Clinical pharmacology studies investigating novel formulations of dopaminergic drugs

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CHAPTER 4

Clinical trial evaluating apomorphine oromucosal solution in Parkinson's disease patients

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ABSTRACT

Background Apomorphine is used to treat *OFF* episodes in patients with Parkinson's disease (PD). Unlike subcutaneous injections, administration of an oromucosal solution is a non-invasive, easy route of administration.

Objectives To assess the safety, tolerability, pharmacokinetics (PK), and dose proportionality of a novel apomorphine hydrochloride (HCl) oromucosal solution, as well as its relative bioavailability to subcutaneous apomorphine injection and apomorphine sublingual film.

Methods In part A of the study, 12 patients with PD received 2 mg oromucosal apomorphine (4% weight/volume) and 2 mg subcutaneous apomorphine in a randomized order, followed by 4 and 8 mg oromucosal apomorphine. In part B of the study, 13 patients with PD received 7 mg oromucosal apomorphine (7% weight/volume) and 30 mg sublingual apomorphine in a randomized order, followed by 14 mg oromucosal apomorphine. Washout between dose administrations in both study parts was at least 2 days. Safety, tolerability and PK were assessed pre- and post-dose.

Results Oromucosal apomorphine was generally well tolerated. Observed side effects were typical for apomorphine administration and included asymptomatic orthostatic hypotension, yawning, fatigue and somnolence. Oromucosal apomorphine exposure increased with dose, although less than dose proportional. The mean (SD) maximum exposure reached with 14 mg oromucosal apomorphine was 753.0 (298.6) ng·min/mL for $AUC_{0\text{-}inf}$ and 8.0 (3.3) ng/mL for C_{max}. This was comparable to exposure reached after 2 mg subcutaneous apomorphine and approximately half of the exposure observed with 30 mg sublingual apomorphine.

Conclusions Apomorphine oromucosal solution was generally well tolerated and resulted in clinically relevant plasma concentrations in PD patients.

INTRODUCTION

Apomorphine is a non-ergoline dopamine agonist. Subcutaneous injections of apomorphine are indicated for the acute, intermittent treatment of "*OFF*" episodes in patients with Parkinson's disease (PD). In general, apomorphine treatment is initiated when patients suffer from *OFF* periods despite optimized oral/transdermal dopaminergic treatment. Notwithstanding its well-known safety and efficacy profile, apomorphine is currently underutilized.[1] This is likely because the available licensed products are mostly administered as subcutaneous injections (APOKYN® and APO-go®), presenting several impracticalities. These include the challenge of self-administering injections during an *OFF* state, along with the potential for needle phobia. Another delivery mode of apomorphine is the sublingual film (KYNMOBI®), which can cause oropharyngeal side effects and takes longer to reach maximum plasma concentrations than subcutaneous administration.[2] The administration of both formulations requires good finger dexterity and muscle coordination, which is often impaired in patients with PD.[3]

Over the years, other non-invasive apomorphine administration routes have been investigated, such as oral, transdermal, intranasal, and inhaled routes.[4-8] Due to the extensive first-pass metabolism of apomorphine, oral administration results in too low bioavailability (< 4%) to allow for clinically relevant apomorphine exposures.[9] Furthermore, due to the delayed absorption from the gastrointestinal tract, oral administration is not suited for use as rescue medication. Transdermal delivery has not been developed so far, although administration via an iontophoretic patch showed promising results and the use of lipophilic di-ester prodrugs may hold promise for the future.[7,10] Intranasal administration, although efficacious, results in nasal irritation.[6] Lastly, inhaled apomorphine looks promising with a rapid absorption and onset of effect.[4,5,8] However, collection of long-term safety data of pulmonary exposure to apomorphine is essential to confirm suitability for long-term use.

To overcome the disadvantages associated with the available licensed and experimental apomorphine formulations, a highly concentrated apomorphine hydrochloride (HCl) oromucosal solution

(APORON) has been developed which is intended for self-administration by the patient, using an easy-to-operate device. This formulation is designed to enable an easy buccal delivery of efficacious doses of oromucosal apomorphine without local side effects. With the recent global discontinuation of the sublingual apomorphine film, the development of a novel non-invasive apomorphine administration has become even more relevant.

In this two-part crossover study, the safety, tolerability, pharmacokinetics (PK), and dose proportionality of the novel apomorphine HCl oromucosal solution was assessed, as well as its relative bioavailability compared to subcutaneous apomorphine injection and apomorphine sublingual film. In the first study part, three ascending doses of apomorphine oromucosal solution (4% weight/volume (w/v)) and a single dose of 2 mg subcutaneous apomorphine were evaluated. In the second study part, a higher percentage (7% w/v) apomorphine oromucosal solution was evaluated at two dose levels, and compared with apomorphine sublingual film.

METHODS

The study is registered in the Netherlands Trial Register (Trial NL9540), and was conducted at the Centre for Human Drug Research (Leiden, the Netherlands) between May and August 2021 (study part A), and between June and August 2022 (study part B). The study was conducted in accordance with Good Clinical Practice guidelines and approved by the Independent Ethics Committee of Foundation Beoordeling Ethiek Biomedisch Onderzoek. Prior to any study-related activity, all participants provided written informed consent.

Study design

This study consisted of two sub-studies, part A and part B. For a depiction of their study design, refer to Figure 1. Part A of the study was an open-label, two-way crossover study in 12 patients with Parkinson's disease to characterize and compare the PK of apomorphine after oromucosal and subcutaneous administration, and to assess the dose proportionality of oromucosal apomorphine. Patients received 2 mg oromucosal and 2 mg subcutaneous apomorphine during two different visits in a randomized order, followed by 4 mg and lastly 8 mg oromucosal apomorphine (the highest dose (6 or 8 mg depending on emerging data) was chosen after review of PK and safety/tolerability data of at least 6 patients). The washout period between dose administrations was a minimum of 3 days and a maximum of 3 weeks. A sample size of 12 was chosen since this could confirm dose proportionality of oromucosal apomorphine with 80% power (one-sided alpha=0.05), assuming an intra-individual CV of 20%.[11] A one-sided alpha was chosen since higher dose levels (i.e., volume) are expected to increase the chance of swallowing and thereby result in lower oromucosal absorption and exposure.

Safety, tolerability and PK data were examined during a dose level evaluation meeting before proceeding to study part B. Based on the oromucosal apomorphine exposure observed in part A, a percentage of 7% apomorphine w/v in the oromucosal solution was selected for use in part B.

Part B was an open-label comparative PK study evaluating the more concentrated oromucosal apomorphine solution and a sublingual apomorphine film in 12 patients with Parkinson's disease. Patients first received 7 mg oromucosal and 30 mg sublingual apomorphine in a randomized order, followed by 14 mg oromucosal apomorphine. There was a 2-day washout period between dose administrations. No formal sample size calculation was performed due to the exploratory nature of the study.

Participation in the trial consisted of a screening visit, pretreatment with 20 mg domperidone three times daily[12,13] from 2 days prior to dosing until last dose (max. 9 consecutive days in part A, and max. 7 days in part B), followed by 4 visits (part A) or 3 visits (part B) of 1 day each to the clinical research unit, and a follow-up phone call.

Participants

In study parts A and B, PD patients aged 30-85 years with Hoehn and Yahr stage I-IV and with clear, self-described motor fluctuations as assessed by the 9-symptom Wearing-off Questionnaire,[14] were eligi-

ble for participation. Patients were excluded if they had symptomatic clinically relevant and/or medically uncontrolled orthostatic hypotension, a history of long QT syndrome and/or a QTcF of >450 ms (male) or >470 ms (female), or aphthous ulcers or mouth sores within 6 months prior to the screening visit.

Investigational drugs

Apomorphine HCl oromucosal solutions (APORON®, Supplemental Figure 1) containing 2.0 mg (4% weight/volume) or 3.5 mg (7% weight/volume) apomorphine HCl per 50 µL-spray pump actuation, were administered to alternating buccal cheeks. Varying the number of spray device actuations allowed for the administration of doses ranging from 2 mg to 14 mg apomorphine HCl. APORON is a non-aqueous solution containing apomorphine HCl, one or more organic solvents of which at least 50% is propylene glycol, and one or more antioxidants (US patent 9,737,526 B2). The 4% solution was used in part A, and the 7% in part B of the study.

In part A, patients received 2, 4 and 8 mg oromucosal apomorphine HCl. Patients were instructed to swallow their saliva prior to the buccal administration of the oromucosal solution, and to not swallow or speak for 2 minutes after dosing. In part B, patients received 7 and 14 mg respectively. Patients were given the same instructions as in part A, with the exception that they should not swallow or speak for 3 minutes after dosing (increased to 3 minutes to be consistent with the instructions in the patient leaflet of apomorphine sublingual film). When 14 mg was administered, the first 7 mg was administered at t=0, and the second 7 mg at t=4 minutes.

In part A, 2 mg subcutaneous apomorphine HCl (APO-go® 10 mg/ml solution for injection) was injected in the abdomen as active comparator. In part B, 30 mg apomorphine HCl sublingual film (KYNMOBI®) was used as active comparator. When receiving sublingual film, patients were instructed to moisten their mouth just prior to administration and to not swallow or speak for 3 minutes after administration. If not fully dissolved after 3 minutes, patients were instructed to not swallow or speak for 1 additional minute.

In clinical practice, subcutaneous apomorphine is initiated at a dose of 2 mg. Hence, 2 mg was considered a safe dose for study part A.

As apomorphine oromucosal solution was expected to have lower bioavailability than subcutaneous apomorphine, 2 mg apomorphine oromucosal solution was considered a safe starting dose. Furthermore, in clinical practice, sublingual apomorphine is initiated at 10 mg and titrated to a dose that is both safe and efficacious (max. 30 mg). In study part B, a dose of 30 mg was considered to be safe, since it was expected to result in a similar or lower maximum plasma concentration (C_{max}) than 2 mg subcutaneous apomorphine in part A (which was well tolerated).[2,15,16]

Safety

Patients were medically screened to confirm their eligibility. Screening included an assessment of the patient's medical history, concomitant medications, electrocardiogram (ECG), vital signs, routine laboratory assessments, and physical and neurological examination. QTcF was 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 adverse events (AEs) (classified by Medical Dictionary for Regulatory Activities (MedDRA) version 25.0), vital signs, ECGs, physical and neurological examination, and clinical laboratory tests. The buccal mucosa was assessed by a physician pre-dose, 1 hour post-dose and prior to leaving the clinical research unit. For AE reporting, a decrease in systolic blood pressure (BP) of ≥20 mmHg or in diastolic BP of ≥10 mmHg upon standing accompanied by dizziness was documented as symptomatic orthostatic hypotension. A decrease in BP of ≥20 mmHg or in diastolic BP of ≥10 mmHg upon standing without dizziness was documented as asymptomatic orthostatic hypotension. If a patient reported dizziness upon standing without the abovementioned drop in BP, this was documented as postural dizziness.

Pharmacokinetics

In part A, whole blood was collected pre-dose and 4, 8, 12, 16, 20, 24, 28, 32, 40, 50, 60, 90, 120 and 240 min post-dose. In part B, collection took place pre-dose and 5, 10, 15, 20, 25, 35, 40, 45, 50, 55, 60, 75,

90, 120, 240 and 360 min post-dose. A longer sampling duration was used in part B to ensure that the apparent terminal half-life ($t_{½}$), and hence the exposure as area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$), could be calculated for all patients since the $t_{½}$ of sublingual and oromucosal apomorphine was expected to be longer than for subcutaneous apomorphine.[2,15] Ascorbic acid was added to the plasma samples prior to freezing to prevent apomorphine oxidation.

Apomorphine was extracted from plasma by Liquid Liquid Extraction, after which apomorphine was quantified using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method. Non-compartmental analysis was used to calculate apomorphine's C_{max}, time to C_{max} (T_{max}), $t_{½}$ and $AUC_{0\text{-}inf}$. Dose proportionality of oromucosal apomorphine over the dose range 2-8 mg in part A was tested by regression of Ln(dose) on Ln($AUC_{0\text{-}inf}$) and Ln(C_{max}) with subject as random factor where the 90% confidence interval (CI) of the slope of the regression had to fall between 1+ (Ln(0.8)/Ln(dose ratio)) < slope < 1 + (Ln(1.25)/Ln(dose ratio)) to conclude for dose proportionality.[17] In part B, dose proportionality between 7 and 14 mg oromucosal apomorphine was tested for dose-normalized Ln(C_{max}) and Ln($AUC_{0\text{-}inf}$) with an ANOVA with treatment as fixed factor and subject as random factor. The 90% CI of the ratio of the geometric means between the two dose levels needed to be within 0.8 and 1.25 to conclude dose proportionality.[17] Bioequivalence between sublingual and oromucosal apomorphine was tested for Ln(C_{max}) and Ln($AUC_{0\text{-}inf}$) with a linear model analysis with treatment as fixed factor and subject as random factor. The 90% CI of the ratio between the two treatments needed to be within 0.8 and 1.25 to be bioequivalent. In this analysis, only patients receiving both treatments were included.

RESULTS

Demographics

Table 1 provides an overview of baseline patient characteristics, and Supplemental Figure 2 and 3 for CONSORT flow diagrams of both study parts. In part A, 12 PD patients were enrolled in the study, of whom 10 patients completed the full study. Two patients were discontinued early, i.e., after the second and third dosing day, due to adverse events that were considered unrelated to apomorphine (refer to Supplemental Figure 2). In part B, 12 PD patients completed the full study, and 1 patient completed only the first study visit. After this visit, the patient withdrew consent due to increased PD symptoms and fatigue. In part A, the majority of participants (83%) had Hoehn and Yahr stage I, 8% had stage II and 8% had stage III. In part B, 15% had stage I, 54% stage II and 31% stage III. No other differences in demographic and baseline characteristics were noted between participants in part A and B.

Pharmacokinetics

In part A, a single dose of subcutaneous apomorphine and three ascending doses of 4% apomorphine oromucosal solution were compared (Figure 2A, Table 2). Subcutaneous apomorphine was more readily available systemically than oromucosal apomorphine; the median T_{max} (range) was 19 (8-40) and 32 (16-120) minutes respectively. The ratio of the geometric least squares mean (90% CI) of 2 mg oromucosal to 2 mg subcutaneous apomorphine was 0.28 (0.24-0.33) for $AUC_{0\text{-}inf}$ and 0.20 (0.15-0.26) for C_{max}. Over the dose range 2-8 mg, oromucosal apomorphine exposure increased less than dose-proportionally (Figure 2C-D), resulting in 8 mg oromucosal apomorphine having a lower exposure than 2 mg subcutaneous apomorphine.

In part B, a 7% apomorphine oromucosal solution was compared to sublingual apomorphine (Figure 2B, Table 2). These administrations showed a similar PK profile with a median T_{max} (range) of 45 (15-75) minutes for sublingual, and 45 (25-77) minutes for oromucosal apomorphine (7 mg). Moreover, oromucosal apomorphine had a similar dose-normalized exposure as sublingual apomorphine (Figure 2C-D). The ratio of the geometric least squares mean (90% CI) of 7 mg oromucosal apomorphine to 30 mg sublingual apomorphine was 0.30 (0.25-0.36) for $AUC_{0\text{-}inf}$ and 0.28 (0.23-0.34) for C_{max}. The ratio of the geometric least squares mean (90% CI) of 14 mg oromucosal apomorphine to 30 mg sublingual apomorphine was 0.51 (0.45-0.57) for $AUC_{0\text{-}inf}$ and 0.52 (0.45-0.61)

for C_{max}. Oromucosal apomorphine exposure increased less than dose-proportionally from 7 to 14 mg for C_{max} and $AUC_{0\text{-}inf}$, while C_{max} showed a trend towards dose proportionality with a 90% CI of the geometric mean ratio of both dose levels of 0.77-1.12.

Safety and local tolerability

Oromucosal apomorphine administration was generally well tolerated with mostly mild and transient AEs (Table 3). The type of AEs that were reported were comparable with subcutaneous and sublingual apomorphine, and are typically associated with apomorphine administration. Asymptomatic orthostatic hypotension, yawning and fatigue and/or somnolence were most frequently reported. There was no clear dose-dependent or exposure-dependent increase in the incidence and severity of AEs. No oropharyngeal AEs were reported and no abnormalities of the buccal and sublingual mucosa were observed after the administration of oromucosal apomorphine for up to 3 treatment days and a single dose of 30 mg sublingual apomorphine.

Seven AEs that were moderate in severity were reported. In two subjects the AEs were considered possibly or probably related to apomorphine administration. One patient reported somnolence moderate in severity approximately 30 minutes after sublingual apomorphine administration that resolved spontaneously within 1.5 hours. Another patient reported postural dizziness and vomited repeatedly, starting 1.5 hours after 14 mg oromucosal apomorphine administration. In addition, the patient's 6 hours post-dose lab showed thrombocytopenia that was moderate in severity (pre-dose 219; 6 hours post-dose $136 \cdot 10^9$/L). Upon retest approximately 1 week later, the thrombocyte count had returned to normal. The patient had tolerated both 30 mg sublingual and 7 mg oromucosal apomorphine well except for some mild asymptomatic orthostatic hypotension and somnolence.

Almost all patients reported that the oromucosal solution had a bitter taste. Two patients also reported a slightly sweet taste on one occasion, and 4 patients reported a (bitter/)sour taste. Taste did not affect the patients' ability to follow the dosing instructions.

DISCUSSION

For over two decades, subcutaneous apomorphine injections and infusions have been used as an efficacious treatment for managing *OFF* episodes.[18,19] However, intermittent subcutaneous administration is still a suboptimal delivery route, especially since it requires a good dexterity, which is typically impaired during an *OFF* episode. Moreover, the need to self-administer injections in areas like the arms, legs and abdominal wall, all typically covered by clothing, makes the use of injections less practical in public settings. The buccal administration of the oromucosal apomorphine solution is expected to solve most of these impractical issues of apomorphine delivery.

After the buccal administration of oromucosal apomorphine, maximum plasma concentrations were observed between 32 and 53 minutes (median T_{max} over dose groups). The median T_{max} in study part A (32 minutes) was lower than in study part B (45 minutes (7 mg) and 53 minutes (14 mg)). This is likely a chance finding due to variability in PK, i.e. T_{max} in part A ranged from 16 to 120 minutes, and in part B from 25 to 82 minutes. The somewhat later T_{max} following 14 mg compared to 7 mg oromucosal apomorphine can be partly ascribed by the 14 mg dose being administered as 2x 7 mg at t=0 and t=4 minutes. T_{max} is calculated counting from the first dose administration. Sublingual apomorphine had a median T_{max} of 45 minutes, which was comparable to the T_{max} of oromucosal apomorphine. As expected, subcutaneous apomorphine was more readily absorbed with a median T_{max} of 19 minutes and had a higher bioavailability compared to oromucosal and sublingual apomorphine.[15,16] Moreover, as has also been described for sublingual apomorphine, oromucosal apomorphine exposure increased less than dose-proportionally.[16] This might be attributed to the fact that higher doses are administered as larger volumes. These volumes are closer to the volume that triggers a swallowing reflex,[20-22] and hence more of the drug might be swallowed prematurely at the higher oromucosal doses. Since apomorphine has a low oral bioavailability, swallowing may have significantly contributed to the lower bioavailability at higher doses.

Based on the observed bioavailability of oromucosal apomorphine in part A of the study, the formulation in part B was changed by increasing the apomorphine concentration from 4 to 7%. Moreover, patients in part B who received 4 spray pump actuations were given these as 2 actuations at t=0 and 2 actuations at t=4 minutes, as opposed to 4 consecutive spray pump actuations in part A. Figure 2 shows that the increased apomorphine concentration led to an increased apomorphine exposure in part B. Four spray pump actuations with the 7% oromucosal apomorphine formulation (14 mg) resulted in a comparable exposure as 2 mg subcutaneous apomorphine, and about half of the exposure to 30 mg sublingual apomorphine. The exposure to 30 mg sublingual apomorphine observed in this study was higher than reported in the literature.[15,16] However, the sample size of our study was relatively small and apomorphine exposure is known to be highly variable between patients receiving identical doses. Furthermore, sublingual apomorphine in our study was administered to a non-titrated patient population, whereas the literature reports patients being titrated to an effective and tolerable dose.[16] Therefore, titration can lead to enrichment of patients with lower PK exposure in the higher dose groups. This hypothesis is supported by a different dose-C_{max} relationship reported by Agbo et al. in titrated PD patients with *OFF* episodes versus untitrated healthy volunteers.[16] The titrated patient population had a lower regression coefficient (i.e., less steep dose-C_{max} relationship), and their exposure tended to plateau at higher doses. In our study, the C_{max} values of 30 mg sublingual apomorphine administered to untitrated patients followed the dose-C_{max} relationship described for untitrated healthy volunteers receiving 10 to 25 mg sublingual apomorphine.[16] This implies that PK exposure in healthy volunteers and untitrated PD patients is comparable, and differences reported between healthy volunteers and PD patients are likely the result of dose titration, but not pathophysiological differences.

The apomorphine concentration at which a patient shows clinical improvement is also subject to high inter-patient variability. However, a previous study in a small group of PD patients has reported a mean minimal effective concentration (MMEC) of 4.7 ng/mL.[23] Using this cut-off, 11 out of 12 PD patients treated with 14 mg oromucosal apomorphine reached plasma concentrations exceeding this MMEC. Moreover, 8 out of 12 patients remained above this MMEC for ≥40 minutes. Therefore, this study has provided clinically relevant plasma concentrations after the administration of 14 mg oromucosal apomorphine. The time to reach the MMEC varied between patients. For subcutaneous apomorphine it ranged between 8-20 minutes and for oromucosal apomorphine between 14-59 minutes. This indicates that not all patients using subcutaneous apomorphine will show a similar onset of efficacy with oromucosal apomorphine. The PK exposure of oromucosal apomorphine is comparable to the exposure of efficacious sublingual apomorphine doses as reported in literature.[24] Consequently, it is expected that the onset of efficacy of oromucosal apomorphine will be comparable to that of sublingual apomorphine in most patients.

In this two-part study, PD patients received oromucosal apomorphine solution in ascending doses up to 14 mg, and its safety was compared with subcutaneous and sublingual apomorphine. Oromucosal apomorphine up to 14 mg was generally well-tolerated with AEs comparable to those observed after single doses of apomorphine sublingual film and subcutaneous injection. All AEs that were considered at least possibly related to oromucosal apomorphine were mild in severity, with the exception of the observation of thrombocytopenia, postural dizziness, and vomiting which was reported by one patient in the 14 mg group. Nausea, vomiting and (postural) dizziness are known side effects of apomorphine.[18] For this reason, all patients were instructed to take an anti-emetic three-times daily from two days prior to dosing.

Apomorphine undergoes autooxidation in aqueous environments at neutral pH such as saliva.[25] This autooxidation process results in the formation of quinone derivatives and reactive oxygen species which have been associated with cytotoxicity.[26,27] Therefore, apomorphine that remains in the oropharyngeal space long enough to undergo autooxidation in the saliva, has the potential to induce oropharyngeal irritation via the formed apomorphine quinones. For apomorphine sublingual film, it is known that oropharyngeal AEs occur after repeated exposure. A phase 3 study with apomorphine sublingual film reported oropharyngeal AEs as the most common

AEs with an incidence of 31% for sublingual apomorphine compared to 7% in the placebo group. These oropharyngeal AEs led to treatment discontinuation in the 12-week maintenance phase in 17% of the patients in the sublingual apomorphine group compared to 2% in the placebo group.[28] The side effects of sublingual apomorphine are likely related to apomorphine particles in the dual layer film that can remain in the vallecula where they degrade into reactive oxygen species in the presence of saliva. For oromucosal apomorphine, it is hypothesized that degradation into reactive oxygen species in the oropharyngeal space is limited since the apomorphine is administered as a dissolved solution and will be swallowed together with the saliva thereby preventing prolonged presence in the oropharyngeal space. The current study did not show any oropharyngeal AEs, including buccal/sublingual mucosa abnormalities for both oromucosal apomorphine solutions (up to 14 mg/day) during up to three treatment days, nor for a single dose of 30 mg sublingual apomorphine. Further verification is needed to confirm the local tolerability of oromucosal apomorphine HCl during longer exposures.

In summary, the buccal administration of the novel oromucosal apomorphine solution evaluated in this two-part clinical study was generally well tolerated and resulted in clinically relevant plasma concentrations in PD patients. It is expected to offer a promising new administration route for the delivery of apomorphine. Due to the use of dissolved apomorphine, it is hypothesized to result in fewer oropharyngeal side effects than sublingual apomorphine. Moreover, oromucosal apomorphine solution administration will be an easier and more user-friendly way to administer apomorphine than the recently discontinued sublingual film and currently available subcutaneous injections.

TABLE 1 **Demographics of participants with Parkinson's disease in study parts A and B.**

Demographic variables	PART A (N=12)	PART B (N=13)[a]
Age (years)		
Median (range)	66 (48-79)	67 (55-79)
BMI (kg/m^2)		
Median (range)	26 (21-30)	26 (19-32)
Sex (n/n (%/%))		
Female/Male	5/7 (41.7/58.3)	4/9 (30.8/69.2)
Race (n (%))		
White	12 (100)	10 (76.9)
Asian	0 (0)	1 (7.7)
Mixed	0 (0)	2 (15.4)[b]
MMSE		
Median (range)	30 (27-30)	29 (25-30)
Hoehn and Yahr stage		
Stage 1	10 (83.3)	2 (15.4)
Stage 2	1 (8.3)	7 (53.8)
Stage 3	1 (8.3)	4 (30.8)
Stage 4	0 (0)	0 (0)
Concomitant PD medication (n (%))		
Levodopa-containing agents	12 (100.0)	13 (100.0)
Dopamine agonists	6 (50.0)	10 (76.9)
COMT inhibitors	3 (25.0)	1 (7.7)
MAO-B inhibitors	1 (8.3)	1 (7.7)
Amantadine	2 (16.7)	4 (30.8)
Other	2 (16.7)[c]	0 (0)

a. One drop-out after the first dosing (30 mg sublingual apomorphine); refer to Supplemental Figure 3 for a CONSORT flow diagram. / b. Mixed, i.e., White/Asian and White/African. / c. Trihexyfenidyl and glycopyrronium, both N=1.
BMI, body mass index; MMSE, Mini Mental State Examination; PD, Parkinson's disease, COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase B.

TABLE 2 **Pharmacokinetic parameters of apomorphine after 2 mg subcutaneous and 2, 4 and 8 mg oromucosal apomorphine administration (part A), and 30 mg sublingual and 7 and 14 mg oromucosal apomorphine administration (part B) to Parkinson's disease patients.**

	PART A				PART B		
	2 mg sc (N=12)	2 mg om (N=12)	4 mg om (N=11)	8 mg om (N=10)	30 mg sl (N=13)	7 mg om (N=12)	14 mg om[a] (N=12)
T_{max} (min)							
Median (range)	19 (8-40)	32 (16-60)	32 (24 -90)	32 (20-120)	45 (15-75)	45 (25-77)	53 (29-82)
C_{max} (ng/mL)							
Mean (SD)	10.5 (6.5)	2.0 (1.2)	3.3 (0.9)	4.3 (1.8)	15.5 (5.7)	4.5 (2.4)	8.0 (3.3)
Median (range)	9 (3-24)	2 (1-5)	3 (2-5)	4 (1-7)	15 (9-25)	5 (2 -10)	7 (3-14)
Geometric LSM ratio om/sc (part A) or om/sl (part B) (90% CI)		0.20 (0.15-0.26)	0.39 (0.30-0.49)	0.53 (0.42-0.66)		0.28 (0.23-0.34)	0.52 (0.45-0.61)
AUC_{0-inf} (min·ng/mL)							
Mean (SD)	617.8 (182.6)	178.3 (75.5)	303.4 (51.2)[b]	431.6 (116.5)[b]	1524.1 (533.2)	454.4 (174.0)	753.0 (298.6)
Median (range)	572 (296-892)	132 (116-316)	296 (225-390)[b]	384 (294-633)[b]	1546 (773-2573)	497 (177-703)	780 (302-1320)
Geometric LSM ratio om/sc (part A) or om/sl (part B) (90% CI)		0.28 (0.24-0.33)	0.53 (0.44-0.63)	0.75 (0.59-0.94)		0.30 (0.25-0.36)	0.51 (0.45-0.57)
$T_{½}$ (min)							
Mean (SD)	48 (7)	44 (6)	45 (4)[b]	47 (6)[b]	54 (8)	51 (7)	54 (7)
Median (range)	46 (39-60)	43 (38-57)	44 (39-54)[b]	48 (37-55)[b]	54 (45-67)	50 (43-63)	51 (45-65)

a. Administered as 2 spray pump actuations at t=0 and another 2 spray pump actuations at t=4 minutes. Calculations are done from t=0. / b. N=9 due to inability to calculate $T_{½}$ because of insufficient span ratio (i.e., time interval over which $T_{½}$ can be determined) (N=2), and due to one early discontinuation during the visit (N=1)
T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; SD, standard deviation; LSM, Least Squares Mean; om, oromucosal; sc, subcutaneous; sl, sublingual; CI, confidence interval; AUC_{0-inf}, area under the plasma concentration-time curve from zero to infinity; $T_{½}$, apparent terminal elimination half-life.

TABLE 3 **Summary of the number of AEs and the number and percentage of participants (n (%)) with any, mild, moderate and severe AE and with a specific AE as indicated per treatment group and study part.**

	PART A				PART B		
	2 mg sc (N=12)	2 mg om (N=12)	4 mg om (N=11)	8 mg om (N=10)	30 mg sl (N=13)	7 mg om (N=12)	14 mg om (N=12)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
#AEs[a]	19	12	14	14	28	27	24
Any AEs	12 (100.0)	8 (66.7)	10 (90.9)	9 (90.0)	11(84.6)	9 (75.0)	8 (66.7)
Mild AEs	11 (91.7)	8 (66.7)	9 (81.8)	9 (90.0)	11(84.6)	9 (75.0)	8 (66.7)
Moderate AEs	1 (8.3)	-	1 (9.1)	-	4 (30.8)	-	1 (8.3)
Severe AEs	-	-	-	-	-	-	-
Most common AEs[b]							
Nausea	-	-	-	-	1 (7.7)	1 (8.3)	2 (16.7)
Fatigue	3 (25.0)	1 (8.3)	3 (27.3)	2 (20.0)	4 (30.8)	1 (8.3)	1 (8.3)
Headache	1 (8.3)	1 (8.3)	1 (9.1)	-	2 (15.4)	3 (25.0)	1 (8.3)
Orthostatic hypotension · Asymptomatic · Symptomatic	7 (58.3) -	5 (41.7) 1 (8.3)	3 (27.3) -	3 (30.0) -	3 (23.1) -	6 (50.0) -	3 (25.0) -
Dizziness postural[c]	1 (8.3)	-	-	-	1 (7.7)	1 (8.3)	2 (16.7)
Increased Parkinson's disease symptoms	1 (8.3)	-	-	-	2 (15.4)	1 (8.3)	-
Dyskinesia	-	-	-	-	1 (7.7)	2 (16.7)	-
Somnolence	-	-	-	-	3 (23.1)	4 (33.3)	3 (25.0)
Yawning	4 (33.3)	2 (16.7)	5 (45.5)	8 (80.0)	4 (30.8)	3 (25.0)	3 (25.0)

a. Not expressed as n (%). This parameter describes the total number of AEs reported, and hence is unitless. /
b. AEs reported by ≥3 participants in part A or B. / c. Dizziness upon standing but no significant blood pressure drop measured at scheduled standing blood pressure measurement.
AE, adverse event; sc, subcutaneous apomorphine; om, oromucosal apomorphine; sl, sublingual apomorphine.

FIGURE 1 Overview of study designs of part A and B.

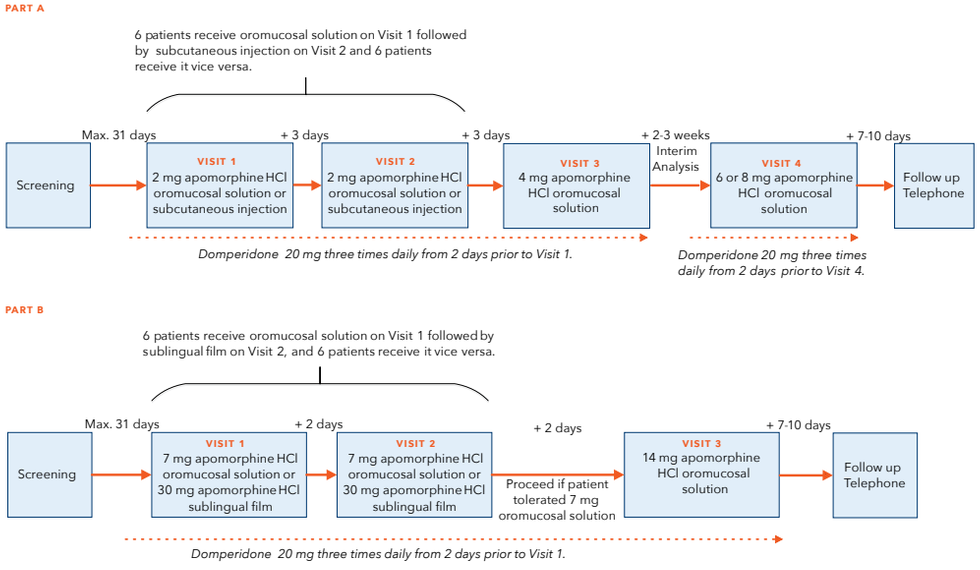
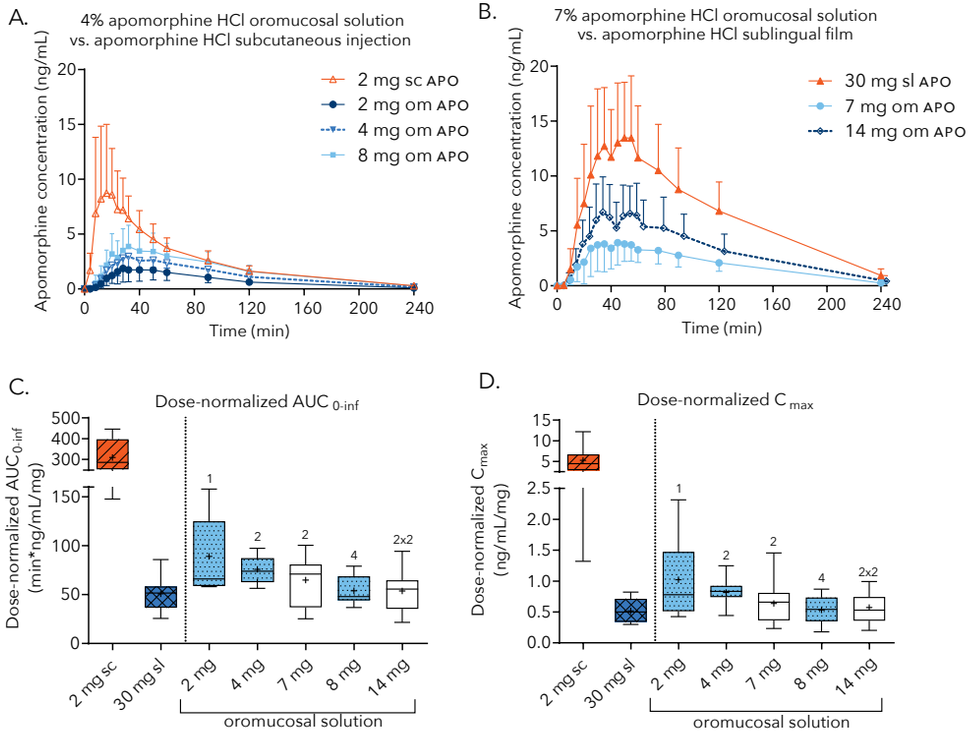


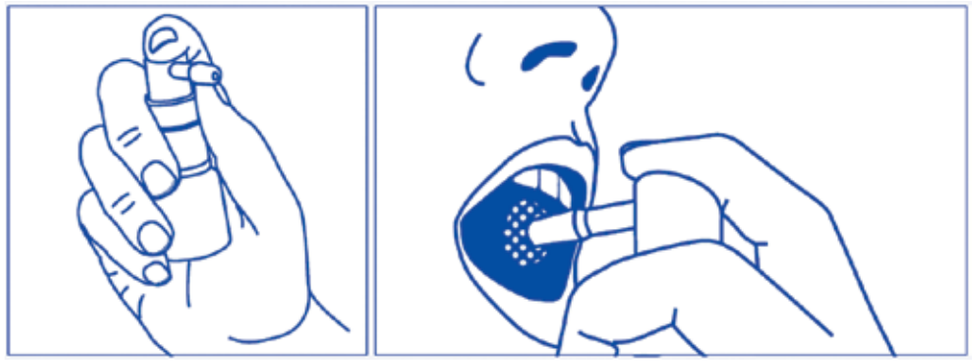
FIGURE 2 Mean (standard deviation) apomorphine concentration time profiles of 2 mg subcutaneous and 2-8 mg oromucosal apomorphine (A), and 30 mg sublingual and 7-14 mg oromucosal apomorphine (B). Dose-normalized $AUC_{0\text{-}inf}$ and C_{max} (C-D); number of spray pump actuations indicated above the whiskers.



sc, subcutaneous; om, oromucosal; sl, sublingual.

SUPPLEMENTARY MATERIAL

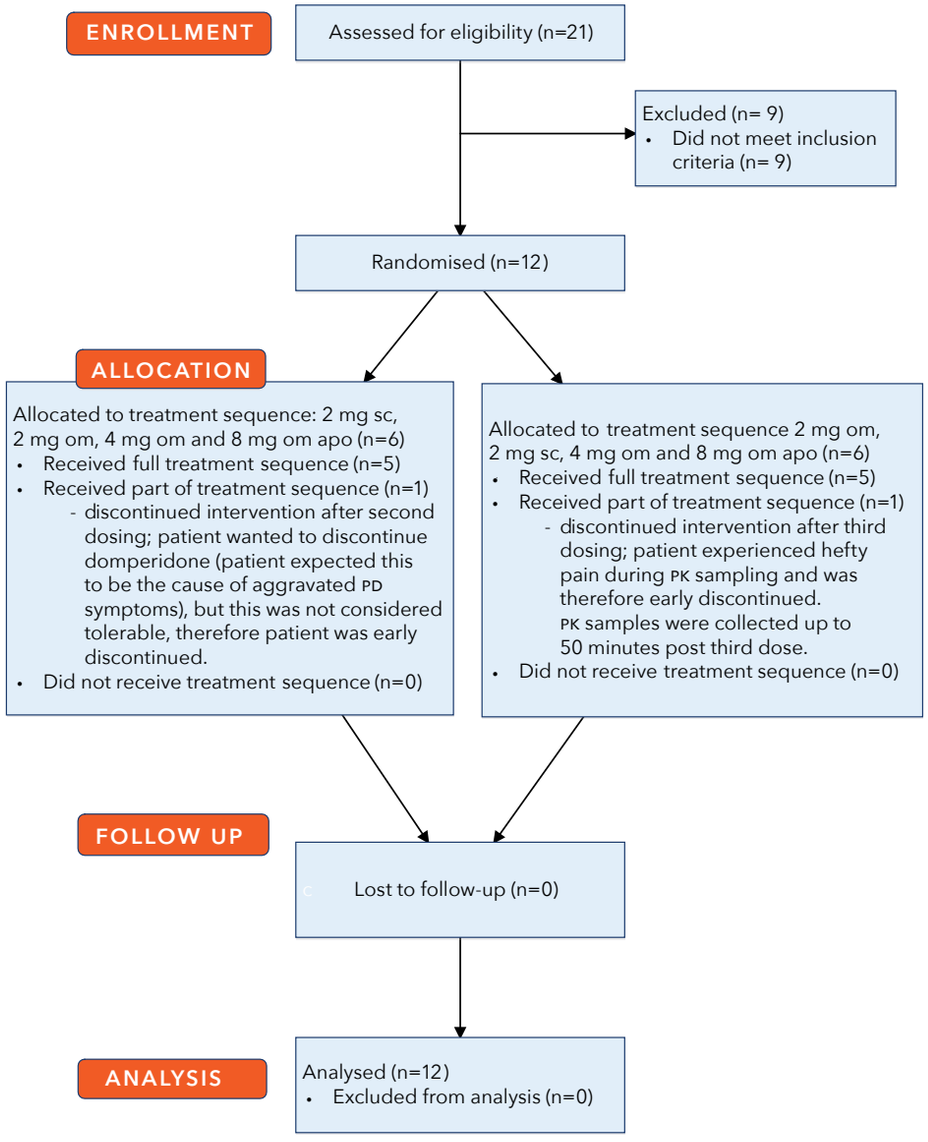
SUPPLEMENTAL FIGURE 1 Buccal administration of apomorphine hydrochloride oromucosal solution, to be administered to alternating cheeks.



SUPPLEMENTAL FIGURE 2 CONSORT flow diagram study part A.

STUDY PART A

APOMORPHINE HCL OROMUCOSAL SOLUTION (4%) AND SUBCUTANEOUS INJECTION

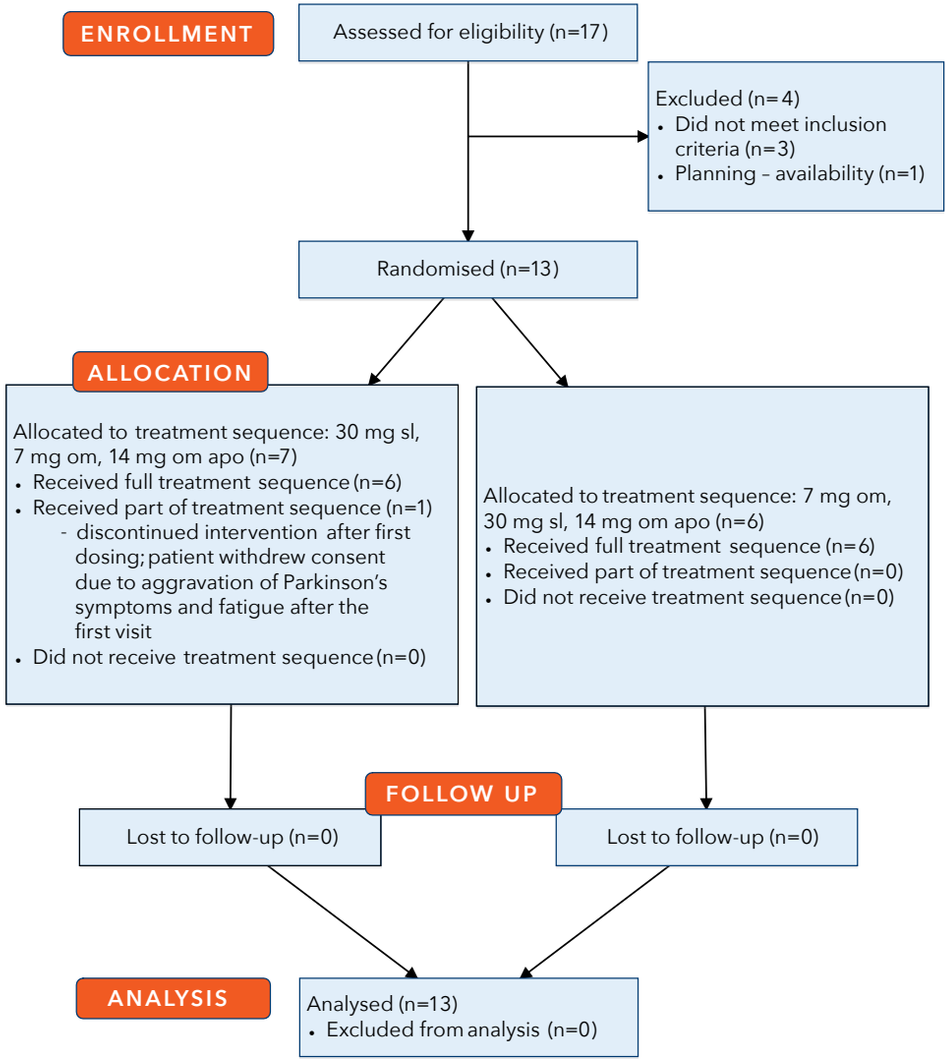


CONSORT, Consolidated Standards of Reporting Trials; sc, subcutaneous; om, oromucosal; PD, Parkinson's disease; PK, pharmacokinetics.

SUPPLEMENTAL FIGURE 3 CONSORT flow diagram study part B.

STUDY PART B

APOMORPHINE HCL OROMUCOSAL SOLUTION (7%) AND SUBLINGUAL FILM



CONSORT, Consolidated Standards of Reporting Trials; sl, sublingual; om, oromucosal; PD, Parkinson's disease; PK, pharmacokinetics.

REFERENCES

1 Auffret M, Drapier S, Vérin M. The Many Faces of Apomorphine: Lessons from the Past and Challenges for the Future. Drugs in R&D 2018 18:2. 2018;18(2):91-107. doi:10.1007/S40268-018-0230-3.

2 Chen YL, Shi L, Agbo F, Yong SH, Tan PS, Ngounou Wetie AG. LC-MS/MS simultaneous quantification of apomorphine and its major metabolites in human plasma: Application to clinical comparative bioavailability evaluation for the apomorphine sublingual film and a subcutaneous product. J Pharm Biomed Anal. 2020;190:113493. doi:10.1016/J.JPBA.2020.113493.

3 Chahine LM, Edison B, Daeschler M, et al. The Most Bothersome Aspects of Off Periods Reported by Individuals with Parkinson's Disease. Mov Disord Clin Pract. 2020;7(3):284-292. doi:10.1002/MDC3.12915.

4 Grosset KA, Malek N, Morgan F, Grosset DG. Phase IIa randomized double-blind, placebo-controlled study of inhaled apomorphine as acute challenge for rescuing 'off' periods in patients with established Parkinson's disease. Eur J Neurol. 2013;20(11):1445-1450. doi:10.1111/ENE.12091.

5 Grosset KA, Malek N, Morgan F, Grosset DG. Inhaled dry powder apomorphine (VR040) for 'off ' periods in Parkinson's disease: an in-clinic double-blind dose ranging study. Acta Neurol Scand. 2013;128(3):166-171. doi:10.1111/ANE.12107.

6 Dewey RB, Maraganore DM, Ahlskog JE, Matsumoto JY. A double-blind, placebo-controlled study of intranasal apomorphine spray as a rescue agent for off-states in Parkinson's disease. Movement Disorders. 1998;13(5):782-787. doi:10.1002/MDS.870130505.

7 Li GL, De Vries JJ, Van Steeg TJ, et al. Transdermal iontophoretic delivery of apomorphine in patients improved by surfactant formulation pretreatment. Journal of Controlled Release. 2005;101(1-3):199-208. doi:10.1016/J.JCONREL.2004.09.011.

8 Thijssen E, den Heijer J, Puibert D, et al. A Randomized Trial Assessing the Safety, Pharmacokinetics, and Efficacy During Morning Off of AZ-009. Movement Disorders. Published online 2022. doi:10.1002/MDS.28926.

9 Gancher ST, Nutt JG, Woodward WR. Absorption of apomorphine by various routes in parkinsonism. Movement Disorders. 1991;6(3):212-216. doi:10.1002/MDS.870060304.

10 Liu KS, Sung KC, Al-Suwayeh SA, et al. Enhancement of transdermal apomorphine delivery with a diester prodrug strategy. European Journal of Pharmaceutics and Biopharmaceutics. 2011;78(3):422-431. doi:10.1016/J.EJPB.2011.01.024.

11 Gancher ST, Woodward WR, Boucher B, Nutt JG. Peripheral pharmacokinetics of apomorphine in humans. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1989;26(2):232-238.

12 Bhidayasiri R, Garcia Ruiz PJ, Henriksen T. Practical management of adverse events related to apomorphine therapy. Parkinsonism Relat Disord. 2016;33:S42-S48. doi:10.1016/j.parkreldis.2016.11.017.

13 Albanese A, Bonuccelli U, Brefel C, et al. Consensus statement on the role of acute dopaminergic challenge in Parkinson's disease. Movement Disorders. 2001;16(2):197-201. doi:10.1002/MDS.1069.

14 Stacy MA, Murphy JM, Greeley DR, Stewart RM, Murck H, Meng X. The sensitivity and specificity of the 9-item Wearing-off Questionnaire. Parkinsonism Relat Disord. 2008;14(3):205-212. doi:10.1016/J.PARKRELDIS.2007.07.013.

15 Agbo F, Isaacson SH, Gil R, et al. Pharmacokinetics and Comparative Bioavailability of Apomorphine Sublingual Film and Subcutaneous Apomorphine Formulations in Patients with Parkinson's Disease and "OFF" Episodes: Results of a Randomized, Three-Way Crossover, Open-Label Study. Neurol Ther. 2021;10(2):693-709. doi:10.1007/S40120-021-00251-6.

16 Agbo F, Crass RL, Chiu YY, et al. Population pharmacokinetic analysis of apomorphine sublingual film or subcutaneous apomorphine in healthy subjects and patients with Parkinson's disease. Clin Transl Sci. 2021;14(4):1464-1475. doi:10.1111/CTS.13008.

17 Smith BP, Vandenhende FR, Desante KA, et al. Confidence Interval Criteria for Assessment of Dose Proportionality. Published online 2000.

18 APO-go Pen 10mg/ml Solution for Injection - Summary of Product Characteristics (SmPC) - (emc). Accessed November 8, 2022. https://www.medicines.org.uk/emc/product/2232/smpc.

19 Apomorphine-Subcutaneous – Bertek/Britannia. Drugs in R & D 2004 5:4. 2012;5(4):211-212. doi:10.2165/00126839-200405040-00004.
20 Rudney JD, Ji Z, Larson CJ. The prediction of saliva swallowing frequency in humans from estimates of salivary flow rate and the volume of saliva swallowed. Arch Oral Biol. 1995;40(6):507-512. doi:10.1016/0003-9969(95)00004-9.
21 Steele CM, Miller AJ. Sensory Input Pathways and Mechanisms in Swallowing: A Review. Dysphagia. 2010;25(4):323. doi:10.1007/S00455-010-9301-5.
22 Lagerlüf F, Dawes C. The Volume of Saliva in the Mouth Before and After Swallowing. http://dx.doi.org/101177/002203458406300502O1. 2016;63(5):618-621. doi:10.1177/00220345840630050201.
23 Van Laar T, Van der Geest R, Danhof M, Boddé HE, Goossens PH, Roos RAC. Stepwise intravenous infusion of apomorphine to determine the therapeutic window in patients with Parkinson's disease. Clin Neuropharmacol. 1998;21(3):152-158. Accessed November 16, 2022. https://pubmed.ncbi.nlm.nih.gov/9617506/.
24 Stocchi F, Peckham EL, De Pandis MF, et al. A Randomized Thorough QT Study of Apomorphine Sublingual Film in Patients With Parkinson's Disease. Clin Pharmacol Drug Dev. 2022;11(9):1068-1077. doi:10.1002/CPDD.1147.
25 Burkman AM. Some Kinetic and Thermodynamic Characteristics of Apomorphine Degradation. J Pharm Sci. 1965;54(2):325-326. doi:10.1002/JPS.2600540242.
26 Bolton JL, Trush MA, Penning TM, Dryhurst G, Monks TJ. Role of quinones in toxicology. Chem Res Toxicol. 2000;13(3):135-160. doi:10.1021/TX9902082.
27 Dos Santos El-Bachá R, Daval JL, Koziel V, Netter P, Minn A. Toxic effects of apomorphine on rat cultured neurons and glial C6 cells, and protection with antioxidants. Biochem Pharmacol. 2001;61(1):73-85. doi:10.1016/S0006-2952(00)00524-4.
28 Olanow CW, Factor SA, Espay AJ, et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study. Lancet Neurol. 2020;19(2):135-144. doi:10.1016/S1474-4422(19)30396-5.