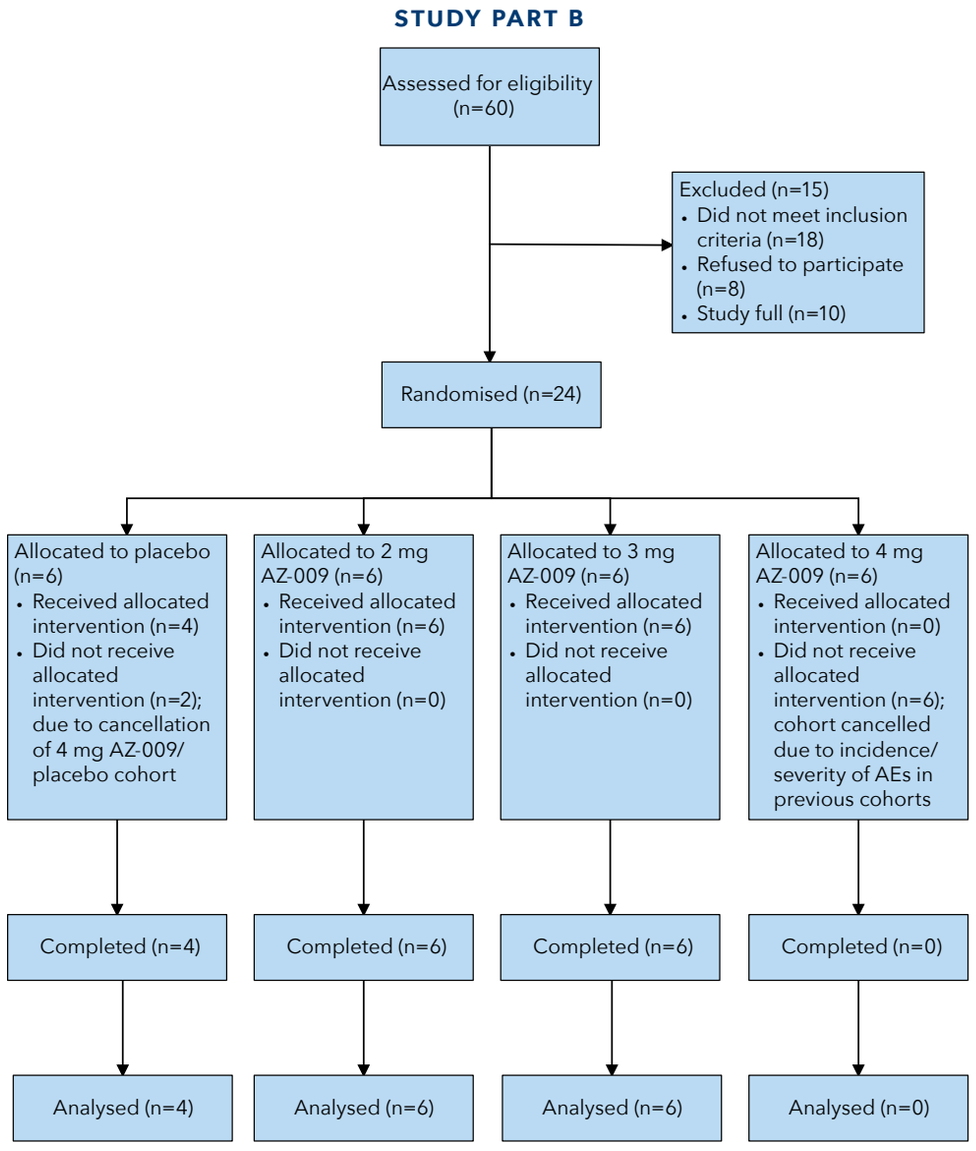


SUPPLEMENTAL FIGURE 2 CONSORT flow diagram for study part A.



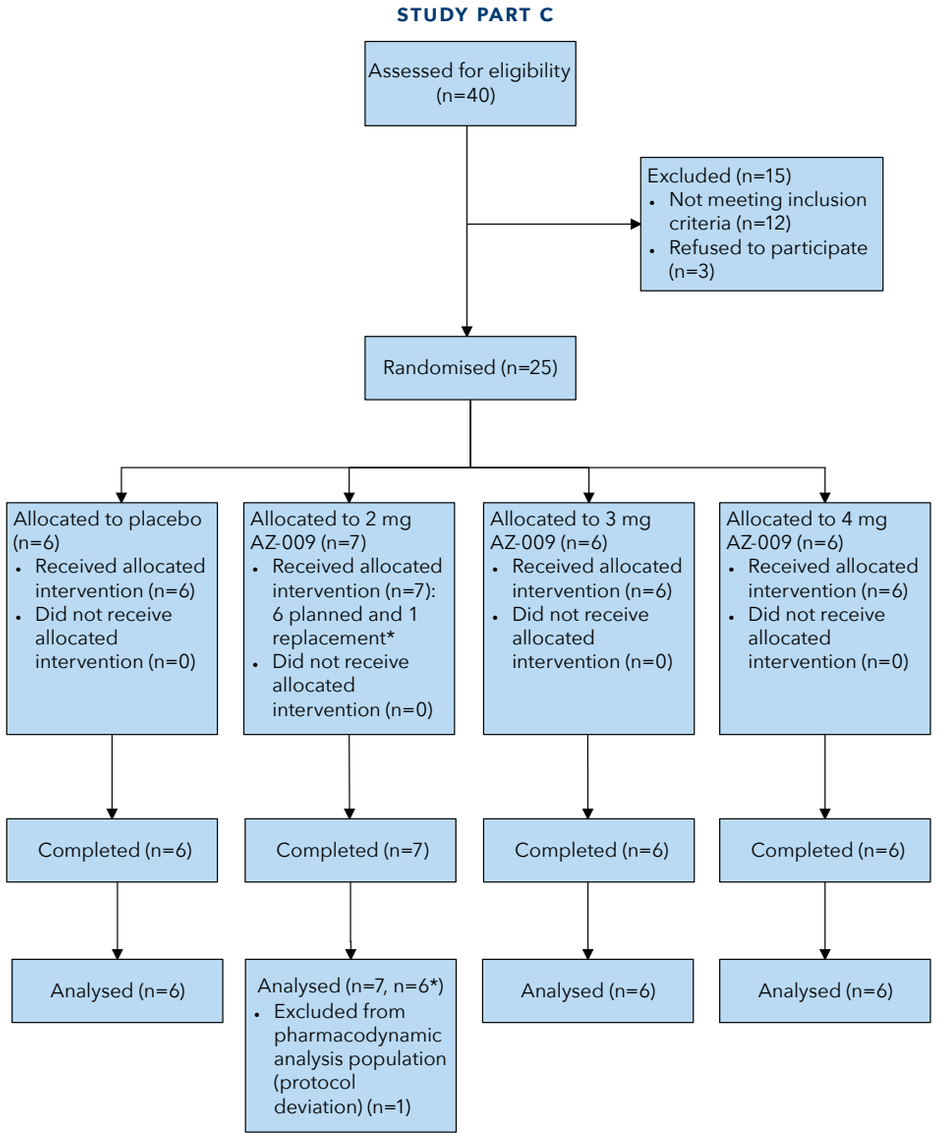
CONSORT, Consolidated Standards of Reporting Trials.

SUPPLEMENTAL FIGURE 3 CONSORT flow diagram for study part B.



CONSORT, Consolidated Standards of Reporting Trials.

SUPPLEMENTAL FIGURE 4 CONSORT flow diagram for study part C.



** A patient in the 2 mg AZ-009 group was replaced due to a protocol deviation (patient confessed post-dose that pramipexole was taken prior to dosing with the study drug). The patient was excluded from the pharmacodynamic analysis population (N=6) but not from the safety and PK analysis population (N=7).*
CONSORT, Consolidated Standards of Reporting Trials.

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