Liraglutide in Type 2 Diabetes: Clinical Pharmacokinetics and Pharmacodynamics

Authors: Jacobsen LV1, Flint A[1], Olsen AK[2], Ingwersen SH[1]

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Corresponding author:

SH Ingwersen. Novo Nordisk A/S, Copenhagen, Denmark. Email: si@novonordisk.com, Phone: +4530794847, Fax: +4544436740

Affiliations:

[1]Clinical Pharmacology, Global Development, Novo Nordisk A/S, Copenhagen, Denmark

[2]NCD Project Management, Non-clinical Development, Novo Nordisk A/S, Copenhagen, Denmark

Correspondence:

SH Ingwersen, Novo Nordisk A/S, Vandtårnsvej 110, DK-2860 Søborg, Denmark

E-mail: si@novonordisk.com

Supplementary table

Table 1. Overview of studies on liraglutide for T2DM therapy focussing on pharmacokinetics and pharmacodynamics

First author, year (reference)	Primary focus	Study population	Number of participants	Liraglutide dose (treatment duration[a])
Studies performed only in individuals without diabetes				
Malm-Erjefält 2010 (32)	Metabolism, excretion and *in vitro* degradation	Healthy males	7	0.75 mg ^{3}H-labelled (single dose)
Agersø 2002 (36)	Pharmacokinetics, pharmacodynamics, safety and tolerability	Healthy males	Liraglutide: 15 Placebo: 10	1.25, 5.0, 7.5, 10 or 12.5 µg/kg [~0.1, 0.38, 0.56, 0.72 or 0.93 mg[b]] (7 days)
Damholt 2006 (37)	Pharmacokinetics by age and gender	Healthy	32	1.0 mg (single dose)
Flint 2010 (38)	Pharmacokinetics and safety in subjects with hepatic impairment	Healthy and subjects with varying degrees of hepatic impairment	24	0.75 mg (single dose)
Irie 2008 (40)	Tolerability, pharmacokinetics and pharmacodynamics	Healthy Japanese males	Liraglutide: 18 Placebo: 6	15, 20 and 25 µg/kg [~0.85, 1.25 and1.63 mg[b]] (1–3 weeks)
Jacobsen 2009 (41)	Pharmacokinetics and safety in subjects with renal impairment	Healthy and subjects with varying degrees of renal impairment	30	0.75 mg (single dose)
Jiang 2011 (42)	Pharmacokinetics, pharmacodynamics and tolerability	Healthy Chinese males	Liraglutide: 28 Placebo: 9	0.6, 1.2 or 1.8 mg (3 weeks)
Kapitza 2011 (43)	Pharmacokinetics by injection site	Healthy	21	0.6 mg (single dose)

Malm-Erjefält 2015 (44)	Drug–drug interaction - atorvastatin, griseofulvin, lisinopril, digoxin	Healthy	70 Cross-over with placebo	1.8 mg (up to 5 weeks)
Elbrønd 2002 (45)	Pharmacokinetics, pharmacodynamics, safety and tolerability	Healthy males	Liraglutide: 54 Placebo: 18	1.25, 2.5, 5.0, 10.0, 12.5, 15.0, 17.5 and 20.0 µg/kg [~0.09, 0.18, 0.39, 0.74, 0.91, 1.14, 1.33 and 1.44 mg[b]] (single dose)
Jacobsen 2011 (53)	Drug–drug interaction - ethinyl oestradiol/levonorgestrel (combination oral contraceptive)	Healthy postmenopausal women	21 Cross-over with placebo	1.8 mg (3 weeks)
Iepsen 2015 (82)	Bone formation and weight loss	Healthy obese women	Liraglutide: 18 Controls: 19	1.2 mg (52 weeks)
Chatterjee 2009 (83)	Cardiac repolarisation; QT_c study	Healthy	51 Cross-over with placebo	1.2 or 1.8 mg (3 weeks)
Studies performed in subjects with T2DM and studies including both healthy subjects and T2DM				
Garber 2009 (10)	Safety and efficacy vs. glimepiride monotherapy	T2DM	Liraglutide: 497 Glimepiride: 248	1.2 or 1.8 mg (52 weeks)
Yang 2011 (34)	Efficacy and safety vs. glimepiride, in combination with metformin	T2DM, Asians	Liraglutide: 697 Glimepiride: 231	0.6, 1.2 or 1.8 mg (16 weeks)
Hermansen 2013 (39)	Effect on postprandial lipid concentration	T2DM	20 Cross-over with placebo	1.8 mg daily (3 weeks)
Klein 2014 (48)	Pharmacokinetics, pharmacodynamics, safety and tolerability in paediatric subjects	T2DM; aged 10–17 years	Liraglutide: 14 Placebo: 7	0.3, 0.6, 0.9, 1.2 and 1.8 mg (5 weeks)
Davies 2014 (49)	Efficacy and safety in subjects with T2DM and renal impairment	T2DM with moderate renal impairment	Liraglutide: 140 Placebo: 137	1.8 mg (26 weeks)
Osonoi 2014 (50)	Effect of haemodialysis on plasma glucose profile, liraglutide concentrations and safety	T2DM Japanese with ESRD	10	0.6 or 0.9 mg (2 days)

Idorn 2015 (51)	Safety and efficacy in dialysis-dependent ESRD subjects	T2DM and T2DM with ESRD	Liraglutide: 10 T2DM with ESRD; 10 T2DM Placebo: 10 T2DM with ESRD; 10 T2DM	1.8 mg (12 weeks)
Kapitza 2011 (54)[c]	Drug–drug interaction - acetaminophen	T2DM	18 Cross-over with placebo	1.8 mg (3 weeks)
Morrow 2011 (56)	Drug–drug interaction - insulin detemir	T2DM	33	1.8 mg (4 weeks)
Juhl 2002 (58)	Effect on fasting and postprandial glycaemia	T2DM	11 Cross-over with placebo	10 µg/kg [~0.87 mg[b]] (single dose)
Chang 2003 (59)	β-cell sensitivity	T2DM and healthy	T2DM: 10 Cross-over with placebo Healthy: 10	7.5 µg/kg [~0.66 mg[b]] (single dose)
Nauck 2003 (60)	Counter regulatory response to hypoglycaemia	T2DM	11 Cross-over with placebo	7.5 µg/kg [~0.68 mg[b]] (single dose)
Flint 2011 (61)[c]	Postprandial glucose response	T2DM	18 Cross-over with placebo	0.6, 1.2 or 1.8 mg (3 weeks)
Horowitz 2012 (62)	Effects on appetite, energy intake, energy expenditure and gastric emptying	T2DM	46 Cross-over with placebo or glimepiride	1.8 mg (4 weeks)
Vilsbøll 2008 (63)	β-cell function and arginine-stimulated insulin secretion	T2DM and healthy	Liraglutide: 29 Placebo: 10 Healthy: 12	0.65, 1.25 or 1.9 mg (14 weeks)
Jendle 2009 (64)	Body composition, alone or in combination with metformin	T2DM	Trial1: 221 Trial 2: 154	Trial 1: 0.6, 1.2 or 1.8 mg (26 weeks) Trial 2: 1.2 or 1.8 mg (52 weeks)
Flint 2013 (65)[c]	Appetite and energy intake	T2DM	18 Cross-over with placebo	1.8 mg (3 weeks)
Degn 2004 (66)	24 hour glycaemia, and β-cell function	T2DM	13	6 µg/kg [~0.55 mg[b]] (8–9 days)

Population pharmacokinetics and exposure–response analysis studies				
Ingwersen 2012 (33)[d]	Exposure–response and population pharmacokinetic evaluations for dosing rationale	T2DM	Trial 1: 190 Trial 2: 163 Trial 3: 745	0.045–1.9 mg (12–52 weeks)
Ingwersen 2015 (35)[e]	Population pharmacokinetics and exposure–response relationship	T2DM, Asians	605	0.6, 1.2 or 1.8 mg (16 weeks)
Watson 2010 (46)[f]	Population pharmacokinetics vs. exenatide	Healthy and T2DM	Liraglutide: 192 patients; 74 healthy Exenatide: 28 patients	Healthy: 1.25–20 µg/kg [~0.09–1.44 mg[b]]; T2DM: 0.65, 1.25 or 1.9 mg
Petri 2015 (47)[g]	Comparison of pharmacokinetics between paediatric and adult populations	Trial 1: T2DM; aged 10–17 years Trials 2 and 3: T2DM	Trial 1 (liraglutide): 13 Trial 2 (liraglutide): 12 Cross-over with placebo Trial 3 (liraglutide and insulin degludec): 32	Trial 1: 0.3, 0.6, 0.9, 1.2 and 1.8 mg Trials 2 and 3: 1.8 mg
Flint 2010 (76)[h]	Relationship between liraglutide plasma concentrations and plasma glucose, gastric emptying and energy intake	T2DM	18	0.6, 1.2 or 1.8 mg (3 weeks)

Unless otherwise indicated, all studies were performed in adults, subjects of both genders and race was not pre-specified. ESRD, end-stage renal disease; T2DM, type 2 diabetes mellitus.

[a]For multiple dose trials, liraglutide doses are once daily and treatment duration includes weekly dose escalations. [b]Unit conversions from µg/kg to mg were approximated based on individual body weight of participants [Novo Nordisk, data on file].

[c]Kapitza 2011 (54), Flint 2011 (61) and Flint 2013 (65) were studies based on the same trial population; [d]Ingwersen 2012 (33) was based on data from Vilsbøll 2008 (63) and Garber 2009 (10); [e]Ingwersen 2015 (35) was based on data from Yang 2011 (34); [f]Watson 2010 was based on data from Agersø 2002 (36), Elbrønd 2002 (45), Juhl 2002 (58) and Nauck 2003 (60); [g]Petri 2015 (47) was based on data from Klein 2014 (48), Hermansen 2013 (39) and Morrow 2011 (56); [h]Flint 2010 (76) was based on the same data as Flint 2011 (61) and Flint 2013 (65).