**SUPPLEMENTARY MATERIAL**

Table S1: List of Institutional review boards that approved the AWARD-1, AWARD-5 and AWARD-6 studies.

|  |  |  |
| --- | --- | --- |
| **AWARD-1 Ethical Review Board’s** **Name and Address** | **AWARD-5 Ethical Review Board’s** **Name and Address** | **AWARD-6 Ethical Review Board’s** **Name and Address** |
| Fundacion Sanatorio GuemesFrancisco Acuna de Figueroa 1240CABA, Buenos Aries C1180AAX Argentina | Comite de Etica de la Facultad de Mediciona de la Unal y Hospital Universitario; | Schulman Associates IRB, Suite 300, 4445 Lake Forest Drive, Cincinnati, OH, 45242, United States |
| Comite de Etica en Investigacion Clinica (CEIC)Larrea 1381 3 ABuenos Aires 1117ABK Argentina | Comité de Bioética Médica del Hospital CIMA Chihuahua Haciendas del Valle #7120, Plaza Las Haciendas Chihuahua , Cihuahua México | William Beaumont Hospital, Human Inv Committee, 3811 West 13 Mile Road, Royal Oak, MI, 48073, United States |
| Hospital Sirio LibanesComite de EticaCampana 4658Ciudad de Buenos AiresCBA 1419 Argentina | Comité de Ética Central Médico Quirúrgica de Aguascalientes. República del Perú No. 122, Fracc. Las Américas Aguascalientes, Ags. México | Comite de Etica del Hosp Santa Cecilia de Monterrey SA de CV, Comite de Etica. Segundo piso, Isaac Garza Ote # 200 Col. Centro, Monterrey, Nuevo Leon, 64000, Mexico |
| Hospital Universitario UANLAv. Francisco I. Madero Pte. s/n y Dr. E. AguirrePequeño. Col. Mitras CentroEdificio Biblioteca Central Facultad Medicina UANL. PBMonterrey, Nuevo Leon 64460 Mexico | Comité de Ética, Investigación y Bioseguridad hospital Bernardette Av. Hidalgo 930 C.P. 44290 Guadalajara, Jal. México | Hospital Universitario UANL, Av, Francisco 1. Madero Pte s/n y. Dr. E. Aguirre Pequeño. Col. Mitras Centro, Monterrey, Nuevo Leon, 64460, Mexico |
| Instituto Jalisciense de Investigacion en Diabetes y ObesidaInstituto Jalisciense de InvestigacionClinicaPenitenciaria No. 20. Col. CentroComité de Ética IJICSAGuadalajara, Jalisco 44100 Mexico | Comité de Ética Instituto Jaliciense de Investigación Clínica Penitenciaría No. 20 Col. Centro. Guadalajara, Jal. C.P. 44100 México | Egeszsegugyi Tudomanyos Tanacs, Arany Janos u. 6-8, Budapest, 1051, Hungary |
| Comite Bioetico para la Investigacion BiolinicaPuebla 422 -despacho 4CBIC Despacho 4Col Roma Sur, Mexico D.F. 06700 Mexico | Comisia Nationala De Etica Pentru Studiu Clinic Al Medicamen48 Aviator Sanatescu St. Sector 1Bucharest011478 | Komisja Bioetyczna przy Okregowej Izbie Lekarskiej w Gdansku, ul. Sniadeckich 33, Gdansk, 80-204, Poland |
| Schulman Associates IRB4290 Glendale Milford RdCincinnati, OH 45242 | Ethikkommission der Aerztekammer NiedersachsenBerliner Allee 2030175 HannoverGermany | Eticka Komise FN Motol, Multicentricka a lokalni eticka komise, V Uvalu 84, Praha 5, 150 06, Czech Republic |
| Thomas Jefferson University1015 Chestnut StreetPhiladelphia, PA 19107 | Komisja Bioetyczna przy Uniwersytecie Medycznym w Lublinie, AI. Raclawickie 1, 20-059 Lubin | Eticka komise IKEM a Thomayerovy nemocnice, Lokalni eticka komise, Videnska 800, Praha 4 – Krc, 140 59, Czech Republic |
| University of Hawaii Committee on Human Studies1960 East West Road Biomedical BldgHonolulu, HI 98613 | Samsung Medical Center Institutional Review Board 50 Ilwon Dong, Kang nam Gu, Seoul, Korea 135-710 | Eticka komise NZZ ResTrial s.r.o, Lokalni eticka komise, V sadech 15/4, Praha 6, 160 00, Czech Republic |
| Maine Medical Center81 Research DriveScarborough, ME 04074 | Seoul National University,Bundang Hospital 166 Gumi-Ro, Bundang-Gu, Seongnam-si, Gyeonggido,463-707, Korea. | Clinica Mediterranea de Neurociencias, Comite Etico Investigacion Clinica, Camino Viejo de Alicante-Elche s/n, Alicante, 03114, Spain |
| UNC Diabetes Care CenterMedical School Bldg 52CB# 7097Chapel Hill, NC 27599 | Institutional Review Board, Korea University Guro Hospital,80, Guro-dong, Guro-gu, Seoul, Korea, 152-703 | CEIC de Islas Baleares, Comite Etico Investigacion Clinica, Camí de Jesús 38A, Palma de Mallorca, Baleares, 07011, Spain |
| Louisiana State University433 Bolivar StreetNew Orleans, LA 70122-2223 | NHIC Ilsan Hospital Institutional Review Board,1232, Baekseok-dong, IlsanDong-Gu, Goyang-Si, Kyunggi-Do.410-719, Korea | Hospital General De Elda, Comite Etico Investigacion Clinica, Ctra. Elda-Sax la Torreta KM.3, Elda, Alicante, 03600, Spain |
| Hospital of Central ConnecticutHuman Studies Committee100 Grand StNew Britain, CT 06050 | Kyung Hee University Hospital IRB/IEC,1 Hoegi-Dong, Dongdaemun-Gu, Seoul, 130-702, Korea | Centre Medic Teknon, Comite Etico Investigacion Clinica, C/Vilana, 12, Barcelona, 08022, Spain |
| WIRB3535 7th Ave SWOlympia, WA 98502-5010 | Inha University Hospital IRB,7-206, 3-Ga, Sinheung-dong Jung-gu, Incheon, Korea 400-711 | CEIC Autonomico de Andalucia Consejería de Salud, Comite Etico Investigacion Clinica, Avda Innovación, Edificio Arena 1Avda Innovacion s/n, Sevilla, 41020, Spain |
| Geisinger Medical Center100 North Academy AvenueDanville, PA 17822-2600 | Eulji Medical Center Institutional Review Board,280-1 Hagye-Dong, Nowon-Gu, Seoul, 139-872, Korea | Hospital de la Ribera, Comite Etico Investigacion Clinica, Carretera Alcira-Corbera s/n, Alcira, Valencia, 46600, Spain |
| University of Illinois College of Medicine PeoriaP.O. Box 1649Peoria, IL 61656-1649 | Bundang CHA General Hospital, 351, Yatapdong, Bundang-gu, Sungnamsi, Kyunggi-do, Seoul, Korea | CEIC Fundacio Unio Catalana Hospital, Comite Etico Investigacion Clinica Attn. Vanessa Masso, Bruc, 72-74, 1a, Barcelona, Catalunia, 08009, Spain |
| Western Institutional Review Board3535 7th Ave SWOlympia, WA 98502-5010 | The Institutional Review Board of Taichung Veterans General HospitalNo. 160, Section 3, Taichung Port Road, Xitun District, Taichung City 407, Taiwan (R.O.C.) | Comisia Nationala de Etica Pentru Studiul Clinic al Medicame, Str Aviator Sanatescu nr. 48, Bucharest, Sector 1, 011478, Romania |
| Florida Hospital Cancer Institute212 E Winter Park StreetOrlando, FL 32804 | Research Ethics Committee of National Taiwan University Hospital No. 1, Chung-Te Street, Taipei City 100, Taiwan (R.O.C.) | EK Kosickeho samospravneho kraja, Nam Maratonu 1, Kosice, Slovak Republic, 04266, Slovakia |
| Intermountain Health Care, Inc36 S. State StreetSalt Lake City, UT 84111 | National Cheng-Kung University Hospital Institutional Review Board No. 138, Shengli Road, Tainan City 704, Taiwan (R.O.C.) | Bratislavsky Samospravny Kraj, Sabinovska 16 PO Box 106, Bratislava, Slovak Republic, 820 05, Slovakia |
| Queens Medical Center and Cancer Institute1301 Punchbowl StHonolulu, HI 96813 | Kaohsiung Medical University Chung-Ho Memorial Hospital Institutional Review Board8th Floor, Building A, No. 100, Tzyou 1st Road, Kaohsiung City 807, Taiwan (R.O.C.) | Nitriansky samospravny kraj, Stefanikova trieda 69, Nitra, Slovakia, 94901, Slovakia |
| Greenville Hospital System110 North Main StreetGreenville, SC16125 | Joint Institutional Review BoardNo. 5-1, Ln. 331, Sec. 2, Shipai Rd., Beitou Dist., Taipei City 112, Taiwan (R.O.C.) | Eticka komisia Trencianskeho sam kraja, K dolnej stanici 7282/20A, 911 01 Trenčin, Starohajska 10, Trencin, 91701, Slovakia |
| State University of NY3435 Main StreetBuffalo, NY 14214-3016 | Chung Shan Medical University Hospital Institutional Review BoardNo. 110, Section 1, Chien-Ku North Road, South District, Taichung City 402, Taiwan (R.O.C.) | Ethikkommission bei der Sächsischen Landesärztekammer, EK-AMG-MCF-10/12-1. Schützenhöhe 16, Dresden, 01099, Germany |
|  | College of Physicians and Surgeons of Alberta 2700, 10020-100 Street NE Edmonton, AB T5J ON3 |  |
|  | IRB Services, 372 Hollandview Trail Ste 300, Aurora, ON L4G 0A5 |  |
|  | University of ManitobaBiomedical Research Ethics BoardBannatyne CampusP126 770 Bannatyne Ave.Winnepeg Manitoba R3E OWs |  |
|  | Comité de Protection des personnes Est IIIHopital de BarboisRue du Morvan54511 VANDOEUVRE-LES-NANCY cedexFrance |  |
|  | LEC of Municipal Healthcare Institution «First City Clinical Emergency Hospital», 1, Suvorova st., Arkhangelsk, 163045, |  |
|  | LEC of State Educational Institution of High Professional Education “Rostov State Medical University of RosZdrav”, 29, Nakhichevansky lane, Rostov-on-Don, 344022 |  |
|  | LEC of State Healthcare Institution "Arkhangelsk regional clinical hospital" 292, prospect Lomonosova, 163045, Arkhangelsk, Russia |  |
|  | LEC of “St. Elizabeth City Clinical Hospital” 14 Vavilovykh str., St. Petersburh, Russia, 163045 |  |
|  | S-B-5 Shastri Nagar St Mary School, Ghaziabad Uttar Pradesh 201-002 |  |
|  | #35 5th Cross, Maleshwaram Circle Bangalore, Kamataka 560003 |  |
|  | 6 Poonam Arcade, 1170/11 Pune 411005 |  |
|  | 201 Silver Brook B Opp Doctor House, Ellisbridge 38006 |  |
|  | 640 1st Main, 1st Stage Indiranagar Bangalore Kamataka 560038 |  |
|  | KEM Hospital Research Centre,Sardar Moodliar Road,Rasta Peth,Pune,411011 |  |
|  | 16/M Millers Tank Bed Area, Thimmalah Road Vasanthnagar Bangalore Kamataka 560 052 |  |
|  | Amrita Lane Ellamakkara POEdapally Kochi Kerala 682026 |  |
|  | Jubilee Hills Hyderbad Andhra Pradesh 500033 |  |
|  | Hospital Universitari Arnau De VilanovaAv Alcalde Rovira Roure 80LleidaCatalonia25198 |  |
|  | Chesapeake Research Review 7063 Columbia Gateway Drive Columbia MD 21046 |  |
|  | Schulman Associates IRB 4920 Glendale Milford Rd Cincinnati OH 45242 |  |
|  | Hunterdon Medical Center 2100 Westcott Dr Flemington NJ 08822 |  |
|  | Emory University 1599 Clifton Rd Atlanta GA 30322 |  |
|  | University of Michigan 517 W William Ann Arbor MI 48103 |  |
|  | Institutional Review Board for the Protection of Human Subjects 750 East Adams St Syracuse NY 13210 |  |
|  | ViaHealth Clin Investigtn Comm 1425 Portland Ave Rochester NY 14621 |  |

Table S2: Least squares mean (95% CI) reductions from baseline in HbA1c (mmol/mol) across the range of baseline HbA1c in AWARD-5, AWARD-6 and AWARD-1

| Study (week 26) | Baseline HbA1c (mmol/mol)  |
| --- | --- |
| Treatment | 47.53 | 53.00 | 58.46 | 63.93 | 69.39 | 74.86 | 80.32 | 85.79 | 91.25 | 96.72 |
| AWARD-51 |  |  |  |  |  |  |  |  |  |  |
| DU 0.75 | - | −7.32(−8.96, −5.68) | −8.85(−10.17, −7.54) | −10.38(−11.59, −9.29) | −12.02(−13.23, −10.82) | −13.55(−14.98, −12.13) | −15.09(−16.83, −13.45) | − | - | - |
| DU 1.5  | - | −7.76(−9.40, −6.12) | −10.17(−11.48, −8.85) | −12.57(−13.77, −11.48) | −14.98(−16.18, −13.77) | −17.38(−18.80, −15.96) | −19.79(−21.53, −18.04) | − | - | - |
| SITA | - | −3.94(−5.47, −2.40) | −5.03(−6.23, −3.72) | −6.12(−7.21, −5.03) | −7.21(−8.42, −6.01) | −8.31(−9.73, −6.89) | −9.40(−11.15, −7.65) | − | - | - |
| AWARD-62 |  |  |  |  |  |  |  |  |  |  |
| DU 1.5  | - | −10.38(−12.02, −8.75) | −13.12(−14.32, −11.81) | −15.74(−16.83, −14.76) | −18.47(−19.68, −17.27) | −21.21(−22.85, −19.57) | −23.83(−26.02, −21.75) | −26.56(−29.30, −23.94) | - | - |
| LIRA 1.8 | - | −9.18(−10.93, −7.54) | −12.13(−13.45, −10.82) | −15.09(−16.18, −13.99) | −18.04(−19.24, −16.83) | −20.99(−22.52, −19.35) | −23.83(−26.02, −21.75) | −26.78(−29.51, −24.16) | − | − |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| AWARD-11 |  |  |  |  |  |  |  |  |  |  |
| DU 0.75  | −6.01(−7.76, −4.26) | −8.75(−10.71, −7.21) | −11.37(−12.68, −10.06) | −14.10(−15.41, −12.79) | −16.83(−18.15, −15.41) | −19.46(−21.10, −17.93) | −22.19(−24.05, −20.33) | −24.92(−27.11, −22.74) | −27.66(−30.17, −25.14) | −30.28(−33.23, −27.44) |
| DU 1.5  | −7.21(−8.96, −5.36) | −10.28(−11.81, −8.75) | −13.34(−14.65, −12.02) | −16.40(−17.71, −15.09) | −19.46(−20.77, −18.15) | −22.52−24.05, −21.10) | −25.58(−27.33, −23.94) | −28.75(−30.72, −26.67) | −31.81(−34.11, −29.51) | −34.87(−37.49, −32.25) |
| EXE | −1.86(−3.61, −0.11) | −4.81(−6.34, −3.28) | −7.76(−9.07, −6.45) | −10.49(−12.02, −9.40) | −13.66(−14.98, −12.35) | −16.62(−18.15, −15.19) | −19.57(−21.32, −17.82) | −22.52(−24.60, −20.55) | −25.47(−27.87, −23.17) | −28.53(−31.15, −25.80) |

The table shows data from patients receiving active treatment in the intention-to-treat populations of AWARD-5, -6 and -1 whose baseline HbA1c met the inclusion criteria for their respective study.

ANCOVA: analysis of covariance; CI: confidence interval; DU: dulaglutide (dose in mg); EXE: exenatide twice daily; LIRA: liraglutide (dose in mg); LOCF: last observation carried forward; SITA: sitagliptin.

1 LOCF ANCOVA Model: Change in HbA1c = Treatment + Country + Baseline HbA1c + Treatment\*Baseline HbA1c

Table S3: Assessment of association of baseline HbA1c and change in HbA1c through backward selection in AWARD-5, AWARD-6 and AWARD-1

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| StudStudya Study | Population | No. | Model (LOCF ANCOVA): Change in HbA1c from baseline to week 26 = | Factor to be excluded as chosen through backward selectiona (*P* value) |
| AWARD-5 | ITT | 1 | treatment + country + baseline HbA1c + baseline HbA1c² | baseline HbA1c² (0.271) |
| 2 | treatment + country + baseline HbA1c | None (i.e. selection stopped) |
| AWARD-6b | ITT | 1 | treatment + pooled country + baseline HbA1c + baseline HbA1c² | baseline HbA1c² (0.704) |
| 2 | treatment + pooled country + baseline HbA1c | treatment (0.341)c |
| 3 | pooled country + baseline HbA1c | None (i.e. selection stopped) |
| AWARD-1 | ITTd | 1 | treatment + country + baseline HbA1c + baseline HbA1c2 | baseline HbA1c (0.971) |
| 2 | treatment + country + baseline HbA1c2 | country (0.505) |
| 3 | treatment + baseline HbA1c2 | None (i.e. selection stopped) |
| AWARD-1 | Baseline HbA1c as per inclusion criteriond | 1 | treatment + country + baseline HbA1c + baseline HbA1c2 | baseline HbA1c² (0.666) |
| 2 | treatment + country + baseline HbA1c | country (0.622) |
| 3 | treatment + baseline HbA1c | None (i.e. selection stopped) |

ANCOVA: analysis of covariance; ITT, intent-to-treat; LOCF: last observation carried forward.

a Criterion for backward selection: *P*-value ≥0.15.

b The LOCF ANCOVA model was a secondary sensitivity analysis for the primary endpoint (Dungan et al., 2014).

c The factor ‘treatment’ was excluded as a result of backward selection because dulaglutide 1.5mg was non-inferior but not superior to liraglutide 1.8mg in AWARD-6 (Dungan et al., 2014).
For the purpose of the current analysis, the factor ‘treatment’ had to be retained in the model.

d Inclusion criterion: 6.5% < baseline HbA1c ≤11.0%
The different results between the ITT population and the population restricted to baseline HbA1c values as per the inclusion criterion, as well as further inspection of baseline HbA1c values, led to the conclusion that the backward selection results for the ITT population were only driven by a few extreme baseline HbA1c values.
Therefore, a linear association between baseline HbA1c and change in HbA1c was also assumed for the ITT population.
For the purpose of the current analysis, the factor ‘country’ was retained in the model to remain consistent with the primary analysis (Wysham et al., 2014).