An open-label, crossover study to assess the pharmacokinetics, safety and tolerability of pulsatile intra-vaginal delivery of insulin aspart in females with diabetes mellitus type 1

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Primary* To explore the pharmacokinetics of insulin aspart after pulsed intra-vaginal delivery using the MedRing and after subcutaneous injection in women with DM1.Secondary* To assess the safety and short-term tolerability of insulin aspart after...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON51108

Source
ToetsingOnline

Brief title
PK of intra-vaginal insulin

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
PK of Insulin

Research involving
Human

Sponsors and support

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

Intervention

Keyword: insulin aspart, intra-vaginal, pharmacokinetics

Outcome measures

Primary outcome

PK parameters by non-compartmental analysis 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

* Hypo- or hyperglycaemic events by continuous blood glucose monitoring.

* 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 drug delivery 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 an innovative 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 intra-vaginal 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.

Study objective

Primary
* To explore the pharmacokinetics of insulin aspart after pulsed intra-vaginal delivery using the MedRing and after subcutaneous injection in women with DM1.

Secondary
* To assess the safety and short-term tolerability of insulin aspart after pulsed intra-vaginal delivery using the MedRing and after subcutaneous injection in women with DM1.

Study design

This is an open-label, crossover study to assess the pharmacokinetics, safety and tolerability of insulin aspart after a single pulsed intra-vaginal delivery and to compare this to the pharmacokinetics, safety and tolerability after a subcutaneous injection in pre-menopausal women with DM1.

Intervention

Insulin aspart (Fiasp), intravaginal administration using the MedRing.
Insulin aspart (Fiasp), subcutaneous administration by s.c. injection

Study burden and risks

Fiasp insulin
Insulin has been on the market for over a century as an exogenous source of insulin in patients with DM1. It can be administered subcutaneously by many dosing systems, including continuous with pumps which are currently on the market.

For this study, a single dose of Fiasp insulin (dose depending on 75% of

patient*s personal inulin need, with a total dose ranging from 4 to 15 IE) will be administered subcutaneously during the first occasion. During the second occasion, the same insulin dose will be given through intra-vaginal administration using the MedRing (for dosing rationale, see Section 1.4.5.).

There is extensive experience with exogenous insulin in clinical practice with subcutaneous administration. In general, in patients with DM1, systemic exposure of insulin in humans is considered safe. Common side effects include hypoglycaemia and cutaneous administration site reactions, such as erythema, swelling and bruising.

Data on local side effects of insulin in the vagina are scarce. In animal studies with intra-vaginally administered insulin, there was no report on local side effects. In other mucosal tissues (nasal, inhaled insulin), there was no irritation of the mucosa following insulin administration (Gupta et al., 2013; Zhang et al., 2021). The higher concentrated solution of insulin used in this study could theoretically lead to irritation of the vaginal mucosa. 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 Fiasp insulin (100IE/mL) solution at 37 degrees Celsius (in case of 6 IE, it will be 60 *L) to be pipetted using a capillary to check for correct output of the ring prior to placement. This output will subsequently be measured according to the Calibration instruction and stored. The ring will be inserted intra-vaginally by the physician and the subject will be subsequently monitored. The ring will stay in place for 2 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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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Eligible subjects must meet all 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 with diabetes mellitus type 1 of childbearing potential (women of childbearing potential, WOCBP) aged between 18 and 45 years (inclusive).
3. Subject is on insulin therapy under multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII).
4. Subject is on continuous glucose monitoring (CGM) with a CGM device or a flash monitoring device (e.g. Abbott Freestyle Libre) more than 24 hours in situ.
5. Subject is in good general health (apart from T1DM), according to the investigator*s judgement based on vital signs, medical history, physical examination, and laboratory tests performed.
6. Body mass index between 18-32 kg*m2 (inclusive) and with a minimum body weight of 50 kg at screening.
7. Ability to communicate well with the investigator in the Dutch language and willing to comply with the study restrictions.
8. Using contraceptives of second generation containing ethinylestradiol and progesterone derivate. 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 abnormality, 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) at screening. 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. Patients on (hybrid) closed loop systems, i.e. Medtronic 670G/780 pump.
3. Patients with unstable glucose regulation in opinion of the investigators, for example frequent hypo- or hyperglycemia or with hypoglycemia unawareness.
4. Being a virgin.
5. History of sexual abuse/violence.
6. First day of last withdrawal bleeding <10 days before both study days.
7. Plan to discontinue oral contraceptive during study period.
8. Positive pregnancy test at screening or at baseline prior to IMP administration and/or lactating.
9. Having given birth vaginally or by caesarean section 6 months prior to screening.
10. Having had sexual intercourse or objects inserted vaginally that could potentially lacerate or damage the vaginal wall 24 hours prior to dosing.
11. Positive screening test for Hepatitis B/C and/or Human Immunodeficiency Virus (HIV) test at screening.
12. Positive screening PCR test for Chlamydia trachomatis or gonorrhoea at screening.
13. 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.
14. 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.
15. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against insulin aspart (Fiasp), or multiple drug allergies (non-active hay fever is acceptable).
16. Participation in any marketed or investigational drug or device study within 3 months or 5 half-lives (whichever is longer) prior to first dosing.
17. Use of prescription medication or any other substance that in the opinion of the investigators may influence the outcome of the study (e.g. systemic steroids) 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.
18. 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.
19. Positive urine drug screen or alcohol test at screening and/or at study days.
20. Loss or donation of blood over 500 mL within four months prior to screening.
21. 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

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Generic name:	MedRing Alpha 1+
Registration:	No
Product type:	Medicine
Brand name:	Fiasp 100 units/mL
Generic name:	Insulin aspart
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-07-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	03-09-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

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: 27259
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-002880-23-NL
CCMO	NL77895.058.21
OMON	NL-OMON27259