Admelog®
insulin lispro
injection 100 Units/mL

sanofi

Comparing the Pharmacokinetics and Pharmacodynamics of Admelog® and Humalog®

Kapitza C, *et al. Diabetes Obes Metab.* 2017;19(5):622–7.

Prescribing Information can be found at the end of this document.

Admelog is indicated for treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis and for the initial stabilisation of diabetes mellitus.[1]

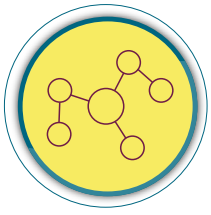
A comparative study of the PK/PD profiles of three rapid-acting insulin lispro products: Admelog, US-approved Humalog and, UK and EU-approved Humalog.

Key takeaway

PK/PD profiles in the biosimilar, Admelog, were similar to those in US-approved Humalog and, UK and EU-approved Humalog, in adult males with T1DM.

Why this matters

The availability of a biosimilar rapid-acting insulin treatment has the potential to reduce diabetes-related health costs, increase choice and accessibility to treatment for diabetes patients.[2]



Producing biologically similar protein-based therapeutics is challenging due to the complexity of manufacturing processes; small changes can impact the molecular structure and, in turn, the pharmacology, safety and efficacy of a drug.[2]

This study demonstrates the suitability of Admelog rapid-acting insulin as a biosimilar candidate.[2]

EU, European Union; PK/PD, pharmacokinetic/pharmacodynamic; T1DM, type 1 diabetes mellitus; UK, United Kingdom; US, United States.

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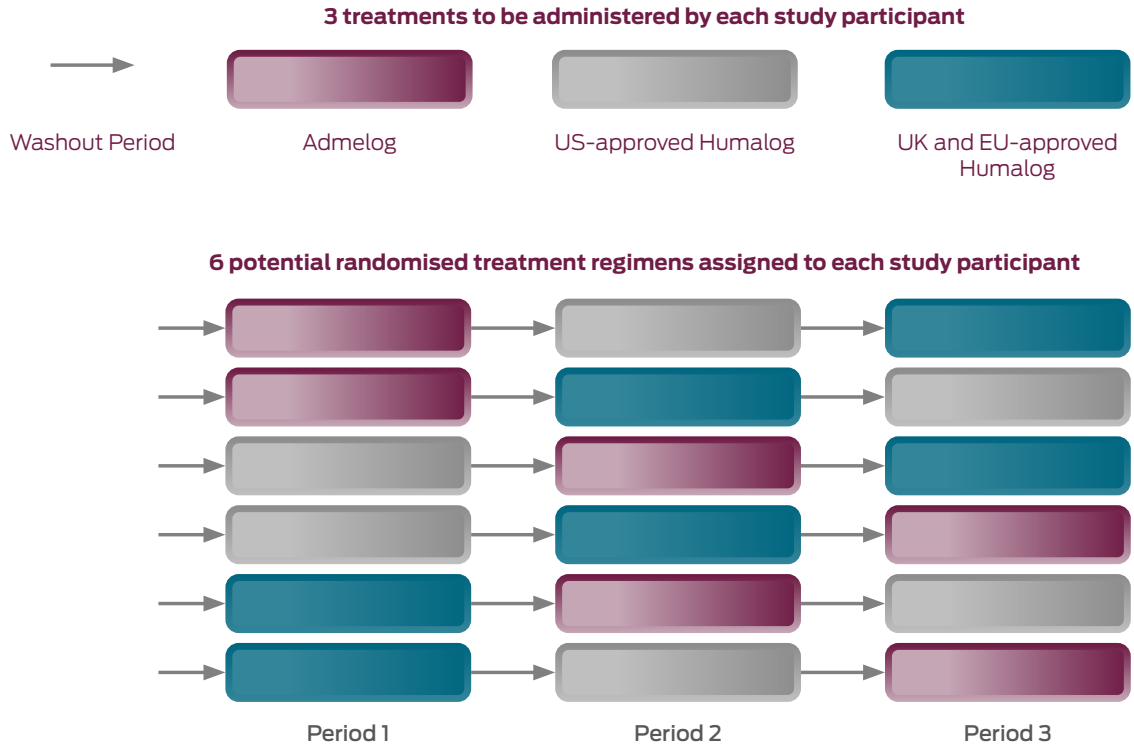
Study design:

- Single-centre, randomised, double-blind, 3-treatment, 6-sequence, crossover, euglycaemic clamp study in T1DM patients[2]
- 30 participants, all males aged 18–65, each received single injections of 0.3 units/kg Admelog, US-approved Humalog or UK and EU-approved Humalog under fasting conditions*[2]
- The order in which the treatments were given was randomised for each patient into 1 of 6 sequences[2]



Adapted from Kapitza C, *et al.* 2017.

- Primary endpoints for PK analyses were INS-C_{max} and INS-AUC. Primary endpoints for PD analyses were GIR_{max} and GIR-$AUC_{0\text{-}12h}$[2]
- The safety and tolerability of Admelog compared with US-approved Humalog and, UK and EU-approved Humalog was assessed using AE reporting, ECG recordings, vital sign assessments, clinical laboratory tests, injection site reaction assessments and the incidence of hypoglycaemia, if any[2]

*Inclusion criteria: Participants had a duration of disease of >1 year, body mass index of 18–30 kg/m^2, glycated HbA_{1c} level ≤9.0% (≤75 mmol/mol), fasting negative serum C-peptide level of <0.3 nmol/L, a total daily insulin dose of <1.2 units/kg. In addition, subjects used the same insulin products in a stable regimen for at least 2 months prior to the study. Of the 30 subjects randomised, 28 completed all 3 treatment periods.

AE, adverse effect; ECG, electrocardiogram; EU, European Union; GIR-$AUC_{0\text{-}12h}$, area under the bodyweight-standardised glucose infusion rate vs. time curve from 0–12 hours; GIR_{max}, maximum smoothed bodyweight-standardised glucose infusion rate; INS-AUC, area under the insulin concentration vs. time curve; INS-AUC_{last}, area under the insulin concentration vs. time curve from time zero to the time corresponding to the last concentration above the limit of quantification; INS-C_{max}, maximum observed plasma insulin lispro concentration; PK/PD, pharmacokinetic/pharmacodynamic; T1DM, type 1 diabetes mellitus; UK, United Kingdom; US, United States.

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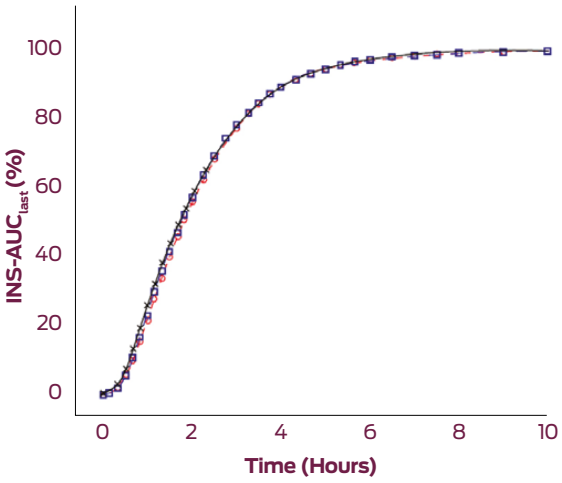
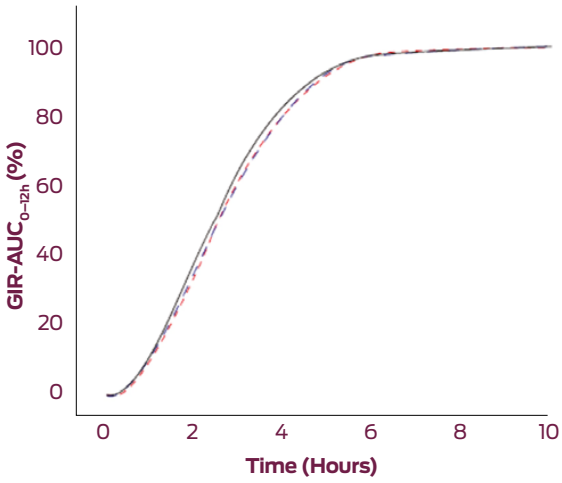
Key findings:

PK/PD profiles for Admelog, US-approved Humalog and, UK and EU-approved Humalog were virtually superimposable[2]

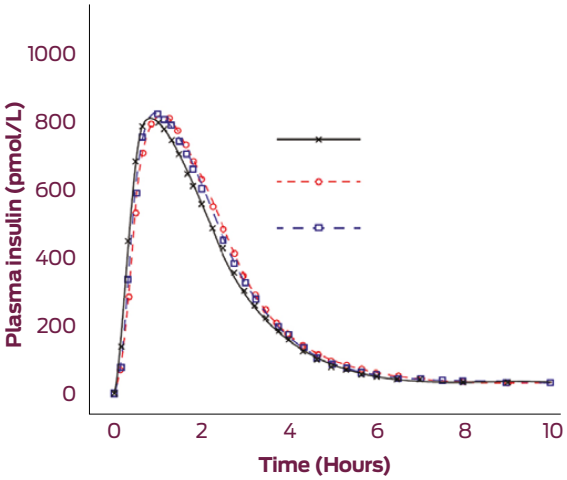
PK parameters: Median of percent cumulative plasma insulin exposure based on AUC_{last}



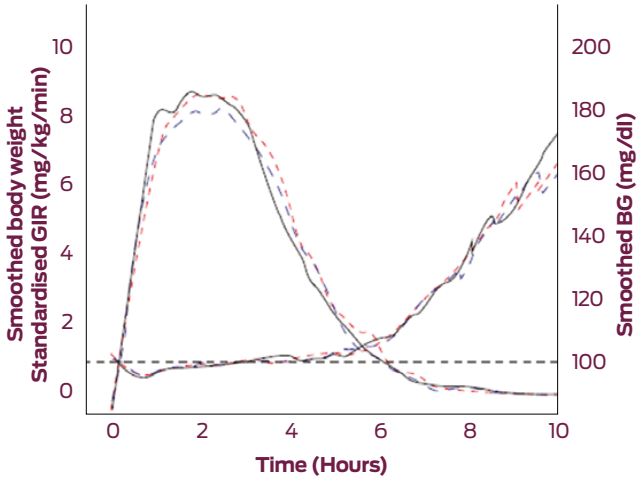
PD parameters: Median of percent cumulative bodyweight-standardised GIR-AUC based on GIR-AUC_{0-12h}



PK parameters: Plasma mean concentration vs. time profiles



PD parameters: Mean smoothed bodyweight-standardised GIR and blood glucose profiles



Admelog — US-approved Humalog — UK and EU-approved Humalog

Adapted from Kapitza C, *et al.* 2017.

- 90% CIs of treatment ratios for INS-C_{max}, INS-AUC_{last}, INS-AUC, GIR_{max} and GIR-AUC_{0-12h} were entirely within pre-defined equivalence interval of 0.8–1.25[2]
- Within-subject variability was low across the three treatments for exposure and activity:[2]
  - 6.8% (90% CI, 5.9; 8.1) for INS-AUC and 15.6% (13.5; 18.6) for INS-C_{max} and 16.7% (14.4; 19.9) for GIR-AUC_{0-12h} and 15.2% (13.1; 18.1) for GIR_{max}
- Safety and tolerability assessments showed that TEAEs were similar for the three insulin lispro products:[2]
  - TEAEs were reported in 6/29 subjects after Admelog administration, in 6/29 following US-approved Humalog administration, and in 3/29 subjects following UK and EU-approved Humalog administration
  - The most commonly reported TEAE for each treatment was headache, reported in 5, 4 and 2 subjects following the administration of Admelog, US-approved Humalog, and, UK and EU-approved Humalog, respectively

BG, blood glucose; CI, confidence intervals; EU, European Union; GIR-AUC_{0-12h}, area under the bodyweight-standardised glucose infusion rate vs. time curve from 0–12 hours; GIR_{max}, maximum smoothed bodyweight-standardized glucose infusion rate; INS-AUC, area under the insulin concentration vs. time curve; INS-AUC_{last}, area under the insulin concentration vs. time curve from time zero to the time corresponding to the last concentration above the limit of quantification; INS-Cmax, maximum observed plasma insulin lispro concentration; PK/PD, pharmacokinetic/pharmacodynamic; TEAE, treatment-emergent adverse effects; UK, United Kingdom; US, United States.

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Study limitations:

- Study pool was homogeneous both in gender and ethnicity
- Study sample of 30 participants is small for a clinical study

Conclusions:

This study demonstrates the **similarity in PK/PD profiles of Admelog** to both US-approved Humalog and, UK and EU-approved Humalog. The PK/PD profiles of all three rapid-acting insulins are virtually superimposable, rendering Admelog a biosimilar candidate.[2]

Prescribing Information: Admelog® (Insulin lispro 100 units/ml)

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Presentations: Admelog 100 units/ml solution for injection in a vial, each containing 10ml of solution for injection, equivalent to 1000 units. Admelog 100 units/ml solution for injection in a cartridge or in a pre-filled pen each containing 3 ml of solution for injection, equivalent to 300 units insulin lispro.
Indication: For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis and for the initial stabilisation of diabetes mellitus.
Dosage and Administrations: The dose should be determined by the physician, according to the requirement of the patient. Admelog may be given shortly before meals, when necessary can be given soon after meals. Insulin lispro takes effect rapidly and has a shorter duration of activity (2-5 hours) given subcutaneously as compared with regular insulin, regardless of injection site. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual and duration of action is dependent on dose, site of injection, blood supply, temperature, and physical activity. Admelog can be used in conjunction with longeracting insulin or oral sulphonylurea medicinal products, on the advice of a physician. Admelog in cartridges are only suitable for subcutaneous injections from a reusable pen. Admelog in pre-filled pen are only suitable for subcutaneous injections. Admelog solution for injection should be given by subcutaneous injection or by continuous subcutaneous infusion pump and may, although not recommended, also be given by intramuscular injection. If necessary, it may also be administered intravenously. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used. *Subcutaneous administration:* Should be in the upper arms, thighs, buttocks, or abdomen. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. Care should be taken when injecting to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use the proper injection techniques. *Administration via an insulin infusion pump (Admelog vials only):* Admelog should not be mixed with any other insulin. Continuous subcutaneous insulin infusion (CSII) may be given in pump systems suitable for insulin infusion; only certain CE-marked insulin infusion pumps may be used. Before infusing, the manufacturer's instructions should be studied to ascertain the suitability or otherwise for the particular pump. Use the correct reservoir and catheter for the pump. The infusion set (tubing and cannula) should be changed in accordance with the instructions in the product information supplied with the infusion set. A pump malfunction or obstruction of the infusion set can result in a rapid rise in glucose levels. If an interruption to insulin flow is suspected, follow the instructions in the product literature. *Intravenous administration (Admelog vials only):* Should be carried out following normal clinical practice for intravenous injections; frequent monitoring of the blood glucose levels is required. **Special Populations:** *Renal/Hepatic impairment:* Insulin requirements may be reduced. Patients with chronic hepatic impairment may have diminished insulin sensitivity and therefore require an increased dose. *Paediatric population:* Admelog can be used in adolescents and children.
Contraindications: Hypoglycaemia, hypersensitivity to insulin lispro or to any of the excipients.
Precautions and Warnings: *Traceability:* In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. *Transferring to another type/ brand of insulin:* Should be done under strict medical supervision and may result in the need for change in dose. For fast-acting insulins, any patient also on basal insulin must optimise dose of both insulins to obtain glucose control across the whole day, particularly nocturnal/fasting glucose control. *Injection technique:* Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered. *Hypoglycaemia or hyperglycaemia:* Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease or medications such as beta-blockers. Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death. Inadequate dose or discontinuation of treatment, especially in insulin dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal. *Dose adjustment:* Insulin requirements may be increased during illness or emotional disturbances. Adjustment of dose may also be necessary if patients undertake increased physical activity or change their usual diet. *In combination with pioglitazone:* Cases of cardiac failure have been reported, especially in patients with risk factors for development of heart failure. Patients using this combination should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. *Medication errors:* Patients must be instructed to always check the insulin label before each injection to avoid mix-ups between Admelog and other insulin products. Patients must visually verify the dialled units on the dose counter of the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device. *Excipients:* This medicine is essentially "sodium-free". *Pregnancy:* It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes. *Breastfeeding:* Patient may require adjustments in insulin dose, diet or both.
Interactions: The physician should be consulted when using other medicinal products in addition to Admelog. Insulin requirements may be increased by medicinal products with hyperglycaemic activity and reduced in the presence of medicinal products with hypoglycaemic activity.
Adverse Reactions: Hypoglycaemia is the most frequent adverse reaction. Oedema has been reported, particularly if previous poor metabolic control is improved by intensified insulin therapy. *Common (≥1/100 to <1/10):* Local allergy. *Uncommon (≥1/1,000 to <1/100):* Lipodystrophy. *Rare (≥1/10,000 to <1/1,000):* Systemic allergy. *Not known (cannot be estimated from the available data):* Cutaneous amyloidosis. *Prescribers should consult the SmPC in relation to other adverse reactions.*
Legal Category: POM.
Marketing Authorisation (MA) Holder: Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK
UK List price and MA Numbers: *Admelog 100 units/ml solution for injection in vial 1 x 10ml:* £14.12 – PLGB 04425/0822. *Admelog 100 units/ml solution for injection in cartridge 5x 3ml:* £21.23 – PLGB 04425/0823. *Admelog 100 units/ml solution for injection in pre-filled pen 5 x 3ml:* £22.10 – PLGB 04425/0824.
Further information is available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. Uk-medicalinformation@sanofi.com.
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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Sanofi Tel: 0800 090 2314. Alternatively, send via email to UK-drugsafety@sanofi.com

EU, European Union; PK/PD, pharmacokinetic/pharmacodynamic; UK, United Kingdom; US, United States.

References: 1. Admelog Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/13083. Date accessed: October 2022.
2. Kapitza C, *et al. Diabetes Obes Metab.* 2017;19(5):622–7.

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