Supplementary Material

Efficacy and safety of fast-acting insulin aspart in people with type 1 diabetes using carbohydrate counting: a post hoc analysis of two randomised controlled trials

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Table S1. Bolus dose titration algorithm

| Pre-prandial glucose (mmol/L) | Dose adjustment (U) | Rules for dose adjustments          |
|------------------------------|---------------------|-------------------------------------|
| <4.0                         | −1                  | ≥1 SMBG below target                |
| 4.0–6.0                      | No adjustment       | 0–1 SMBG above target               |
|                              |                     | No SMBG below target                |
| >6.0                         | +1                  | ≥2 SMBG above target                |
|                              |                     | No SMBG below target                |

Adjustments were made twice weekly, once by the investigator and once by the participant.

SMBG, self-measured blood glucose; U, units.
Fig. S1: Trial design of onset 1 and onset 8

†Insulin detemir in onset 1 and insulin degludec in onset 8.

ClinicalTrials.gov: NCT01831765 (onset 1) and NCT02500706 (onset 8). Baseline is at randomisation.

Follow-up was at 7–30 days. Change from baseline in HbA1c at week 26 was the primary endpoint in both onset 1 and onset 8. An additional 26-week treatment period was included in onset 1 to document long-term safety (data not included in the post hoc analysis).

Faster aspart, fast-acting insulin aspart; T1D, type 1 diabetes.
**Fig. S2:** Non-cumulative meal-related severe or BG-confirmed hypoglycaemia rates after 26 weeks for a) mealtime and b) post-meal faster aspart in onset 1, and c) mealtime and d) post-meal faster aspart in onset 8, all versus insulin aspart, by dose adjustment method.

|                  | Estimate (meal-related episode/PYE) | Estimated treatment rate ratio (95% CI) | Estimate (meal-related episode/PYE) | Estimated treatment rate ratio (95% CI) |
|------------------|-------------------------------------|----------------------------------------|-------------------------------------|----------------------------------------|
| **a)** Faster aspart (mealtime) | Insulin aspart | Faster aspart/insulin aspart | Faster aspart (post-meal) | Insulin aspart |
| >1−2 h           | 5.51 4.75 | 1.16 (0.94;1.43) | 4.49 4.75 | 0.95 (0.76;1.17) |
|                  | 4.53 3.85 | 1.16 (0.89;1.55) | 4.19 3.85 | 1.09 (0.82;1.44) |
|                  | 7.29 6.41 | 1.14 (0.82;1.57) | 4.94 6.41 | 0.77 (0.56;1.07) |
| >2−3 h           | 8.80 8.32 | 1.06 (0.88;1.27) | 8.14 8.32 | 0.98 (0.81;1.17) |
|                  | 7.76 7.36 | 1.05 (0.83;1.34) | 8.00 7.36 | 1.09 (0.86;1.38) |
|                  | 10.51 9.91 | 1.06 (0.80;1.41) | 8.29 9.91 | 0.84 (0.63;1.11) |
| >3−4 h           | 8.09 8.78 | 0.92 (0.78;1.09) | 8.31 8.78 | 0.95 (0.80;1.12) |
|                  | 7.25 7.52 | 0.96 (0.77;1.12) | 7.69 7.52 | 1.02 (0.82;1.28) |
|                  | 9.48 10.95 | 0.87 (0.66;1.13) | 9.30 10.95 | 0.85 (0.65;1.11) |

Data from ‘all subjects’ in each trial are included alongside data from the dose adjustment method groups.

CI, confidence interval; ETR, estimated treatment ratio; faster aspart, fast-acting insulin aspart; PYE, patient-year of exposure.
Supplementary Appendix

onset 1 independent ethics committees/institutional review boards

Belgium: Ethics Committee UZA, Edegem; Ethics Committee Erasme-ULB, Brussels; Commissie Medische Ethiek van de Universitaire Ziekenhuizen K.U. Leuven, Leuven; Ethics Committee UZ Gent, Gent; Imelda vzw Commissie Medisch Ethiek, Bonheiden. Canada: Comité d’éthique de la Recherche - Institut de Recherches Cliniques de Montreal, Montreal, QC; University of Alberta, Research Ethics Office, Health Research Ethics Board, Edmonton, AL; Hamilton Integrated Research Ethics Board (HIREB), Hamilton, ON; Institutional Review Board (IRB) Services, Aurora, ON; The University of Manitoba, Biomedical Research Ethics Board, Winnipeg, MB; Comité d’éthique de la recherche CHU de Québec – Université Laval, Quebec, QC; Western University Health Science Research Ethics Board, London, ON; Mount Sinai Hospital Research Ethics Board, Toronto, ON; Health Research Ethics Board of Alberta, Clinical Trials Committee, Edmonton, AB; Vancouver Island Health Authority Research Ethics Board, Victoria, BC; Institutional Review Board (IRB) Services, Aurora, ON. Czech Republic: Multicentrická Etická komise Fakultní nemocnice u Sv. Anny v Brně, Brno; Etická komise IKEM a FTNsP (Fakultní Thomayerova nemocnice s poliklinikou), Prague; Etická komise Fakultní nemocnice Hradec Králové, Hradec Králové; Etická komise pro multicentrická klinická hodnocení, Etická komise VFN, Prague. Finland: Helsinki and Uusimaa Hospital District Ethics Committee, Department of Medicine Biomedicum Helsinki 2C, Helsinki. Germany: Ethikkommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelmsuniversität, Muenster. Hungary: Medical Research Council Ethics Committee for Clinical Pharmacology, Budapest. Poland: Komisja Bioetyczna przy Okregowej Izbie Lekarskiej w Bialymstoku, Bialystok. United Kingdom: NRES Committee London – South East Bristol REC Centre, Bristol. United States: Sterling Institutional Review Board, Atlanta, GA; Veterans Affairs Institutional Review Board, Lexington, KY; Christiana Care Institutional Review Board, Newark, DE; University of Texas Southwestern Medical Center at Dallas Institutional Review Board, Dallas, TX; Western Institutional Review Board, Puyallup, WA;
Icahn School of Medicine at Mount Sinai Institutional Review Board, New York, NY; University of North Carolina Office of Human Research Ethics, Chapel Hill, NC; Johns Hopkins Institutional Review Board, Baltimore, MD; Park Nicollet Institute Institutional Review Board, Minneapolis, MN; Baylor Research Institute Institutional Review Board, Dallas, TX; Chesapeake Institutional Review Board, Columbia, MD; Oregon Health & Science University Research Integrity Office, Portland, OR; University of Miami Human Subjects Research Office, Miami, FL; St. Luke's Health System Institutional Review Board, Boise, ID; Washington State University Institutional Review Board, Pullman, WA; Rochester General Health Systems IRB, Rochester, NY; UMass Medical School IRB, The Committee for Protection of Human Subjects in Research, Worcester, MA; Edward Hines Jr. VA Hospital/Captain James A. Lovell Federal Health Care Center Institutional Review Board, Hines, IL

**onset 8 independent ethics committees/institutional review boards**

**Austria:** Ethikkommission der Stadt Wien TownTown, Wien; Ethikkommission der Medizinischen Universität Graz, Graz; EK für das Bundesland Salzburg, Salzburg. **Bulgaria:** Ethics Committee for Multicentre Clinical Trials, Sofia. **Canada:** Comité d’éthique de la Recherche - Institut de Recherches Cliniques de Montréal, Montreal, QC; Nova Scotia Health Authority Research Ethics Board, Halifax, NS; Health Research Ethics Board of Alberta Clinical Trials Committee, Edmonton, AL; Comité d’Éthique de la Recherche de l’IUCPQ-Université Laval, Quebec, QC; Institutional Review Board Services, Aurora, ON. **Germany:** Landesärztekammer Brandenburg Ethikkommission, Cottbus. **Israel:** Hadassah Helsinki Committee, Jerusalem; Rabin Helsinki Committee, Petah-Tikva; Rambam Helsinki Committee, Haifa; Assuta Helsinki Committee, Tel Aviv; Wolfson Helsinki Committee, Holon; Meir Helsinki Committee, Kfar Saba. **India:** Institutional Ethics Committee, Ramdevrao Hospital, Kukatpally; Institutional Review Board, Christian Medical College, Vellore; Madras Diabetes Research Foundation Institutional Ethics Committee, Chennai; Institutional Ethics Committee, Govt. Medical College, Kozhikode, Kerala; Institutional Ethics Committee, Poona Medical Research Foundation, Pune; Institute Ethics Committee, AIIMS, New Delhi; Cuttack Diabetes Research Foundation Ethics
Committee, Pune; KEM Hospital and Research Centre, Ethics Committee, Pune; Multispeciality Ethics Committee, Mithakhali, Ellisbridge, Ahmedabad; Sterling Hospital Ethics Committee, Ahmedabad; Integrity Ethics Committee, Convenient Hospitals, Chennai; Ethics Committee, Prof. M. Viswanathan Diabetes Research Institute, Chennai; Ethics Committee, PT. Sharma UHS, Institutional Rohtak, Haryana; PGIMER, Institutional Ethics Committee, Chandigarh; Institutional Ethics Committee, King George Hospital, Visakhapatnam; Ethics Committee of Diabetes Thyroid Hormone Research Institute, BCM Health Island, Indore. **Italy:** COMITATO ETICO DELL’IRCCS FONDAZIONE S. RAFFAELE DEL MONTE TABOR DI MILANO, Milan; COMITATO DI BIOETICA DELLA.O. Papa Giovanni XXIII, Bergamo; Comitato Etico Policlinico Universitario "Agostino Gemelli", Rome; COMITATO ETICO DELL’AZIENDA OSPEDALIERO UNIVERSITARIA OSPEDALI RIUNITI UMBERTO I - G.M. LANCISI - G. SALESI DI ANCONA, Ancona; COMITATO ETICO REGIONE CALABRIA sez. Area Centro, Catanzaro; Comitato Etico IRCCS MultiMedica Sezione del Comitato Etico Centrale IRCCS Lombardia, Sesto San Giovanni. **Japan:** Kojin-kai Sapporo Dermatology Clinic IRB, Hokkaido; Iryo Houjin Manda Memorial Hospital IRB, Hokkaido; Kojin-kai Sapporo Dermatology Clinic IRB, Hokkaido; Seino Clinic IRB, Fukushima; Iryo Houjin Kenseikai NAKAKINEN CLINIC IRB, Naka; Clinic of the Institute for Adult Diseases Asahi Life Foundation IRB, Tokyo; H. E. C Science Clinic IRB, Yokohama; Nihonbashi Sakura Clinic IRB, Tokyo; Takatsuki Red Cross Hospital IRB, Osaka; Nakameguro Atlas Clinic IRB, Tokyo; Osaka City University Hospital IRB, Osaka; Iryohojinshadan Sinwakai Adachi, Tokyo; Iryo Houjin Shadan Jinnouchikai Jinnouchi Hospital IRB, Kumamoto; Nihonbashi Sakura Clinic IRB, Tokyo; Iryo Houjin Shadan Kowakai Heiwadai Hospital IRB, Miyazaki; The Jikei University Hospital IRB, Tokyo; Shinshu University Hospital IRB, Nagano; Tokyo Women’s Medical Hospital IRB, Tokyo; Juntendo University Hospital IRB, Tokyo; Tokai Kinen Hospital IRB, Aichi; Shin-Koga Hospital IRB, Fukuoka; JCCR-IRB, Tokyo. **Serbia:** Committee Clinical Centre of Serbia, Belgrade. **Russian Federation:** Ethics Committee at Ministry of Health of the Russian Federation, Moscow; Local Ethics Committee of St. Petersburg GUZ “City St. Elizabeth Hospital”, Saint-Petersburg; Ethics Committee of the SBEI APE Russian Medical Academy of Postgraduate Education, Moscow; Ethics Committee of “Astarta” LLC,
Saint-Petersburg; Local Ethics Committee of Federal State Budgetary Scientific Institution "Research Institute of Clinical and Experimental Lymphology", Novosibirsk; Local Ethics Committee of SHI Regional Clinical Hospital, Saratov; Local Ethics Committee of St. Petersburg State Medical University n.a. I.P. Pavlov of MoH of Russia, Saint-Petersburg; Ethics Committee of Regional State Budgetary Healthcare Institution “City Hospital #5 of Barnaul town”, Barnaul; Ethics Committee of the State Budgetary Educational Institution of Highest Professional Education “First Moscow State Medical University named after I.M. Sechenov” of the Ministry of Health of Russian Federation, Moscow; Ethics Committee of State Budget Educational Institution of Higher Professional Education "Novosibirsk State Medical University" of the Ministry of Healthcare of Russian Federation, Novosibirsk; Ethics Committee of Tyumen State Medical Academy, Tyumen; Ethics Committee of State Budgetary Educational Institution of Additional Professional Education “Kazan State Medical Academy” of Ministry of Health of Russian Federation, Kazan. **Taiwan**: Cheng Hsin General Hospital Institutional Review Board, Taipei; Mackay Memorial Hospital Institutional Review Board, Taipei City; Chang Gung Medical Foundation Institutional Review Board, Taipei. **United States**: Sterling Institutional Review Board, Atlanta, GA; Park Nicollet IRB HealthPartners Institute, Bloomington, MN; Office of Human Research Ethics, Chapel Hill, NC; Rochester Regional Health Clinical Investigation Committee, Rochester, NY; Western Institutional Review Board, Olympia, WA