# An open-label study to assess the pharmacokinetics and safety/tolerability of pulsatile intra-vaginal delivery of a single dose of oxybutynin in healthy females

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Primary* To evaluate the pharmacokinetics of oxybutynin and its main hepatic metabolite N-desethyloxybutynin after pulsed intra-vaginal delivery of a single dose of oxybutyninSecondary* To assess the safety and tolerability of the intra-vaginal...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Bladder and bladder neck disorders (excl calculi) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON51105

**Source**
ToetsingOnline

**Brief title**
PK of intra-vaginal oxybutynin

### Condition

- Bladder and bladder neck disorders (excl calculi)

**Synonym**
NA, pharmacokinetics of oxybutynin

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** LiGalli BV
**Source(s) of monetary or material Support:** LiGalli BV

## Intervention

**Keyword:** Intra-vaginal delivery, MedRing, oxybutynin, Pharmacokinetics

## Outcome measures

### Primary outcome

PK parameters by non-compartmental analysis of the plasma concentration-time

data:

* AUCinf, AUClast, Cmax, tmax, t1/2, tlag, CL/F, Vz/F

* Dose-normalized PK parameters: AUCinf, AUClast, Cmax

### Secondary outcome

* Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at

every study visit

* Anticholinergic side effect (pupil size, salivary flow, visual near point

acuity and pulse rate) per assessment schedule

* Concomitant medication throughout the study at every study visit

* Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg), Diastolic

blood pressure (mmHg)) as per assessment schedule

* Physical examination including in speculum examination per assessment

schedule

# Study description

### Background summary

Controlled release technologies, including sustained release of oral medication, implants and transdermal drug delivery, have been developed to mimic physiological concentrations and endogenous substance profiles. However, there is still a need to develop novel controlled release technologies. The intra-vaginal delivery route may facilitate such novel technology as it offers several advantages over more commonly used systemic drug delivery routes. It is a non-invasive route of administration, features a suitable residence time for long-term treatment and could be used for placement of medical devices designed for pulsatile drug delivery.

Currently, no intravaginal controlled delivery method is available to achieve temporary peak concentration at pre-determined time intervals. Therefore, the vaginal MedRing was designed. The MedRing contains a drug formulation reservoir, a miniature peristaltic pump, a miniature electronic circuit board that controls the device, and a battery. The system can wirelessly connect to an external device (smartphone, tablet or laptop computer) from which drug delivery can be programmed and which receives data (volume delivered, temperature) from the ring.
The competitive muscarine receptor antagonist oxybutynin alleviates symptoms of an overactive bladder/urge incontinence, and is often administered orally. Oxybutynin is subject to an extensive first pass effect, resulting in the formation of the active metabolite N-desethyloxybutynin with systemic, anticholinergic side effects. An intravaginal route of administration of oxybutynin has potential advantages compared to oral administration. By this route it bypasses the first-pass effect and may have local efficacy. In contrast to intra-vaginal devices in which oxybutynin is released continuously[1], the MedRing is developed to administer the compound pulsatile and on-demand. Oxybutynin *on demand* could be of potential use in the treatment of overactive bladder/urge incontinence. Other potential indications are the treatment of post-menopausal or aromatase inhibitor-induced hot flashes.
In this study we will investigate the feasibility of pulsed intra-vaginal delivery via the LiGalli MedRing and explore systemic exposure after a single dose of oxybutynin.

**Study objective**

Primary
* To evaluate the pharmacokinetics of oxybutynin and its main hepatic metabolite N-desethyloxybutynin after pulsed intra-vaginal delivery of a single dose of oxybutynin

Secondary
* To assess the safety and tolerability of the intra-vaginal delivery of oxybutynin via the MedRing device in healthy females

## Study design

This is an open-label single dose study to assess the pharmacokinetics and safety/tolerability of oxybutynin after a single pulsed intra-vaginal delivery in healthy pre- and post-menopausal females. After a single oxybutynin intra-vaginal dose, PK and safety data will be collected and reviewed for a total period of 24 hours post-dose. Safety data will be collected by telephone 7 (+/- 2 days) after the dose administration.

## Intervention

All subjects will receive a single-dose oxybutynin intra-vaginally.

## Study burden and risks

Oxybutynin
Oxybutynin has been on the market for several years as a competitive acetylcholine antagonist of the postganglionic muscarine receptors. It can be administered orally in a dose of 2.5 mg 3dd, up to 20 mg 4dd oral, via transdermal patches, or vesicular lavage.

For this study, a single dose up to 6 mg oxybutynin HCl (dissolved in 50% propylene glycol / 50% water for injection) will be administered intra-vaginally in a concentration of 100 mg/mL (for dosing rationale, see Section 1.4.5.).

There is extensive experience with oxybutynin in clinical practice with oral, intravesical and dermal administrations. In general, the systemic exposure of oxybutynin in humans is considered safe. Common side effects are caused by the anti-cholinergic mode of action of the drug: obstipation, nausea, dry mouth, dizziness, fatigue, and, rarely, confusion. A large part of the side effects are thought to be mediated by the main metabolite N-desethyloxybutynin. With an intra-vaginal route of administration these side effects may be less pronounced.

Data on local side effects are scarce. In earlier studies with intra-vaginally administered oxybutynin, no local side effects where observed. The higher concentrated solution of oxybutynin used in this study could theoretically lead to irritation. However, only a single dose with a small volume is administered and if irritation complaints should occur, the extent of irritation should be investigated by an experienced physician. Furthermore, the vagina may be irrigated after removal of the MedRing in case of tolerability issues during the clinical phase.
MedRing intra-vaginal ring
Pre-dose, the MedRing will be instructed to release the intended dose of oxybutynin solution at 37 degrees Celsius (in case of 6 mg, it will be 60 ul)

to be pipetted using a capillary to check for correct output of the ring prior to placement. This output will subsequently be measured and dissolved in a *calibration reservoir* to enable determination of the calibration concentration. The ring will be inserted intra-vaginally by the physician and the subject will be subsequently monitored. The ring will stay in place for 6 hours. Thereafter, it will be removed by the physician under the same conditions as during insertion. After removal, the ring is cleaned and will be post-calibrated in a similar fashion to the pre-calibration process.

# Contacts

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NL
**Scientific**
LiGalli BV

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NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria at screening:

1. Willing to give written informed consent and willing and able to comply with the study protocol;
2. Female subjects of child bearing potential (women of child bearing potential, WOCBP) aged between 18 and 45 years (inclusive)
OR
Female postmenopausal subjects aged between 50 and 69 years (inclusive); Postmenopausal status is defined as age * 50 years and having > 12 months amenorrhoea in the absence of hormonal therapy that may cause amenorrhoea.
3. Subject is in good general health, according to the investigator*s judgement based on vital signs, medical history, physical examination, and laboratory tests performed.
4. Body mass index between 18-32 kg*m2 (inclusive) and with a minimum body weight of 50 kg at screening
5. Ability to communicate well with the investigator in the Dutch language and willing to comply with the study restrictions
6. Using contraceptives of second generation containing ethinylestradiol and progesterone derivate (WOCBP subjects only). This includes a hormone-containing IUD (e.g. Mirena), second generation oral contraceptive pill, hormonal contraception using parenteral medroxyprogesteron or subcutaneous etonogestrel.

## Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria at screening:
1. (A history of) any clinically significant medical condition or abnormalities, as judged by the investigator, in physical examination, laboratory test results (including chemistry panel with hepatic and renal panels, complete blood count, and urine dipstick) or electrocardiography (ECG). In the case of uncertain or questionable results, tests performed during screening may be repeated to confirm eligibility or judged by the investigator to be clinically irrelevant for healthy subjects.
2. Being a virgin.
3. History of sexual abuse/violence.
4. First day of last withdrawal bleeding <10 days before Day 0
5. Plan to discontinue oral contraceptive during study period.
6. Positive pregnancy test at screening or at baseline prior to IMP administration and/or lactating.
7. Having given birth vaginally or by caesarean section 6 months prior to screening
8. Having had sexual intercourse or objects inserted vaginally that could potentially lacerate or damage the vaginal wall 24 hours prior to dosing.
9. Positive screening test for Hepatitis B/C and/or Human Immunodeficiency Virus (HIV) test at screening
10. Positive screening PCR test for Chlamydia trachomatis or gonorrhea at screening

11. Medical history of intra- and/or transvaginal operations that in the opinion of the investigator may interfere with placement or stability of the MedRing or absorption of the IMP. Exceptions may include endometrial curettage for e.g. miscarriage or abortion or LIS-excision of the cervix for CIN if performed > 3 months prior to screening.
12. High risk for sexual transmitted diseases (STD) (a. 3 or more different sexual contacts in last 6 months, and/or b. is a sex worker or visits them and/or c. has a partner with an STD risk as described (a. and/or b.), and/or d. partner is a male who has sex with male).
13. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against oxybutynin, or multiple drug allergies (non-active hay fever is acceptable).
14. Participation in any marketed or investigational drug or device study within 3 months or 5 half-lives (whichever is longer) prior to first dosing.
15. Use of any prescription medication and any other substance that in the opinion of the investigators may influence the outcome of the study within 21 days prior to study drug administrations, or less than five half-lives (whichever is longer, and during the course of the study). Exceptions are the incidental use of OTC medications paracetamol (up to 4 g/day) and ibuprofen (up to 1 g/day) which are allowed within two days of clinical assessments
16. Use of alcohol during the 24 hours prior to screening and/or an unwillingness to abstain from alcohol consumption during the stay at the clinical unit, and for at least 24 hours prior to each study visit;
17. Positive urine drug screen or alcohol test at screening and/or at study days.
18. Intake of grapefruit or grapefruit juice within 5 days of IMP administration, and/or unwillingness to abstain from the consumption of these products from 5 days prior to IMP administration until the last study visit;
19. Loss or donation of blood over 500 mL within four months prior to screening.
20. Any other condition that in the opinion of the investigator would complicate or compromise the study or the well-being of the subject.

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 10-12-2020 |
| Enrollment: | 8 |
| Type: | Actual |

## Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Oxybutynin HCl |
| Generic name: | Oxybutynin HCl |
| Registration: | Yes - NL outside intended use |

# Ethics review

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| Approved WMO Date: | 16-11-2020 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-12-2020 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 01-02-2021 |
| 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: 20539
Source: NTR
Title:

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2020-005044-30-NL |
| CCMO | NL75627.056.20 |
| OMON | NL-OMON20539 |