Safety and pharmacokinetics of multiple dosing with inhalable apomorphine (AZ-009), and its efficacy in a randomized crossover study in Parkinson's disease patients

Thijssen, E.; Heijer, J.M. den; Puibert, D.; Brummelen, E.M.J. van; Naranda, T.; Groeneveld, G.J.

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Safety and pharmacokinetics of multiple dosing with inhalable apomorphine (AZ-009), and its efficacy in a randomized crossover study in Parkinson's disease patients

Eva Thijssen [a,b], Jonas M. den Heijer [a,b], David Puibert [c], Emilie M.J. van Brummelen [a], Tatjana Naranda [d], Geert Jan Groeneveld [a,b,*]

[a] Centre for Human Drug Research (CHDR), Zernikedreef 8, 2333 CL, Leiden, Netherlands
[b] Leiden University Medical Centre (LUMC), Albinusdreef 2, 2333 ZA, Leiden, Netherlands
[c] Ferrer HealthTech, Diagonal 549, 08029, Barcelona, Spain
[d] Alexza Pharmaceuticals, 2091 Stierlin Court, Mountain View, CA, 94043, USA

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ABSTRACT

Introduction: Apomorphine is used to treat OFF periods in Parkinson's disease (PD) patients. AZ-009 is a novel apomorphine formulation that delivers a thermally-generated aerosol to the deep lung via inhalation with a single breath.

Methods: Part A was a randomized, placebo-controlled, double-blind study investigating the safety and pharmacokinetics of multiple ascending doses of AZ-009. PD patients (n = 24) received placebo or 2, 3 or 4 mg AZ-009 once daily for 5 days, followed by three times daily for 2 days with 2 h between doses. Part B was a double-blind crossover study in 8 PD patients who experience OFF periods. During an OFF state, patients received 4 mg AZ-009 and placebo on two consecutive days in a randomized order. MDS-UPDRS III and ON/OFF state were assessed pre- and post-dose.

Results: Three times daily dosing with 2, 3 and 4 mg AZ-009 was relatively well tolerated with no apparent accumulation or changes in safety profile. Mild and transient throat irritation and cough were reported most often. AZ-009 was rapidly absorbed with median T_{max} between 1 and 2 min. When corrected for placebo response, the maximum effect of 4 mg AZ-009 based on MDS-UPDRS III scores was observed at 10 and 30 min post-dose with mean (SD) reductions of 6.8 (9.4) and 6.1 (9.1) points respectively. Whereas 0% of patients turned ON after placebo, 50% turned ON 10 min after 4 mg AZ-009 treatment.

Conclusion: AZ-009 is rapidly systemically absorbed and safe to dose three times daily. AZ-009 could provide a faster-acting and easier to use formulation than currently available therapies.

1. Introduction

Parkinson's disease (PD) patients can begin to experience motor and/or non-motor fluctuations within a few years of disease onset [1,2]. Fluctuating symptoms impact activities of daily living and worsen quality of life [3].

When motor fluctuations persist despite optimized oral levodopa therapy, other treatment options can be sought or added. First-line treatments are usually oral or transdermal drugs, such as dopamine agonists and enzyme inhibitors that prolong the effect of levodopa, i.e. COMT and MAO-B inhibitors. When the above interventions are insufficiently effective, advanced treatment options are available, such as intermittent or continuous subcutaneous apomorphine administration, continuous percutaneous infusion of levodopa-carbidopa intestinal gel and deep brain stimulation (DBS) surgery [4]. For relief of sudden and intermittent OFF periods, subcutaneous apomorphine injections have long been the only treatment option. Its onset of action has been reported between 5 and 15 min [5–7], with maximum motor improvements as assessed by part III of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) after 20–40 min [6,8,9]. Despite its efficacy, the use of intermittent injections is sometimes limited by injection site reactions, pain and difficulty self-administering

* Corresponding author. Centre for Human Drug Research, Zernikedreef 8, 2333 CL, Leiden, the Netherlands.
E-mail address: ggroeneveld@chdr.nl (G.J. Groeneveld).

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the injection during an OFF period [10]. With the FDA approval of inhalable levodopa (2018) and sublingual apomorphine (2020), the treatment options for on-demand therapy of OFF periods have increased [11]. Inhalable levodopa and sublingual apomorphine have an initial onset of effect at 10 and 15 min respectively, and show maximum MDS-UPDRS III improvements at 30–60 and 60 min respectively [12–14]. Both are considered less invasive treatment options than subcutaneous apomorphine injections. Inhalation of apomorphine could be another user-friendly alternative with potentially a faster action than already available therapies.

AZ-009 is a breath-actuated, oral inhalation device using the Staccato technology [15,16]. Inhalation leads to the thermal generation of fine apomorphine aerosol particles that are appropriate for rapid deep lung delivery and subsequent systemic exposure. The aim of this study was to assess the safety and pharmacokinetics (PK) of multiple (daily) dosing with 2, 3 and 4 mg AZ-009 in PD patients. Patients received AZ-009 or placebo once daily for 5 days, followed by three times daily for 2 days. Moreover, efficacy of AZ-009 relative to placebo was evaluated in PD patients during an induced OFF state in a separate crossover design study.

2. Methods

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study was registered in ClinicalTrials.gov (NCT04157933) and approval was obtained by the Independent Ethics Committee of Foundation Beoordeling Ethiek Biomedisch Onderzoek (BEBO) (Assen, The Netherlands). All patients provided written informed consent prior to their participation. The study was conducted at the Centre for Human Drug Research (CHDR) (Leiden, the Netherlands) between September 2019 and March 2020.

2.1. Study design

The study was composed of two parts: part A and B. Part A was a randomized, placebo-controlled, double-blind study investigating multiple ascending doses (MAD) of AZ-009 (2, 3 and 4 mg). Patients were dosed once daily for 5 days, followed by three times daily for 2 days with 2 h between doses. Each cohort was composed of 8 PD patients (6 active: 2 placebo). This 6:2 ratio was not based on formal sample size calculations, but is common for phase I studies for an initial evaluation of safety and PK. Before commencing to the next cohort, safety data were evaluated. Part B was a randomized, double-blind, placebo-controlled crossover study in 8 PD patients who experience OFF periods. Patients received 4 mg AZ-009 and placebo on Day 1 and 2 in a randomized order during an OFF state. OFF was induced by overnight medication withdrawal. No formal sample size calculation was performed for part B due to its exploratory nature.

The study was composed of a screening visit, pretreatment with 20 mg domperidone three times daily from 2 days prior to dosing until last dose, 4 visits of 1 day each followed by 1 visit of 3 days or if preferred by the patient 1 visit of 7 days (part A) or 1 visit of 3 days (part B) at the clinical research unit, and a follow-up telephone call.

2.2. Patients

In both study parts, non-smoking PD patients between 30 and 85 years with a body mass index (BMI) of 18–32 kg m^{-2} were eligible for participation. Patients in part A had to be classified as Hoehn and Yahr stage I-IV in the ON state, and patients in part B as stage I-III in the ON state and experiencing motor fluctuations with recognizable OFF periods. Main exclusion criteria were use of $5HT_3$ antagonists, use of apomorphine (historical use was allowed), systolic blood pressure (BP) $<$ 100 mmHg at screening or baseline, symptomatic clinically relevant and medically uncontrolled orthostatic hypotension, history of long QT syndrome and/or a QTcF of $>$450 ms (male) or $>$470 ms (female), history of clinically significant pulmonary (e.g. asthma, COPD) conditions, previous significant complication from oral dopamine agonist therapy including hospitalization, hallucinations, or any other clinically relevant neuropsychiatric adverse event (AE). In addition, in part B, a MMSE score $<$18 rendered a patient ineligible.

2.3. Investigational product

AZ-009/Staccato apomorphine was administered as a single nominal dose of 1 or 2 mg apomorphine hydrochloride per inhalation device. Doses of 3 mg were achieved by 3 inhalations of 1 mg, and doses of 4 mg by 2 inhalations of 2 mg. Matching placebo was identical to AZ-009 but contained no apomorphine. Devices were packaged in heat-sealed multilaminate pouches to protect apomorphine from light and moisture. Devices were marked with patient and visit number to maintain the blind. The device manufacturer was Alexza Pharmaceuticals, Inc. (Mountain View, CA, USA). Instructions to the participant were to first exhale, then inhale through the mouthpiece with a steady deep breath, and finally to hold the breath for as long as possible for up to 10 s.

The device makes use of the Staccato technology [15,16], which is already FDA and EMA approved for the administration of loxapine [17–19]. The device is breath-actuated, a single breath through the device leads to rapid heating ($<$0.5s) of a metal substrate coated with a thin film of excipient-free apomorphine. As a result pure drug vapor is formed that rapidly cools and condenses into aerosol particles appropriate for deep lung delivery.

2.4. Assessments

2.4.1. Safety

Safety was evaluated by AE monitoring (classified by Medical Dictionary for Regulatory Activities (MedDRA) version 21.1), and assessment of ECGs, vital signs, physical examinations, and laboratory measurements. A drop in systolic BP $\geq$ 20 mmHg and/or a drop in diastolic BP $\geq$ 10 mmHg upon standing was classified as orthostatic hypotension. QTcF was reviewed after domperidone pretreatment and prior to first dose, as well as prior to each subsequent dose.

2.4.2. Pharmacokinetics

Single dose PK has been described previously [20] and therefore we only report PK of the MAD study here. AZ-009's PK profile was evaluated in the MAD study (part A) on Day 1, 3 and 5 (once-daily dosing), and on Day 7 (three times daily dosing; dosing at t = 0, t = 120 and t = 240 min). Blood samples were collected pre-dose and at 1-, 2-, 5-, 10-, 20-, 30-, 45-, 60-, 120- and 240-min post-dose on Day 1, 3 and 5. On Day 7, samples were taken pre-dose and at 2, 5, 10, 30, 60 and 120 min after each dose, where the 120-min sample was taken just prior to the next dose. Apomorphine plasma concentrations were determined by a liquid chromatography–tandem mass spectrometry method (LC-MS/MS) validated for a range of 0.0263–13.1 ng mL^{-1}. Concentration-time data were analyzed by non-compartmental methods in Phoenix™ WinNonlin® (Version 8.1, Certara, L.P.). Actual sample times were used in the analysis. Maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), apparent terminal elimination half-life ($T_{1/2}$) and area under the concentration-time curve from zero to infinity (AUC_{inf}) values were derived.

Inter- and intra-individual variability (CV%) of C_{max} and AUC_{inf} were calculated for each dose group using data of Day 1, 3 and 5. For C_{max}, also data of the first dose of Day 7 were used. The variance of the natural logarithm of C_{max} and AUC_{inf} was computed for each day and for each patient, these were averaged to obtain inter- and intra-variance, and subsequently used to calculate the CV% as follows: 100*sqrt(exp(variance)-1).

2.4.3. Efficacy

In study part B, efficacy was assessed by the motor examination part of the MDS-UPDRS, i.e., part III. The same trained physician assessed a patient throughout the study. In one patient this was not possible, but all pre-and post-dose assessments of visit 1 were performed by the same physician, and all assessments of visit 2 were performed by another physician. MDS-UPDRS III was performed on Day −1, the day before first dosing and when patients were still using their own anti-Parkinson medication, and on Day 1 and Day 2 pre-dose and 10-, 30- and 60-min post-dose. Mean change from baseline (CFB) MDS-UPDRS III total score, with and without correction for placebo, was calculated and presented graphically.

In addition, a patient's disease state was assessed by a physician pre-dose and 10-, 20- and 45-min post-dose on Day 1 and 2. Percentage of patients being ON (with or without dyskinesia), partial ON and OFF at each time point were presented in a stacked bar graph. Partial ON was defined as a partial response, i.e. the patient showed some improvement after drug administration but did not reach a full ON state.

2.5. Statistical analysis

Only descriptive statistics were conducted.

3. Results

3.1. Demographics

Demographic characteristics of the patients enrolled in both studies are described in Table 1. In the MAD study (part A), 26 PD patients were enrolled of which 2 patients discontinued early. One patient withdrew consent after the second dosing day and one was discontinued early due to an AE (atrial fibrillation). In total, 24 patients completed the full study. In the crossover study (part B), 9 PD patients were enrolled of which 1 patient only completed the first (placebo) dosing day. In total, 8 patients completed the full study. Refer to Supplemental Figs. 1 and 2 for CONSORT flow diagrams providing an overview of number of participants screened, randomized, completed, and analyzed per study part.

3.2. Pharmacokinetics of multiple (daily) dosing

AZ-009 was rapidly absorbed with median T_{max} between 1 and 2 min during once-daily dosing in PD patients (Fig. 1). Descriptive statistics of the PK parameters are summarized in Supplemental Table 1. Mean $T_{1/2}$ ranged from 38 to 44 min. There was no carryover of apomorphine across study days. Mean C_{max} increased with an increase in dose on Day 1, 3 and 5. On Day 1 and 3, mean AUC_{inf} increased from 2 to 3 mg, but was comparable between 3 and 4 mg AZ-009. On Day 5, mean AUC_{inf} increased with dose from 2 to 3–4 mg AZ-009.

On Day 6 and 7, AZ-009 was administered three times daily with 2 h between doses. PK sampling took place on Day 7 (Fig. 1). Descriptive statistics are summarized in Supplemental Table 2. After the first administration on Day 7, mean C_{max} increased with an increase in dose. After the second and third administration, mean C_{max} increased from 2 to 3 mg, but not from 3 to 4 mg AZ-009. Mean C_{max} after each 2 mg dose, and after each 4 mg dose (at t = 0, t = 2 and t = 4 h) was comparable. In contrast, there was an increase in concentration with multiple dosing in the 3 mg cohort, where mean C_{max} after the second and third dose was higher compared to C_{max} after the first dose. Following three times daily dosing, mean AUC_{inf} increased with dose from 2 to 3 mg, but was comparable after 3 and 4 mg AZ-009. Mean $T_{1/2}$ ranged from 34 to 38 min.

Inter-individual variability (CV%) of C_{max} was 160%, 152% and 72%, and of AUC_{inf} 118%, 81% and 43% in the 2, 3 and 4 mg AZ-009 group respectively. Intra-individual variability (CV%) of C_{max} was 77%, 59% and 57%, and of AUC_{inf} 32%, 32% and 42% in the 2, 3 and 4 mg AZ-009 group respectively.

3.3. Safety of multiple (daily) dosing

In the AZ-009-treated groups more treatment-emergent AEs (TEAEs) (68–87) were reported than in the placebo group (12) (Table 2). The most frequently reported TEAEs by patients receiving 2, 3 or 4 mg AZ-009 were cough and throat irritation (incidence between 71.4 and 100%) and fatigue (50.0–57.1%). Most TEAEs were mild and all were transient. The number and severity of TEAEs was not affected when dosed three times daily as opposed to once daily. One TEAE, classified as

Table 1
Demographics.

	MAD study					Crossover study
	All patients (N = 26)	2 mg AZ-009 (N = 6)	3 mg AZ-009 (N = 7)	4 mg AZ-009 (N = 7)	Placebo (N = 6)	All patients (N = 9)
Age (years)						
Mean (SD)	64.2 (9.2)	63.2 (11.1)	64.6 (11.2)	60.9 (8.3)	68.7 (4.6)	63.3 (6.3)
Median (range)	65 (48–83)	61 (51–81)	60 (50–83)	65 (48–68)	69 (62–75)	66 (55–70)
BMI (kg m^{-2})						
Mean (SD)	25.5 (2.7)	25.9 (2.0)	25.0 (2.8)	25.6 (3.1)	25.8 (3.4)	23.2 (3.4)
Median (range)	25 (21–31)	26 (23–29)	24 (23–30)	24 (22–31)	26 (21–30)	23 (19–31)
Sex (n/n (%/%))						
Female/Male	7/19 (27/73)	2/4 (33/67)	3/4 (43/57)	1/6 (14/86)	1/5 (17/83)	5/4 (56/44)
Race (n (%))						
Asian	1 (4)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)
Black or African American	1 (4)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)
White	24 (92)	6 (100)	7 (100)	6 (86)	5 (83)	9 (100)
Hoehn and Yahr stage (n (%))[a]						
Stage 1	5 (19)	2 (33)	1 (14)	2 (29)	0 (0)	0 (0)
Stage 2	4 (15)	2 (33)	2 (29)	0 (0)	0 (0)	8 (89)
Stage 3	9 (35)	1 (17)	0 (0)	4 (57)	4 (67)	1 (11)
Stage 4	8 (31)	1 (17)	4 (57)	1 (14)	2 (33)	0 (0)
Concomitant PD medication (n (%))						
Levodopa-containing agent	25 (96)	5 (83)	7 (100)	7 (100)	6 (100)	9 (100)
Dopamine agonist	20 (78)	5 (83)	5 (71)	6 (86)	4 (67)	4 (44)
COMT inhibitor	3 (12)	0 (0)	1 (14)	1 (14)	1 (17)	3 (33)
MAO-B inhibitor	2 (8)	0 (0)	0 (0)	1 (14)	1 (17)	0 (0)
Amantadine	5 (19)	1 (17)	3 (43)	0 (0)	1 (17)	1 (11)
Deep brain stimulator	5 (19)	2 (33)	2 (29)	1 (14)	0 (0)	1 (11)

[a] Hoehn and Yahr stage defined at screening (MAD study) or at the day prior to dosing while still on regular anti-Parkinson medication (crossover study).

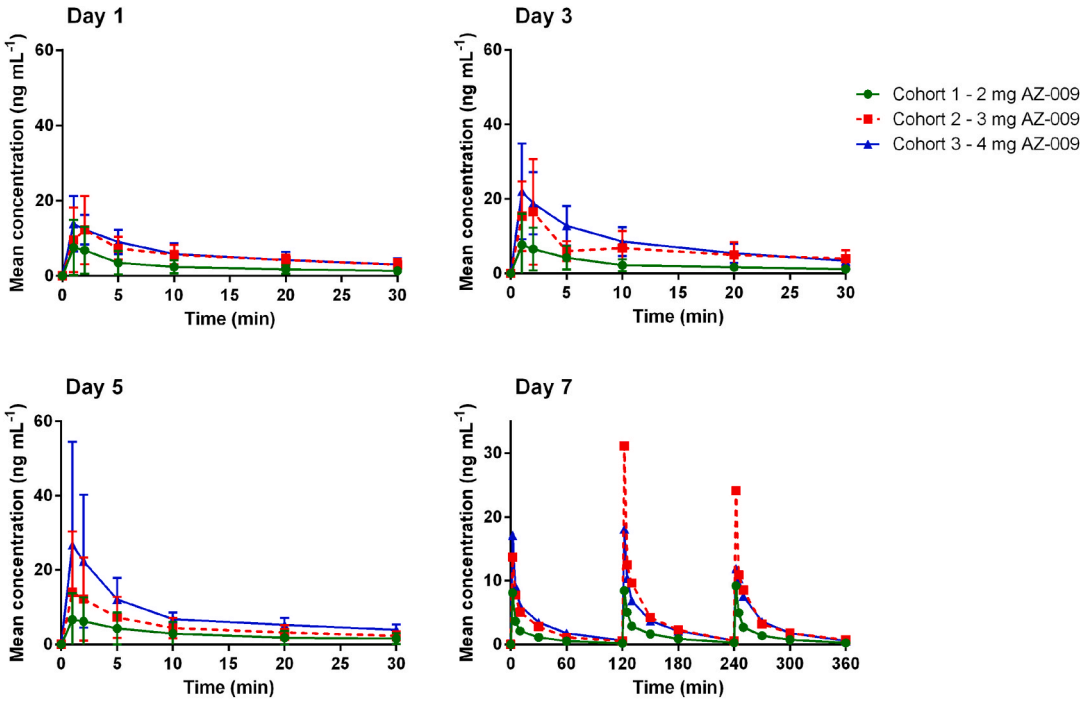

Fig. 1. Mean (SD) apomorphine concentration-time profiles of the MAD study (part A) on a linear scale depicting Day 1, 3 and 5 after once daily dosing, and Day 7 after three times daily dosing (every 2 h) with 2, 3 or 4 mg AZ-009. For Day 7, only the mean concentration-time profile is shown for legibility.

Table 2
Summary of the number of treatment-emergent adverse events (TEAEs) and the number and percentage of participants (n (%)) with any, mild, moderate and severe TEAE and with a specific TEAE as indicated per treatment group in the MAD study (part A).

	2 mg AZ-009 (N = 6)	3 mg AZ-009 (N = 7)	4 mg AZ-009 (N = 7)	Placebo (N = 6)
	n (%)	n (%)	n (%)	n (%)
#TEAEs [a]	87	68	69	12
Any TEAEs	6 (100)	7 (100)	7 (100)	5 (83.3)
Mild TEAEs	6 (100)	7 (100)	7 (100)	5 (83.3)
Moderate TEAEs	1 (17)	0 (0)	1 (14)	0 (0)
Severe TEAEs	0 (0)	0 (0)	0 (0)	0 (0)
Most common TEAEs [b]				
Throat irritation	6 (100.0)	7 (100.0)	5 (71.4)	1 (16.7)
Cough	6 (100.0)	6 (85.7)	5 (71.4)	0 (0)
Fatigue	3 (50.0)	4 (57.1)	4 (57.1)	2 (33.3)
Headache	1 (16.7)	4 (57.1)	2 (28.6)	0 (0)
Yawning	2 (33.3)	2 (28.6)	2 (28.6)	0 (0)
Dizziness	1 (16.7)	1 (14.3)	1 (14.3)	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 ≥ 15% of participants.

possibly related to AZ-009, led to early discontinuation of a patient. The patient developed first onset atrial fibrillation as detected on ECG approximately 15 min after the first 4 mg AZ-009 inhalation. Approximately 4 h post-dose, the patient spontaneously converted back to sinus rhythm. One serious AE (SAE) was reported in a patient receiving 4 mg AZ-009. The SAE, tooth abscess, was assessed as being unrelated to the study drug. No consistent or clinically relevant QTcF prolongation was reported.

3.4. Efficacy in a crossover study with placebo

When patients received placebo, they showed a mean deterioration over time, i.e., an increase of mean MDS-UPDRS III (SD) compared to baseline of 1.6 (7.4) points, 2.8 (9.0) points and 4.1 (9.8) points at 10-, 30- and 60-min post-dose respectively (Fig. 2A). In contrast, 4 mg AZ-009 led to a mean reduction in MDS-UPDRS III total score at 10- and 30-min post-dose of 4.8 (5.7) and 6.3 (6.0) points respectively (Fig. 2A). At 60-min post-dose, the patients treated with 4 mg AZ-009 no longer showed an improvement compared to baseline (−0.7 (10.6) points) (Fig. 2A). At 10 min post-dose, MDS-UPDRS III could only be assessed in half of the AZ-009-treated patients, since known AEs for apomorphine, i.e., presyncope and hypotension, prevented its conduct. At 30 min post-dose, the patients treated with AZ-009 all recovered sufficiently to perform the assessment again, except for one patient (n = 7). When corrected for individual placebo response, the maximum effect of 4 mg AZ-009 was observed at 10 min post-dose with a mean (placebo-corrected) reduction (SD) of 6.8 (9.4) points (Fig. 2B). This effect was comparable to the effect observed at 30 min post-dose, i.e. −6.1 (9.1) points.

A physician evaluated whether a patient was ON, partial ON or remained OFF pre-dose and 10-, 20- and 45-min post-dose (Fig. 2C). Prior to dosing all patients were OFF. None of the placebo-treated patients achieved a full ON response, but 22% did turn partial ON from 10 min post-dose onwards. In contrast, at 10 min post-dose, 25% of the patients receiving 4 mg AZ-009 transitioned to a partial ON state and 50% of patients to a full ON state. At 45 min post-dose, there were no AZ-009-treated patients still in an OFF state (12% (1 patient) was not evaluable).

4. Discussion

Here, we report the first safety and PK data of multiple dosing with AZ-009, a new apomorphine inhalation device to treat OFF periods in PD patients. AZ-009 was rapidly absorbed with median T_{max} between 1 and 2 min, which is considerably faster than currently available on-demand therapies for OFF periods. For subcutaneous and sublingual

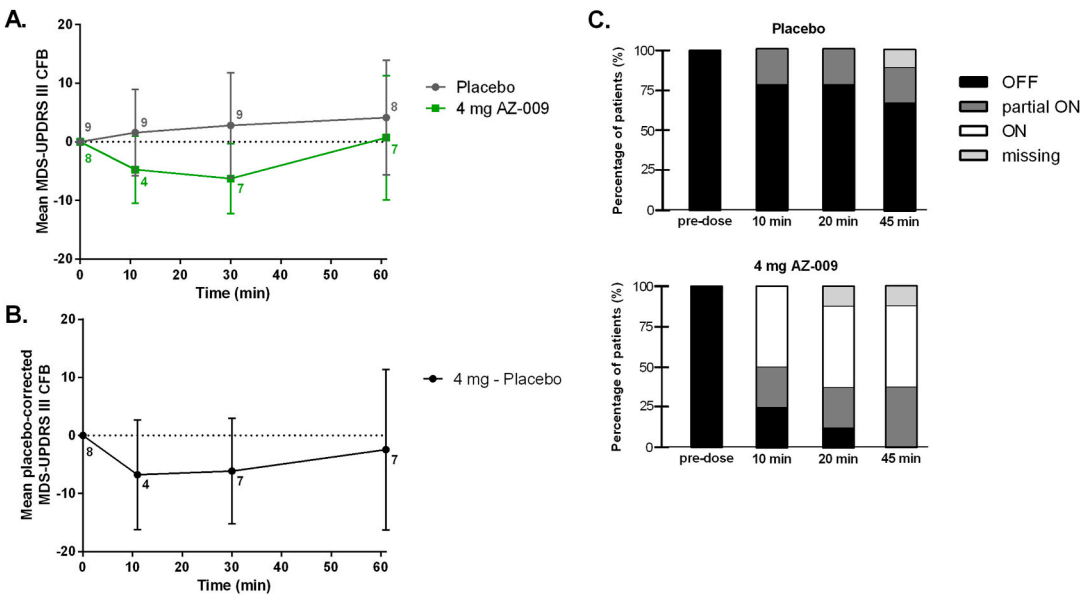

Fig. 2. Parkinson's disease patients received placebo and 4 mg AZ-009 (crossover) during an induced OFF state. Efficacy is shown as mean change from baseline (CFB) MDS-UPDRS III total score with standard deviation (SD) without (Fig. 2A) and with individual correction for placebo response (Fig. 2B). Number of patients assessed at each time point are indicated in the graph. Fig. 2C presents the percentage (%) of patients that are OFF, partial ON and full ON at the indicated time points.

apomorphine, median T_{max} differs between studies, but usually ranges between 15-23 and 38–51 min respectively [21–23]. For inhaled levodopa, a median T_{max} of 15 min has been reported [24,25]. Another inhalable apomorphine formulation (VR040) shows more comparable PK, i.e. T_{max} ranging between 1 and 7 min [26,27]. Since group sizes in this study were relatively small and inter-individual variability relatively high, no conclusions could be drawn on dose proportionality over the dose range 2–4 mg. Future larger trials are needed for this assessment. Inter-individual variability in exposure parameters (CV%) ranged between 72 and 160% for C_{max}, and 43–118% for AUC_{inf}, with a trend towards decreased variation with an increase in AZ-009 dose. This is higher than reported for subcutaneous apomorphine injections where CV% for C_{max} has been reported between 20 and 71% and for AUC_{inf} between 20 and 32% [21,22,28–30]. For sublingual apomorphine, also relatively high inter-individual variability has been reported, i.e. 73% for C_{max} and 68% for AUC_{inf} in a study with larger sample size (n = 19 and n = 16 for C_{max} and AUC_{inf} respectively) than in this study [21]. As expected, intra-individual variability was lower than inter-individual variability.

5-Day once-daily dosing, followed by 2 days three times daily dosing (every 2 h) with AZ-009 at doses of 2, 3 and 4 mg was relatively well tolerated by PD patients. Most patients reported mild throat irritation and cough directly after inhalation which usually resolved within minutes. No apparent accumulation or changes in safety profile during three times daily dosing were observed. Mean $T_{1/2}$ of apomorphine ranged between 34 and 44 min, meaning that after 2 h on average 3 half-lives have passed. Therefore, theoretically some accumulation will occur, but with the observed variability and the sample size used, it is not surprising that this accumulation was not objectified.

One patient developed first onset atrial fibrillation as detected on ECG approximately 15 min after the first 4 mg AZ-009 inhalation. The patient was asymptomatic and spontaneously converted back to sinus rhythm approximately 4 h post-dose. The patient was a 65-year old male, diagnosed with Parkinson's disease for 14 years and treated with levodopa/benserazide 100/25 mg 7 times daily and pramipexole 1.5 mg once daily. In addition, the patient had a DBS for 7 years. The patient had no history of cardiovascular disease. In literature, a few cases of atrial fibrillation in PD patients after apomorphine administration have been described [31–33]. It has been hypothesized that atrial fibrillation is caused by an imbalance of autonomic tone with predominance of vagal activity [31,34,35].

Usability of this specific Staccato device has not yet been adequately investigated in the PD population. Future studies will investigate the usability of the commercial device by PD patients while OFF. Previous research with a dry powder inhaler has shown that most PD patients after adequate training are able to handle a dry powder inhaler, have sufficiently high inspiratory flow rates and are able to hold their breath for up to 5 s after inhalation [36]. Another study evaluated the ability of PD patients to correctly open a pouch wherein the inhaler was stored and to prepare the inhaler for use [37]. The study showed that 58% of PD patients in an OFF state were able to open pouch 1 as intended (via the tear notch), whereas this was much higher (75%) for pouch 2, indicating that pouch 2 would be better suited for use in a PD population. This underlines that evaluation of device packaging, preparation and use in the target population is crucial. Encouraging results on inhalation device use have been reported in a phase IIb study with inhalable dry powder levodopa: patients were able to prepare and self-administer the treatment, even though some indicated concerns about inhaler system use during telephone contact (7% placebo, 14% levodopa) [12]. Similarly, in a phase IIa study with inhalable apomorphine (VR040), 23 out of 24 patients were able to load and use the device correctly [26].

When corrected for individual placebo response, the maximum effect of 4 mg AZ-009 was observed at 10 and 30 min post-dose with mean (SD) reductions of 6.8 (9.4) and 6.1 (9.1) points at 10 and 30 min respectively. This is in line with results from a phase I, parallel design study, where 4 mg AZ-009 led to reduction of 10.3 (3.7) points and placebo to 4.8 (4.9) points at 10 min post-dose [20]. In contrast, subcutaneous apomorphine reaches its maximum MDS-UPDRS III response after 20–40 min [6,8,9], sublingual apomorphine after 60 min [14], and inhalable levodopa after 30–60 min [12,13]. The time to maximum effect of AZ-009 resembles that reported for another apomorphine inhaler (VR040) under clinical investigation, i.e. maximum MDS-UPDRS III response at 20 min post-dose [27,38]. Mean MDS-UPDRS III differences between apomorphine dry powder inhalation and placebo in these studies were 8.4 (95% CI 1.2–15.5) and 11.6 (95% CI 2.3–20.9). Both were ascending dose titration studies which might explain the larger effects found. The observed effect in the present study is expected to be

an underestimation since the administered dose was not optimized per individual after up titration, as is done in the clinical setting for subcutaneous and sublingual apomorphine. This likely led to suboptimal dosing, where for some the dose was too high and therefore resulted in AEs (known for apomorphine) preventing the conduct of MDS-UPDRS III, and for others might have been too low to reach optimal efficacy. Therefore, in clinical practice, AZ-009 would have to be initiated at a lower dose and titrated to a dose that balances efficacy and side effects. Future studies should address AZ-009's efficacy when administered at a patient's optimal dose. Nevertheless, this study clearly showed a conversion from OFF to partial or full ON after 4 mg AZ-009 treatment. At 10 min post-dose, 75% of patients turned partial or full ON, and at 45 min no patients (1 patient not evaluable) were left in an OFF state. In contrast, none of the placebo-treated patients achieved a full ON response, even though 22% did turn partial ON from 10 min post-dose onwards.

With AZ-009's median T_{max} of 1–2 min and expected maximum MDS-UPDRS III improvements at 10 and 30 min post-dose, this inhalable apomorphine formulation could provide an easy and fast-acting formulation for rescue of OFF periods.

Declaration of competing interest

Alexza Pharmaceuticals Inc. is a wholly-owned indirect subsidiary of Ferrer. Alexza Pharmaceuticals Inc. owns the rights to AZ-009 and funded this research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.02.014.

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