A phase 1/2 study investigating the pharmacokinetics, safety and efficacy of a highly concentrated buccal formulation of apomorphine (APORON®) in subjects with Parkinson's Disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON52414

Source
ToetsingOnline

Brief title
Buccal Apomorphine (APORON) administration

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Criceto
Source(s) of monetary or material Support: Pharmaceutical Company

Intervention

Keyword: Apomorphine, Buccal, OFF state, Parkinson

Outcome measures

Primary outcome

Primary part A

-Apomorphine plasma concentrations

o Derived parameters including but not limited to Cmax, Tmax, Tlag, T1/2, AUC,

relative bioavailability

o Dose-normalized AUC and Cmax

o Ratio of buccal to subcutaneous AUC and Cmax

Primary part B

* Apomorphine plasma concentrations (parameters as above, with the only change

that in part B the ratio of buccal to sublingual AUC and Cmax will be

calculated)

* Treatment-emergent (serious) adverse events ((S)AEs).

* Concomitant medication

* Clinical laboratory tests

o Haematology

o Chemistry

o Coagulation

o Urinalysis

* Vital signs

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

o Orthostatic hypotension (delta mmHg sit-sta)

o Respiratory rate (breaths/min)

o Pulse oximetry (SpO2) (%)

* ECG

o Heart Rate (HR) (bpm), PR, QRS, QT, QTcF

Primary part C

- Treatment-emergent (S)AEs

- Concomitant medication

- Clinical laboratory tests (as above)

- Vital signs (as above)

- ECG (as above)

- C-SSRS

Secondary outcome

Secondary Part A

- Treatment-emergent (S)AEs

- Concomitant medication

- Clinical laboratory tests (as above)

- Vital signs (as above)

- ECG (as above)

Secondary part B

- Apomorphine plasma concentrations (parameters as above for part A)

- Treatment-emergent (S)AEs

Secondary part C

- Percentage of patients in each response category (no improvement/ slight improvement /moderate improvement/ full ON response within 30 minutes after administration of buccal apomorphine) as based on interview by phone and on patient diaries.

- Question during phone call which determines patient preference for buccal or subcutaneous administration.

- Average buccal dose used in Part C of the study

- Daily used subcutaneous dose in clinical practice before entering the study

Study description

Background summary

APORON is a novel formulation of apomorphine. Apomorphine is a registered drug indicated for the treatment of off-periods in patients with Parkinson's disease. Currently, apomorphine is often administered via subcutaneous injections, which can cause pain, local injection site reactions and may be difficult to use for patients when they are experiencing an off-period. APORON is a highly concentrated apomorphine buccal spray formulation which is expected to be easy and painless to self-administer and and has the same efficacy as the subcutaneous injection or sublingual administration.

Study objective

The primary objective of the study as a whole (part A-C) is to assess the PK and safety of buccal apomorphine relative to registered apomorphine formulations (subcutaneous, sublingual). Secondary objectives are the characterization of the PK-AE relationship, and to evaluate the patient-reported efficacy of buccal apomorphine administration.

Study design

Part A is a single-centre, open label, cross-over study to characterize the PK of apomorphine after buccal and subcutaneous administration in 12 patients with Parkinson*s disease.
Part B is a single-centre, open-label comparative PK study evaluating an improved buccal apomorphine formulation and an US-marketed apomorphine dual film for sublingual administration (Kynmobi) in 12 patients with Parkinson*s disease.
Part C is a single-centre, 12-week open label study to characterize the safety and (local) tolerability of daily buccal apomorphine administration in 16-18 patients with Parkinson*s disease

Intervention

Part A: 2 mg subcutaneous apomorphine (APO-go® 5 ml ampoules 10 mg/ml) and 3 doses of buccal apormorphine (APORON) (increasing doses, up to 8 mg)
Part B: 2 doses buccal apomorphine spray (APORON) (dose based on data from part A), 1 dose KYNMOBI 30 mg.
Part C: Buccal apomorphine spray (APORON) (dosage as used in part B)

Study burden and risks

Subjects will visit CHDR multiple times. During the study, several assessments and activities will be performed, such as blood collection, measurement of vital signs, ECGs, physical and neurological examinations and questionnaires.

Apomorphine is a well-known drug, so the risk of unexpected systemic side effects is limited. Apomorphine can cause nausea, vomiting and orthostatic hypotension, mainly in apomorphine-naive patients. To prevent these side effects, patients in study part A and B are given 20 mg domperidone 3 times daily starting 2 days prior to dosing and on dosing days. The patients in study part A and B might become dyskinetic due to dosing with both their normal Parkinson medication and subcutaneous or buccal apomorphine. To prevent this, patients are allowed to skip or postpone their own medication as needed.

APORON might result in local side effects. Therefore, the buccal mucosa is closely monitored throughout the study. After 2 mg buccal apomorphine administration, both safety (adverse events) and PK data will be reviewed

before proceeding to a higher dose.

Contacts

Public
Criceto

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Part A and B
1) Male or female, 30-85 years of age, inclusive at screening.
4) Clinical diagnosis (confirmed by a neurologist) of Parkinson*s disease and classified by the investigator as Hoehn and Yahr stage I to IV in the ON state.
5) Having clear, self-described motor fluctuations.
6) Mini-Mental State Examination (MMSE) score >= 20 and assessed by the investigator or qualified designee as able to provide informed consent.

Part C

1) Male or female, 30-85 years of age, inclusive at screening.
4) Clinical diagnosis (confirmed by a neurologist) of Parkinson*s disease and classified by the investigator as Hoehn and Yahr stage I to III in the ON state.
5) Mini-Mental State Examination (MMSE) score >= 20 and assessed by the investigator or qualified designee as able to provide informed consent.
8) On a stable dose of 1 to 4 mg subcutaneous apomorphine (APO-GO PEN) for the management of OFF episodes for at least 4 weeks prior to first study drug administration.
9) Subject*s at-home subcutaneous apomorphine injection location is the abdomen.
11) Subjects who experience motor fluctuations with recognizable OFF periods at least once per day.

Exclusion criteria

Part A and B:
1) Atypical or secondary parkinsonism e.g., multiple-system atrophy or progressive supranuclear palsy, or evidence of drug-induced parkinsonism.
2) Subjects with a borderline QT interval corrected for heart rate according to Fridericia's formula (QTcF) of >450 ms for male and >470 ms for female, PR interval > 220 msec or QRS duration > 120 msec at screening or history of long QT syndrome.
6) Currently taking medication that can influence the efficacy of apomorphine in the opinion of the investigator, such as dopamine antagonists and dopamine depleting drugs, with the exception of domperidone.

Part B
As in part A, but with the following differences:
2) Subjects with a borderline QT interval corrected for heart rate according to Fridericia*s formula (QTcF) of >450 ms for male and >470 ms for female, PR interval > 220 msec or QRS duration > 120 msec at screening or prior to first dose, or history of long QT syndrome.
3) Contraindications to the excipients of the buccal or sublingual apomorphine formulation, or contraindications to domperidone.
12) Elevated hepatic panel, defined as serum levels of ALT, AST, GGT, ALP or TBL higher than 2 times the upper limit of normal.
19) Use of any apomorphine formulation in the 4 weeks prior to first dosing.
20) Use of 5HT3 antagonists.

Part C:
1) Atypical or secondary parkinsonism e.g., multiple-system atrophy or progressive supranuclear palsy, or evidence of drug-induced parkinsonism.
2) Subjects with a borderline QT interval corrected for heart rate according to Fridericia*s formula (QTcF) of >450 ms for male and >470 ms for female, PR interval > 220 msec or QRS duration > 120 msec at screening or history of long

QT syndrome.
4) Use of apomorphine formulations other than subcutaneous injections in the 4 weeks prior to first dosing.
7) Currently taking medication that can influence the efficacy of apomorphine in the opinion of the investigator, such as dopamine antagonists and dopamine depleting drugs, with the exception of domperidone.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-04-2021
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	APO-go
Generic name:	Subcutaneous injection of apomorphine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	APORON
Generic name:	Buccal apomorphine
Product type:	Medicine
Brand name:	KYNMOBI®

Generic name:	APOMORPHINE HYDROCHLORIDE HEMIHYDRATE
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2022

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26898
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-003315-60-NL
CCMO	NL71179.056.20
OMON	NL-OMON26898