



FLAMEL TECHNOLOGIES



FT-105

Once-A-Day Controlled Release Basal Insulin

DTM November 11-13, 2010

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Overview

- **Flamel Technologies**, based in France, has developed two innovative drug delivery technology platforms:
 - **MICROPUMP**[®] for oral small molecule drugs and
 - **MEDUSA**[®] for injectable proteins and peptides
- FDA approved MICROPUMP[®] project with GlaxoSmithKline (GSK), for controlled release Carvedilol (Coreg CR[®]).
- Flamel's proprietary technologies may be applied to improve new chemical entities, new proteins or currently approved drugs.

Current partnerships: GSK, Pfizer, Wyeth, MerckSerono...

Rationale for a protein and peptide Delivery System

Medusa* Technology for the sustained release of biologics is based on reversible association with polyaminoacid nanocarriers.

- The **biological activity is maintained**: no modification of the carried protein /peptide
- Potential **improvement of therapeutic benefit and safety profile by having** a lower C_{max} and a more regular concentration profile
- Ability to **solubilize** and **stabilize** insoluble and/or unstable proteins/peptides

SAFE

STABLE

PATENTED

**Medusa is a trademark of Flamel Technologies S.A.*

Medusa Polymer Drug Delivery System

Polymer design

- Uses naturally occurring aminoacids as main constituent
- Tailored to have high affinity for proteins

Polymer synthesis

- Simple polymerization process
- Polymers isolated as ready-to-formulate aqueous solutions

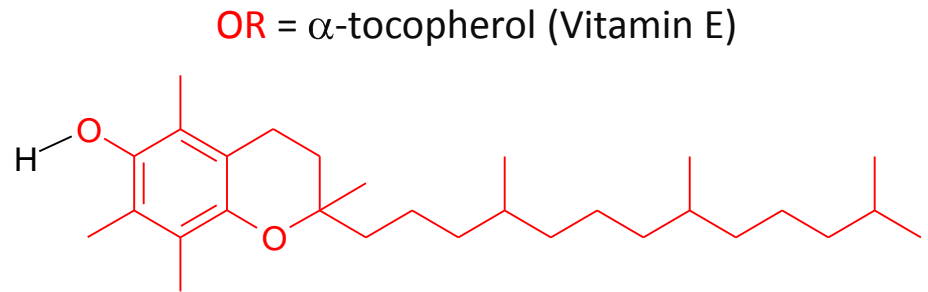
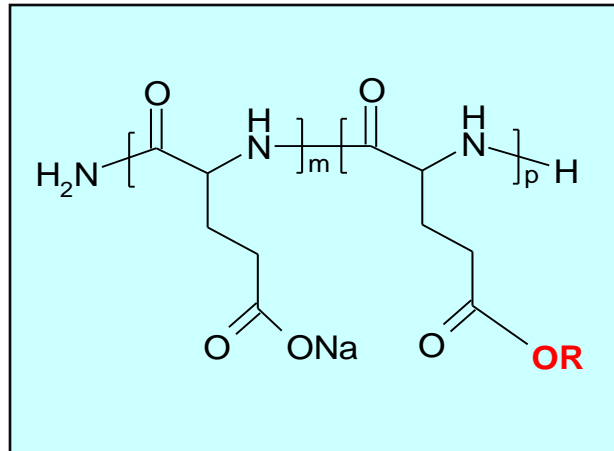
Protein or peptide formulation

- Gentle, fully aqueous solution based production preserves the protein or peptide's properties

→ *Polymer is biodegradable and biocompatible*

Medusa (pGluVE) Polymer

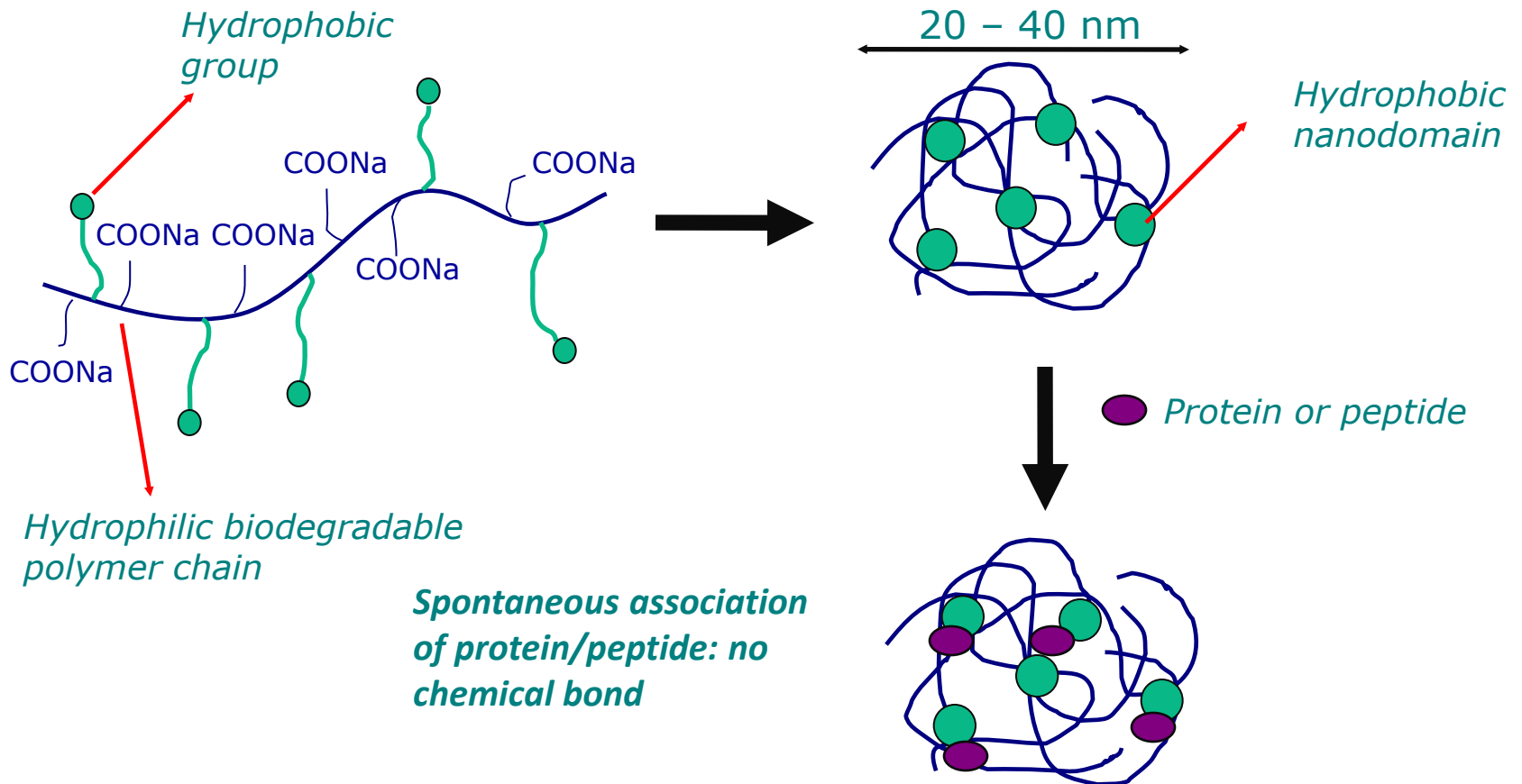
pGluVE: polyglutamate grafted with hydrophobic vitamin E



Degradation (in-vitro) of polymer leads to glutamic acid and vitamin E, both are GRAS compounds.

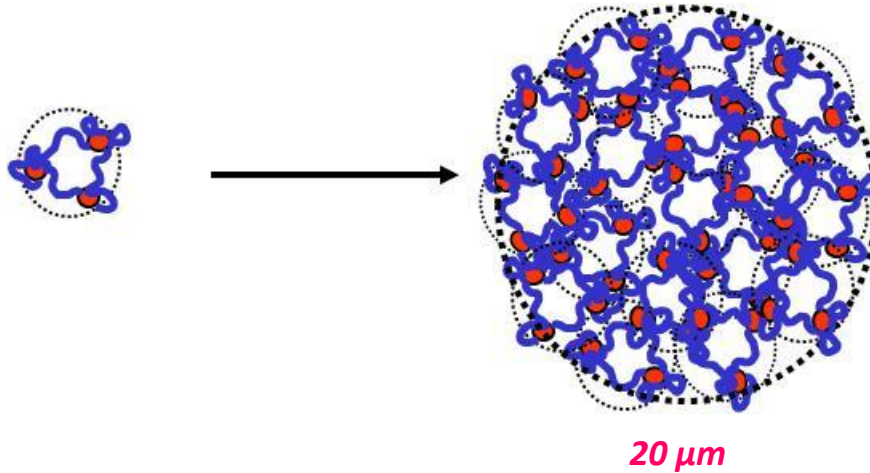
Over 100 patients/healthy volunteers administered to date with good safety profile

Protein Adsorption onto Medusa Nanogel



Medusa Nanoparticles can be Aggregated to Form Microparticles

Protein loaded nanogels



Suspension
Injectable through
29 G to 31 G needles

Fully water based process: no shear, no surfactant and no organic solvent.

FT105 Drug Product

Ready to use doses for reconstitution of 1 ml of 100 UI/ml insulin (clinical study vials)



Composition per vial :

Dry powder:

100 IU insulin (~3.5 mg)

20 mg Medusa

Stability: 2 years at 5°C & 25°C

Properties of suspension:

Insulin 100 IU/mL

pH 6.5

Osmo 300 mOsmol

Particle size 10-20 μm (d_{50})

Viscosity < 10 mPa.s

Easy to inject thru 30/31G needle

Goals for FT-105

- PK/PD profile as flat as possible to mimic the natural release of basal insulin in healthy subjects,
- Once-daily injection schedule (24-hour glycemic control) for every patient,
- Less risk of hypoglycemia than with existing products,
- Good local tolerance,
- Injection through small gauge needle (30 G needle)
- Delivery of fully active non-modified human insulin.

Current Long-Acting Insulins Have Limitations

1. Lantus[®] from Sanofi-Aventis

Lantus[®] is an insulin analogue with a pharmacodynamic coverage from 12 to over 24 hours explaining why some patients take the drug twice daily.

2. Levemir[®] from Novo Nordisk

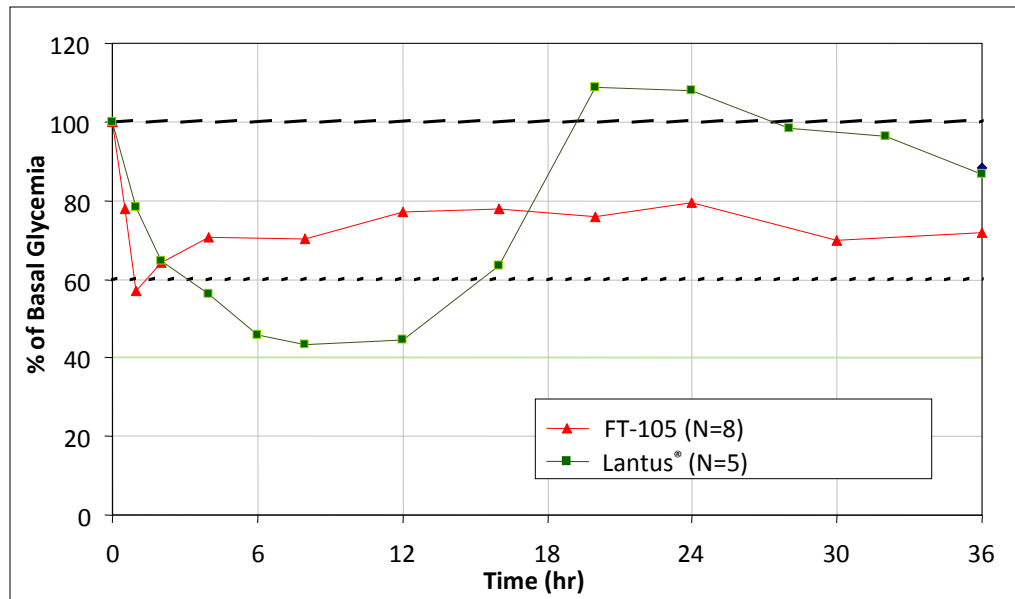
Levemir[®] is a modified insulin requiring two injections per day for most patients.



FT105 Dog Study

FT-105 Provides Glycemic Control for More Than 36 Hours in Dog Models

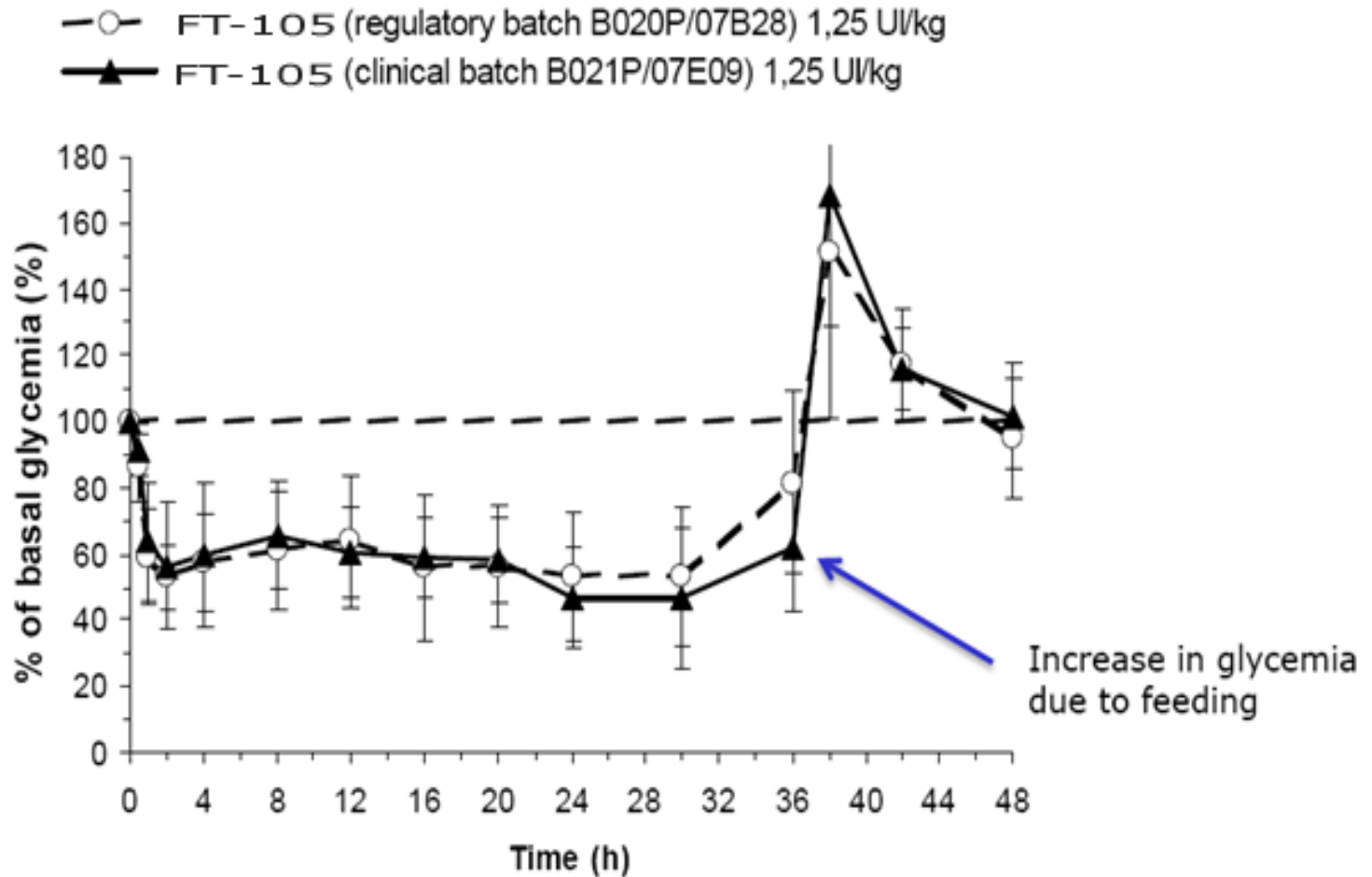
Dose= 1 IU/Kg



Treatment	AUC _{0-36h} (%*hr)	C _{min} (%)	T50% _{AUC} (hr)
FT-105	948 ± 491	49 ± 17	16.5 ± 6.2
Lantus®	798 ± 215	35 ± 11	9.2 ± 2.1

Study PDF105-0602

Different GMP Batches Exhibit Same Pharmacodynamics



Study PDF105-0707



FT105 Human Trial

FT-105 Phase I Objectives and Dosages

- **Primary objective: determine the pharmacokinetic and pharmacodynamic properties of FT-105 in humans.**

- **Secondary objectives:**
 - Investigate safety and tolerability, including local tolerability.
 - Examine PK-PD dose-response proportionality.
 - Compare PK and PD properties of FT-105 with those of the reference product Lantus®.

- **Doses given :**
 - **FT-105** subcutaneous injection at **0.3 IU/kg in 210µl.**
 - **FT-105** subcutaneous injection at **0.6 IU/kg in 420µl.**
 - **Lantus®** subcutaneous injection of **0.6 IU/kg in 420 µl.**

Study PKFT 105-0701

FT-105 Phase I Materials and Methods

- **18 healthy volunteers.**
- **Open label, randomized 3-way cross-over design** (2 dosages FT-105 vs. 1 dosage lantus).
- **Washout period : 7 days.**
- **36-hour glucose euglycemic clamp.**
- **Injection site: thigh/arm/abdomen.**
- **Assessments**
 - Plasma concentration of insulin and C-peptide by Immunoassay.
 - Glucose Infusion Rate (GIR) during the 36-hour clamp.
 - Blood glucose by Beckman Glucose Analyser.
 - Clinical and laboratory safety including assessment of local tolerability.
- Performed by Icon (former Medeval), Phase I unit in UK.

Study PKFT 105-0701

FT-105 Demonstrates Good Safety / Local Tolerance in Humans

- 17 of 18 subjects completed the study procedures*.
- No Serious Adverse Event reported.
- Few, slight local tolerance reaction: no difference between FT-105 and Lantus®.
- No change in laboratory values.
- No change in ECG.

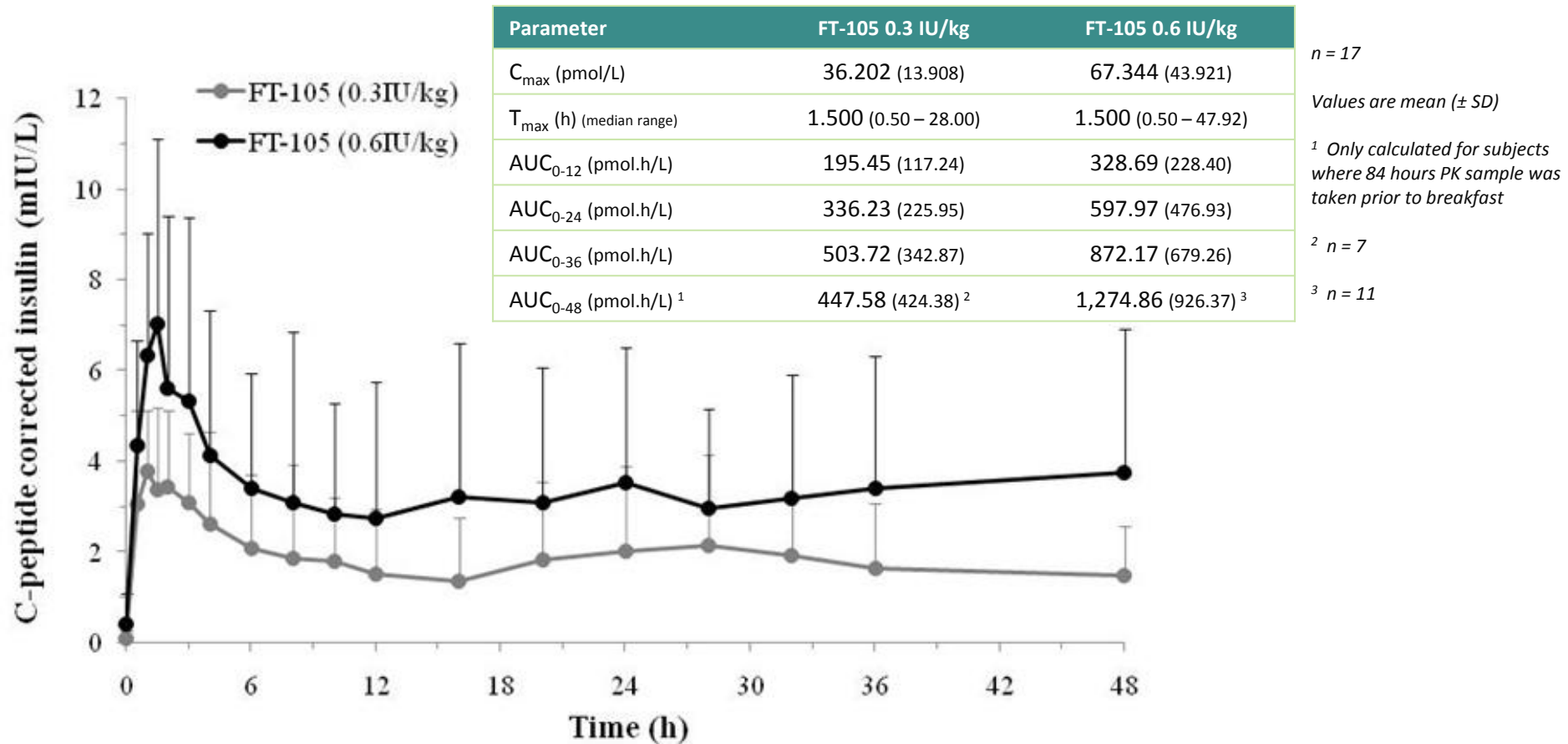
Barely visible reaction at site of injection



Good safety/tolerance is observed at 0.3 and 0.6 IU/kg



FT-105 Demonstrates Long and Flat PK Profile for 48 Hours in Humans



➤ Good dose proportionality is observed.

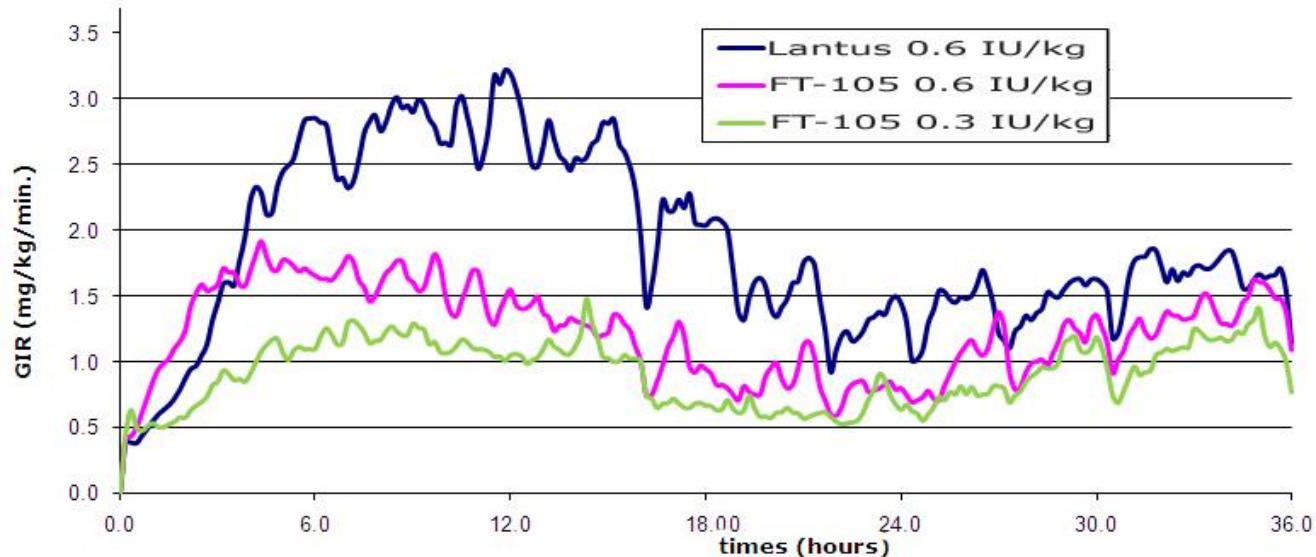
Study PKFT 105-0701

FT-105 Presents a Flat PD Profile with Low Peak to Trough Ratio

Parameter	FT-105 0.3 IU/kg	FT-105 0.6 IU/kg	Lantus 0.6 IU/kg
GIR _{max} (mg/kg/min)	4.5206 (3.8081)	5.1718 (2.1058)	8.7116 (4.3476)
T _{GIRmax} (h)	19.330 (0.33 – 36.00)	14.830 (3.17 – 35.83)	14.00 (4.17 – 35.67)
AUC _{GIR, 0-12} (mg/kg)	11.770 (7.324)	17.759 (11.635)	26.057 (13.295)
AUC _{GIR, 0-24} (mg/kg)	21.746 (11.401)	29.917 (16.110)	50.475 (18.051)
AUC _{GIR, 0-36} (mg/kg)	33.872 (16.832)	44.120 (23.293)	69.217 (23.783)

n = 17

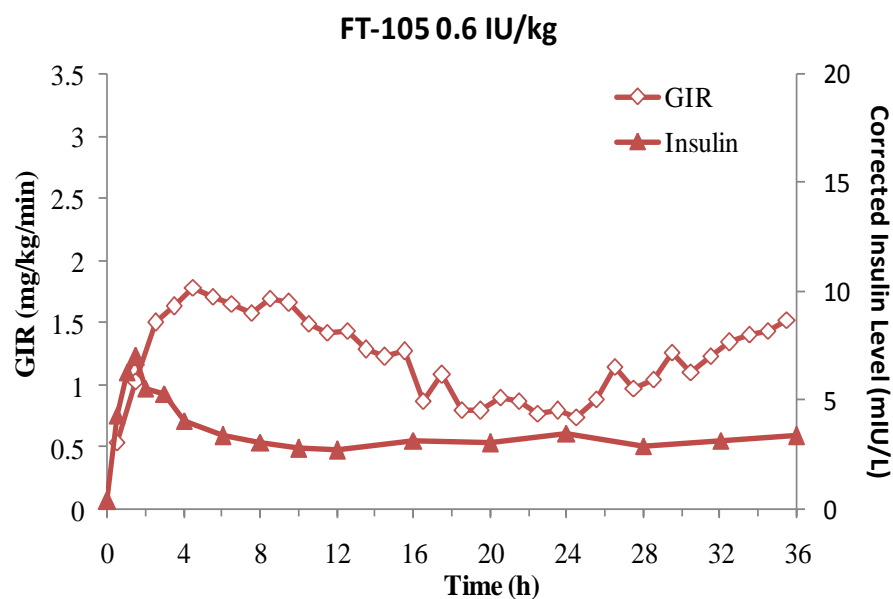
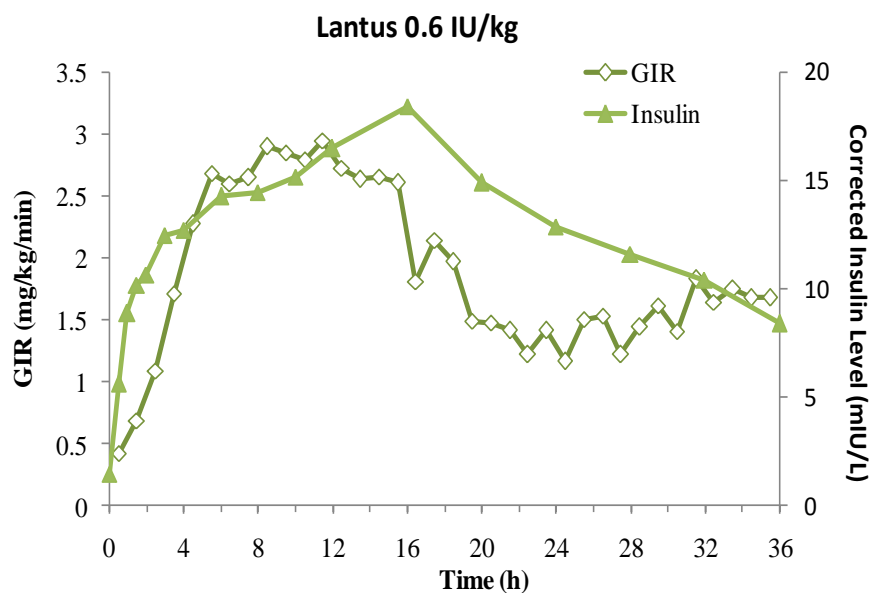
*values are mean
(± SD)*



Average across all patients

Study PKFT 105-0701

PK/PD correlation for Lantus and FT105



- The 12 – 24 hours GIR decrease is « night effect ».
- 24 to 36 hours GIR rises for FT-105.

Study PKFT 105-0701

FT-105 Proof-Of-Concept is Demonstrated

- **Flat PK/PD profile for more than 48 hours**
- **Good dose proportionality**
- **Excellent local tolerance and safety profile**



FT105 Rat Studies

FT-105 Diabetic Rats

Daily Subcutaneous Administration Over 7 days

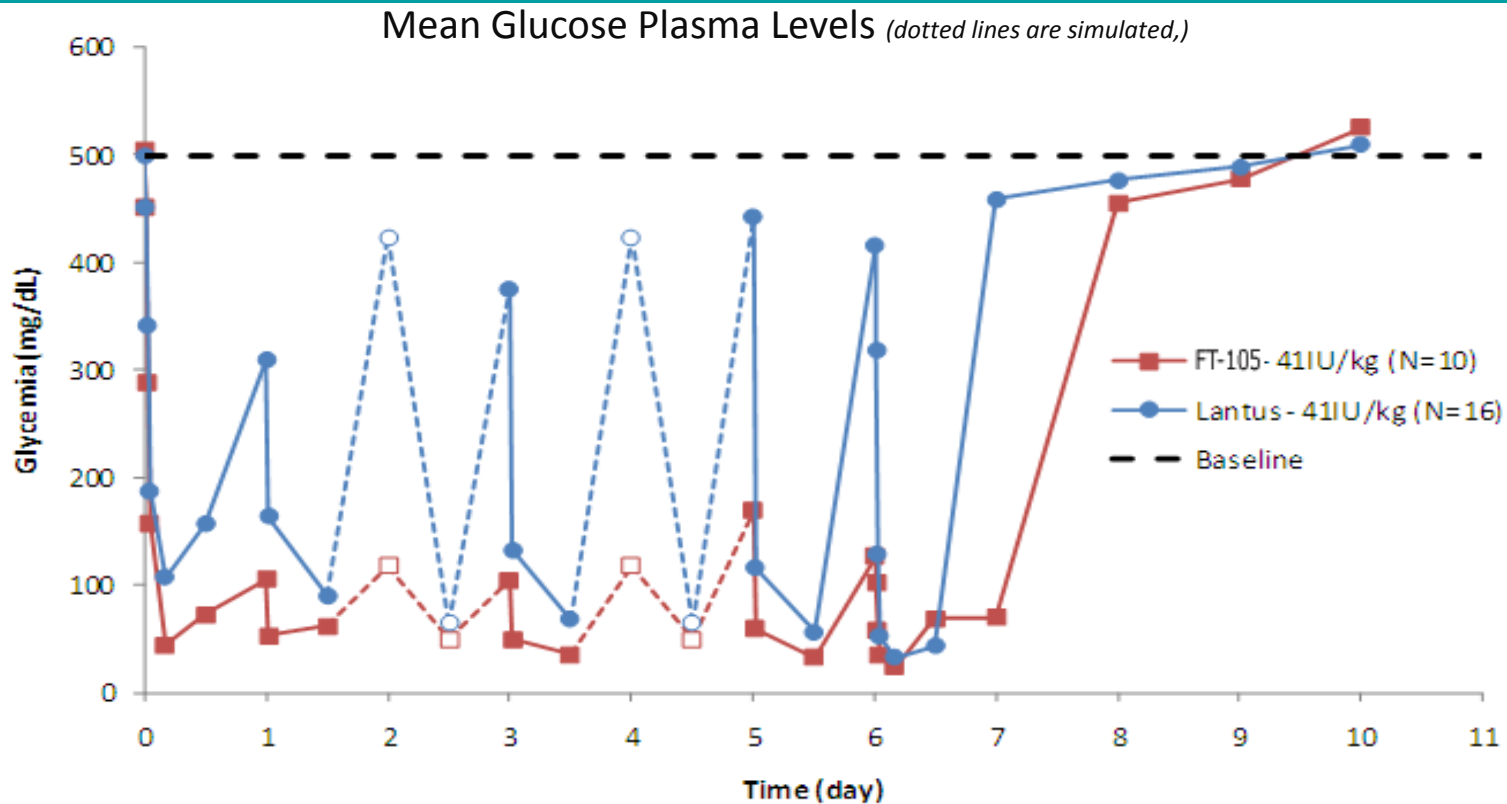
- **16 STZ-induced diabetic rats per group**
 - 40mg/kg STZ 3 days prior to start
- **Repeated once-a-day subcutaneous administrations for 7 days of**

Formulation	[insulin] (IU/ml)	N	Dose (IU/kg)
FT-105	100	16	41
Lantus	100	16	41

- **Blood sampling :**
 - D1: predose and 15, 30 min, 1h, 4h, 12h
 - D2 / D4 / D6 : predose, 30 min, 12h
 - D7: predose, 15, 30 min, 1h, 4h, 12h, 24h, 48h, 72h and 96h
- **Determination of glycemia (16 rats per group) and insulinemia (8 rats per group as 2 sub-groups)**
- Study performed by PreClinOmics.

Study PRFT105-0803

FT-105 Shows a Tighter PD Profile than Lantus



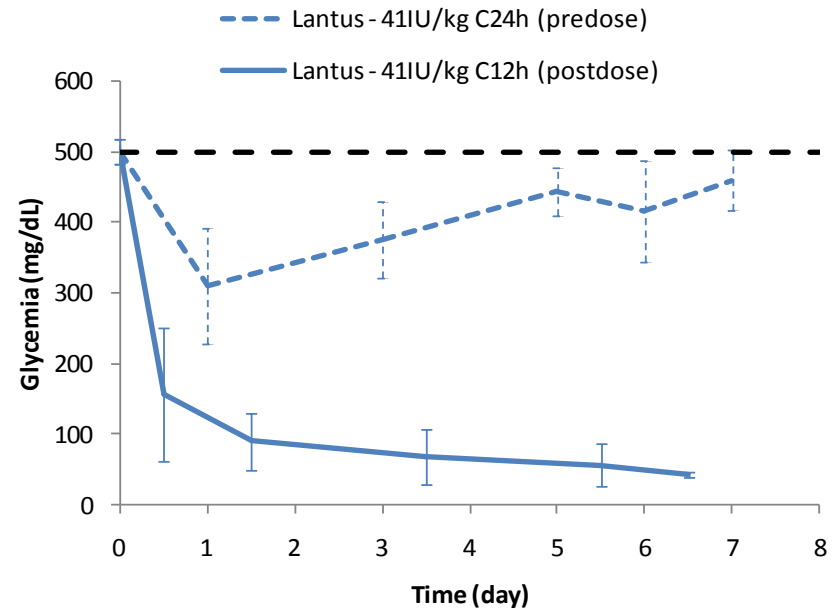
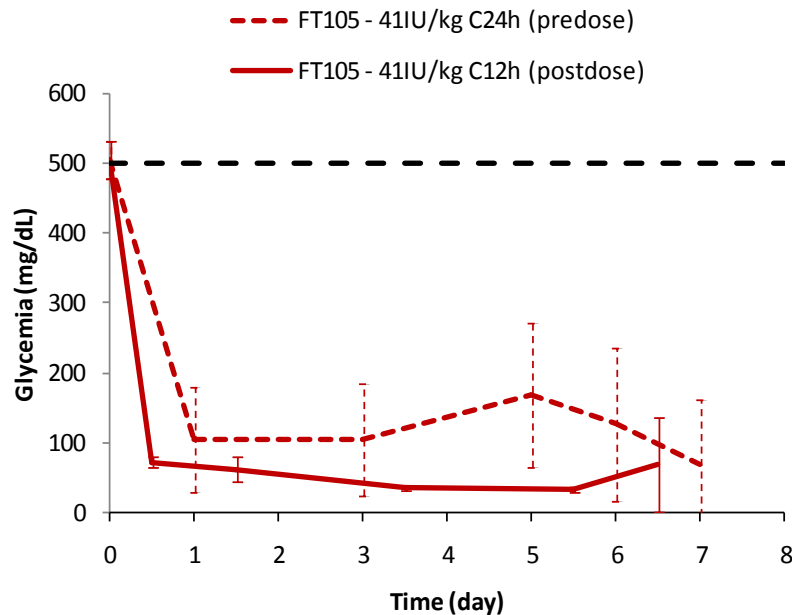
- Multiple administration of FT-105 in diabetic rats highlighted a tighter PD profile than Lantus with longer duration of action and lower peak-to-trough ratio.

Study PRFT105-0803

FT-105 Enables Tighter Control of Glycemia

Mean PD Profiles

Arithmetic mean \pm CI95%



- Multiple daily administrations of FT-105 in diabetic rats led to tighter regulation of glucose levels as characterized by smaller C12-C24 hour differences.

Study PRFT105-0803

Rat Studies Confirm Behavior Obtained in both Dog and Human Studies

- **FT-105 appears more effective than Lantus in controlling glucose**
- **FT-105 significantly decreases peak to trough ratios compared to Lantus.**

Summary and conclusions

- A new long-acting insulin formulation based on its **MEDUSA** proprietary drug delivery technology has been developed:
 - Reversible association between insulin and the MEDUSA polymer;
 - Delivery of an **unmodified fully active insulin**.

- In preclinical and clinical trials, **FT-105** demonstrated sustained release of insulin over more than 48h with a flat profile.

- After 3 or 4 daily administrations, a **steady state basal insulin level** is reached and should :
 - ✓ **Decrease intra-subject** variability because insulin concentration will be the accumulation of 3 or 4 doses.
 - ✓ **Reduce safety concerns** for missed dose because skipping one administration only decreases basal insulin level a third.
 - ✓ **Reduce hypoglycemia events** due to the constant insulin concentration level.