DOI: 10.1111/dme.13886

Research: Treatment

Baseline characteristics in the VERIFY study: a randomized trial assessing the durability of glycaemic control with early vildagliptin-metformin combination in newly diagnosed Type 2 diabetes

D. R. Matthews[1,2], P. M. Paldánius[3], P. Proot[3], J. E. Foley[4], M. Stumvoll[5] and S. Del Prato[6]

[1]Oxford Centre for Diabetes Endocrinology and Metabolism, [2]Harris Manchester College, Oxford, UK, [3]Novartis Pharma AG, Basel, Switzerland, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [5]Divisions of Endocrinology and Diabetes, University Hospital Leipzig, Germany and [6]Department of Clinical and Experimental Medicine, Section of Metabolic Diseases and Diabetes, University of Pisa, Pisa, Italy

Accepted 18 December 2018

Abstract

Aim To assess the long-term clinical benefits of early combination treatment with vildagliptin-metformin vs. standard-of-care, metformin monotherapy in the ongoing VERIFY study.

Methods We randomized 2001 participants with multi-ethnic background, aged 18–70 years, having HbA_{1c} levels 48–58 mmol/mol (6.5–7.5%) and BMI 22–40 kg/m^2. Baseline data included HbA_{1c}, fasting plasma glucose and homeostasis model β-cell and insulin sensitivity. Standardized meal-tests, insulin secretion rate relative to glucose, and oral glucose insulin sensitivity were assessed in a subpopulation.

Results Out of 4524 screened, data were collected from the 2001 eligible participants (53% women) across Europe (52.4%), Latin America (26.8%), Asia (17.2%), South Africa (3.1%) and Australia (0.5%). The median (interquartile range) disease duration was 3.4 (0.9, 10.2) months; mean (±SD) age 54.3±9.4 years; weight 85.5±17.5 kg and BMI 31.1±4.7 kg/m^2. Baseline HbA_{1c} was 52±3 mmol/mol (6.9±0.3%), fasting plasma glucose 7.5±1.5 mmol/l and the median (interquartile range) of fasting insulin was 109 (75–160) mU/l. Homeostasis model β-cell and insulin sensitivity values were 84% (60, 116) and 46% (31, 68), respectively. In those undertaking meal-tests, insulin secretion rate relative to glucose was 28±12 pmol/min/m^2/mmol/l and oral glucose insulin sensitivity was 353±57 ml/min/m^2.

Conclusions Our current, multi-ethnic, newly diagnosed VERIFY population reflects a characteristic presence of early insulin resistance in participants with increased demand for insulin associated with obesity. The VERIFY study will provide unique evidence in characterizing therapeutic intervention in a diverse population with hyperglycaemia, focusing on durability of early glycaemic control.

Diabet. Med. 36: 505–513 (2019)

Introduction

There is debate about the optimum early pharmacological treatment of diabetes, although most authorities recommend metformin [1]. Beyond metformin it is usual to add a second therapy, but often this intensification occurs late, long after good glycaemic control is lost [2]. Second line agents include dipeptidyl peptidase-4 (DPP-4) inhibitors, which are good candidates for early combination therapy [1]. DPP-4 inhibitors improve glucose homeostasis synergistically with metformin even in mild hyperglycaemia, without the adverse effects of weight gain and hypoglycaemia [3,4].

VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of Type 2 diabetes) is an ongoing, 5-year, multinational, multi-ethnic study being conducted in 254 centres across 34 countries (Appendix: Table A1). We aimed to investigate, for the first time, the long-term benefits of early treatment intensification with a DPP-4 inhibitor (vildagliptin)-metformin combination over

Correspondence to: David R. Matthews.
E-mail: david.matthews@ocdem.ox.ac.uk
(Clinical Trials Registry No.: NCT 01528254)

What's new?

- The VERIFY study is the first study to assess the long-term clinical benefits of early combination treatment with a dipeptidyl peptidase-4 inhibitor (vildagliptin)-metformin vs. standard-of-care metformin monotherapy in people newly diagnosed with Type 2 diabetes.
- This report describes the baseline characteristics of a newly diagnosed population with Type 2 diabetes from a diverse geographical and ethnic background, demonstrating a classic profile of presence of early insulin resistance associated with elevated BMI as a surrogate for obesity.
- The study anticipates generating unique evidence on the progression of β-cell function, insulin resistance, early complications of diabetes, and effect on health status upon treatment with early vildagliptin-metformin combination.

standard-of-care metformin monotherapy in maintaining durable glycaemic control in people with newly diagnosed Type 2 diabetes.

In contrast to many cardiovascular outcome studies, we aimed to recruit a population reflecting the typical characteristics of newly diagnosed people living with diabetes worldwide.

Methods

Study design

The study design has been described in detail elsewhere [5]. Briefly, the VERIFY trial (NCT01528254) is an ongoing randomized, double-blind, parallel-group study consisting of a screening visit, a 3-week metformin-alone run-in period, and a 5-year treatment period during which the treatment is consecutively intensified, when clinically indicated at the investigators' discretion. Durability of glycaemic control, time to insulin initiation, changes in β-cell function and insulin sensitivity have been assessed over time.

The study protocol was approved by the Institutional Review Boards, Independent Ethics Committees and Competent Health Authorities in accordance with European Community Directive 2001/20/EC or as per national and international regulatory requirements in participating countries.

Study population

Participants aged 18–70 years, newly diagnosed with Type 2 diabetes (≤24 months) as per local diagnostic criteria, having centrally confirmed HbA_{1c} levels between 48 mmol/mol (6.5%) and 58 mmol/mol (7.5%), and BMI 22–40 kg/m^2, were included in the study [5]. Individuals undergoing anti-diabetes treatment (except for short-term metformin) within 3 months prior to screening, or using any weight-loss medications were excluded, as were pregnant or breastfeeding women, and those with chronic liver disease or ongoing congestive heart failure [New York Heart Association (NYHA) III or IV].

Study assessments

Baseline measurements were obtained at the screening visit, or at the next visit prior to initiation of metformin up-titration. The primary efficacy assessments include HbA_{1c} measurements to determine the time to initial treatment failure and the rate of loss in glycaemic control over time. Participants visit the study site every 13 weeks for 5 years to comply with the study procedures [5]. Laboratory samples are collected at each visit and analysed. Vital signs, electrocardiogram, body weight, haematology and biochemistry, fasting lipid profile and triglycerides, liver and renal function tests, urinalysis and adverse events are the key safety assessments. Major adverse cardiovascular events are independently adjudicated (exploratory endpoint) and an independent data safety committee monitors an unblinded periodic review of all safety data.

In a large subpopulation (n=462), standardized and locally adapted, annual meal-tests are performed for assessment of plasma glucose levels, insulin, and C-peptide concentrations. Indices of β-cell function (insulin secretion rate relative to glucose and homeostasis model assessment of β-cell function (HOMA-ß)), insulin sensitivity (oral glucose sensitivity index), and insulin resistance (HOMA-% sensitivity) are calculated [6,7].

Statistical analysis

Blinded baseline demographics and key glycaemic variables were analysed descriptively and summarized for all randomized participants. Categorical variables including age, gender and BMI were summarized with frequency and percentage, whereas continuous variables including duration of disease and HbA_{1c} were summarized with mean ±SD.

Results

Recruitment of participants

Recruitment for the VERIFY trial started in March 2012 and randomization was completed in April 2014. A total of 2001 people, newly diagnosed with mild hyperglycaemia, were randomized out of the 4524 screened. The major reason for screening failure was an HbA_{1c} value outside the protocol-defined, centrally assessed range of 48–58 mmol/mol (6.5–7.5%). A total of 66 participants were classified as run-in failures because of metformin-intolerance prior to up-titration to the lowest targeted dose of 1000 mg/day. Details of participants' dispositions are shown in Figure 1.

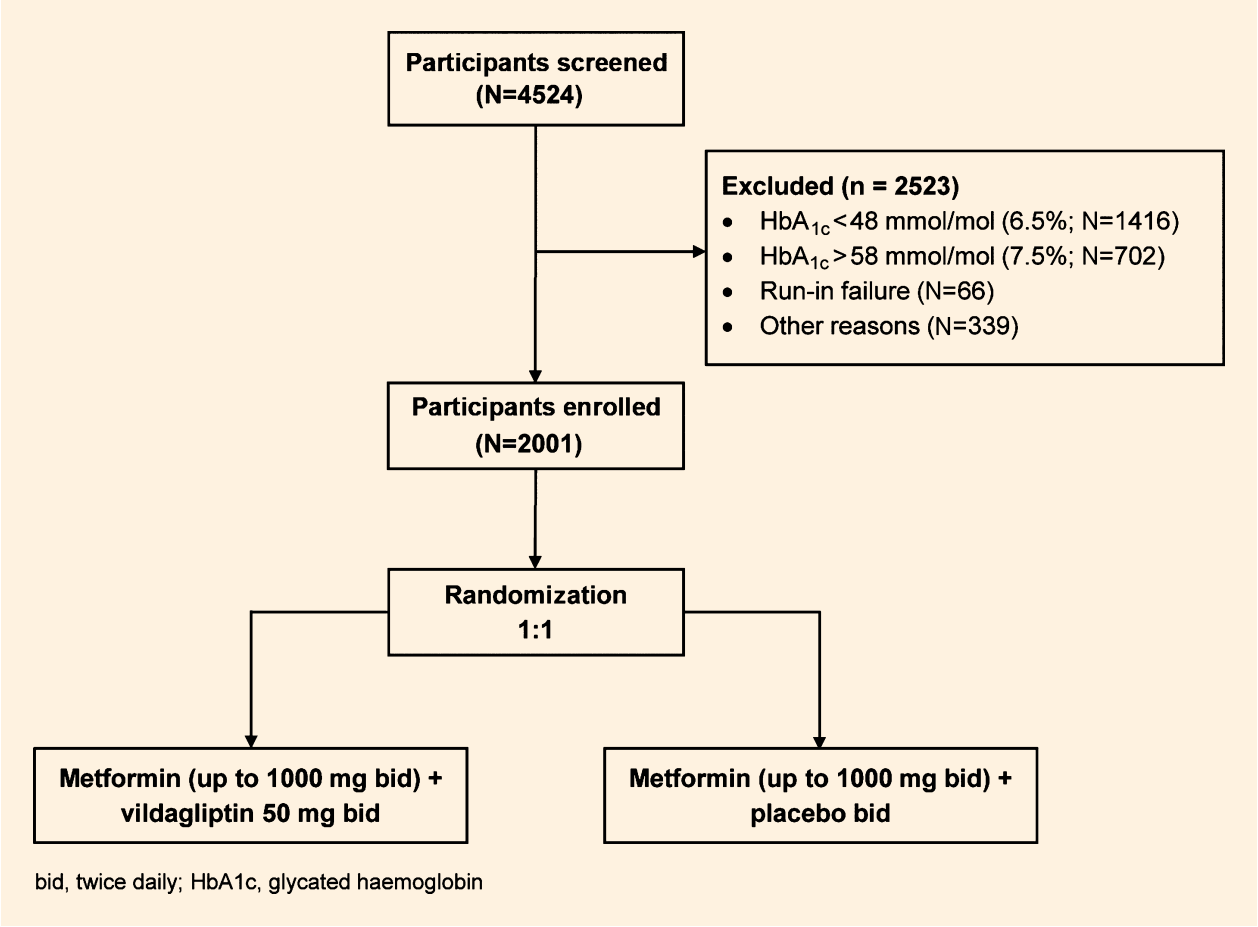

FIGURE 1 Disposition of participants screened in the VERIFY trial

The geographical distribution of participants enrolled for this trial was: Europe (52.4%), Latin America (26.8%), Asia (17.2%), South Africa (3.1%) and Australia (0.5%).

Baseline characteristics

Overall demographics and baseline characteristics of participants are presented in Table 1.

The median (interquartile range) age of participants was 55 (48, 62) years, baseline HbA_{1c} 52±3 mmol/mol (corresponding to 6.9±0.3%), fasting plasma glucose 7.5±1.5 mmol/l, and median (interquartile range) duration of diabetes 3.4 (0.9,10.2) months. Overall, men and women were often enrolled equally in the study despite some country-level differences. The mean baseline GFR was 87.4±18.5 ml/min/1.73m^2. Overall, 14.5% of the study population were smoking at baseline. Presence of early microvascular complications were reported in 8% of the participants enrolled.

At baseline the median (interquartile range) of fasting insulin was 109 (75–160) mU/l, and HOMA-ß and HOMA-% sensitivity values were 84% (60, 116) and 46% (31, 68), respectively. In the subset of participants (n=462) undertaking meal-tests, 2-hour plasma glucose values were 9.3±2.8 mmol/l, insulin secretion rate relative to glucose was 28±12 pmol/min/m^2/mmol/l, and oral glucose sensitivity index value was 353±57 ml/min/m^2. Table 2 shows the variability of the meal-test measurements by geographic distribution.

Discussion

The VERIFY study cohort explores a newly diagnosed population with Type 2 diabetes with mild hyperglycaemia who have the potential for preservation of their β-cell function, and for achieving a long-term durable response to early therapy.

One principal goal of treating newly diagnosed drug-naive individuals is to achieve glycaemic control approaching normoglycaemia [8]. This trial explores the concept that optimization of therapy, in this case with an early vildagliptin-metformin combination, could overcome β-cell functional deterioration and thereby extend the durability of treatment over time.

Previous intervention studies on initial combination therapy have recruited participants with baseline HbA_{1c} levels ≥64 mmol/mol (≥8.0%) [9–15]. Additionally, A Diabetes Outcome Progression Trial (ADOPT) [16] and Diabetes Prevention Program (DPP) [17] reported limited baseline variables with

Table 1 Demographics and baseline characteristics of participants

Variable	Total
Patient population, n	2001
Women, n (%)	1060 (53.0)
Age, years	
Median (IQR)	55 (48, 62)
Race, n (%)	
White European	1217 (60.8)
Black	49 (2.4)
Asian	373 (18.6)
Native American	210 (10.5)
Other	152 (7.6)
Duration of Type 2 diabetes, months	
Median (IQR)	3.4 (0.9, 10.3)
HbA_{1c}, mmol/mol (%)	52±3 (6.9±0.3)
FPG, mmol/l	7.5±1.5
Fasting insulin, median (IQR) (mU/L)	109 (75–160)
HOMA-%β, median (IQR) (%)	84 (60, 116)
HOMA-%sensitivity, median (IQR) (%)	46 (31, 68)
BMI, kg/m^2	31.1±4.7
Pulse rate, bpm	72.8±9.3
Systolic BP, mmHg	132.3±14.4
Diastolic BP, mmHg	80.6±8.6
HDL cholesterol, mmol/l	1.3±0.3
LDL cholesterol, mmol/l	2.9±0.9
Triglycerides, mmol/l	1.9±1.0
UALCRR, mg/mmol	
Median (Min–Max)	1.0 (0.1–262.3)
GFR (MDRD), $mL/min/1.73m^2$	87.4±18.5
History of diabetes and complications*, n (%)	
Proliferative retinopathy	1 (0.0)
Non-proliferative retinopathy	11 (0.5)
Nephropathy	26 (1.3)
Neuropathy	116 (5.8)
Foot ulcers	5 (0.2)
Metformin daily dose, mg	1597.3±396.5
Most common metformin dose; 2000 mg, n (%)	796 (39.8)

*Retinopathy and neuropathy were assessed according to the local protocols. BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-%β, homeostatic model assessment-%β; HOMA-% sensitivity, homeostatic model assessment-%sensitivity; IQR, interquartile range; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; SOC, system organ class; UALCRR, urinary micro albumin/creatinine ratio; ± indicates standard deviation (SD).

populations having a higher range of baseline HbA_{1c}. By contrast, the VERIFY trial will assess the durability of glycaemic response in individuals recruited at, or close to, diagnosis and with near-normal HbA_{1c}. The data show a 16.5% median decrease in β-cell function but marked reduction in insulin sensitivity to 46%. Insulin resistance is the reciprocal of the sensitivity, so those recruited have an insulin resistance that is double that found in people without diabetes.

Data obtained from the meal-test substudy are reflective of regional variations observed in plasma glucose, C-peptide, and insulin concentrations, which may prove important in the subgroup analysis of β-cell failure. Previously published data [18,19] demonstrated variations in postprandial glucose response, fasting insulin, and C-peptide concentrations between various ethnic groups. Such regional differences in the inter-relationships of early signs of increased insulin resistance (reduced sensitivity) and reduced β-cell function would be important to both document and interpret for optimized clinical decision making.

Long-term clinical trials normally pose a big challenge with low study participant retention. Evaluating the durability of treatment prospectively necessitates retention throughout the duration of the study. The VERIFY trial has an active retention programme, tailored to the needs of individuals, but over time the study is also carrying out innovative, relational real-time data monitoring to improve the retention rates.

The presence of baseline microvascular complications, including proliferative and non-proliferative retinopathy, nephropathy, neuropathy, and foot ulcer conditions, demonstrates the asymptomatic nature of Type 2 diabetes and early onset of foundation for its complications, emphasizing the importance of early treatment interventions to prevent or slow down the disease progression prior to advent of further diabetic complications.

The major strength of the VERIFY trial is the selection of a geographically distributed diverse, multi-ethnic population and long-term duration of 5 years for all the participants, ensuring the generalizability of the trial results and providing guidance in clinical decision making for the increasing number of people with newly diagnosed Type 2 diabetes. The enrolled participants display a classic profile of presence of early insulin resistance associated with elevated BMI as a surrogate for obesity. The study anticipates the generation of unique evidence for many geographical areas with limited or no prior epidemiological or other data on β-cell function, insulin resistance, early complications of diabetes, and effect on health status upon treatment with a DPP-4 inhibitor-metformin combination. The study is currently underway and will report in 2019.

Table 2 2-hour meal-test data by variables and geographical distribution

Variable	Europe	Latin America	Asia*	South Africa
Distribution, n (%)	267 (57.8)	152 (32.9)	32 (6.9)	11 (2.4)
Plasma glucose (mmol/l) Median (Min–Max)	9.3 (4.0–16.5)	7.9 (4.2–24.0)	10.4 (6.4–15.1)	9.8 (5.6–17.1)
Insulin (pmol/l) Median (Min–Max)	58.9 (3.5–286.6)	55.7 (7.6–404.5)	97.8 (20.7–435.6)	–
C-peptide (nmol/l) Median (Min–Max)	1.9 (0.4–5.7)	1.8 (0.3–4.8)	2.1 (0.5–5.0)	–

*values for Asia exclude India.

Funding sources

This work was supported by Novartis Pharma AG.

Competing interests

D.R.M. has served on advisory boards or as a consultant for Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis, Janssen and Servier; receives current research support from Janssen; and has given lectures for Novo Nordisk, Servier, Sanofi-Aventis, Eli Lilly, Novartis, Janssen and Aché Laboratories. P.M.P. and P.P. are employed by and own stocks in Novartis. J.E.F. was an employee of Novartis Pharmaceuticals Corporation at the time of manuscript development. M.S. received speaker's honoraria and consulting fees from Novartis, Novo Nordisk, AstraZeneca, Aegerion, Eli Lilly and Company, Boehringer Ingelheim. S.D.P. serves or has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Hanmi Pharmaceuticals, Intarcia, Janssen Pharmaceutics, Merck Sharp & Dohme Ltd, Novartis, Novo Nordisk, Sanofi, Servier and Takeda; serves or has served on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen Pharmaceutics, Merck Sharp & Dohme Ltd, Novartis, Novo Nordisk, Sanofi and Takeda; and has received research support from Boehringer Ingelheim, Merck Sharp & Dohme Ltd and Novartis.

Acknowledgements

The authors would like to thank Dr. Wolfgang Kothny, Novartis Pharma AG, Basel, Switzerland for his contribution and scientific advice during the study design and initiation phase. The authors would also like to thank Rangan Gupta and Amit Kumar Garg for editorial assistance, collation, and incorporation of comments from all authors, conducted in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3).

References

1 Zinman B. Initial combination therapy for type 2 diabetes mellitus: is it ready for prime time? *Am J Med* 2011; **124**: S19–S34.
2 Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: A retrospective cohort study of more than 80,000 people. *Diabetes Care* 2013; **36**: 3411–3417.
3 Matthews DR, Dejager S, Ahren B, Fonseca V, Ferrannini E, Couturier A *et al*. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes Obes Metab* 2010; **12**: 780–789.
4 Bosi E, Dotta F, Jia Y, Goodman M. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2009; **11**: 506–515.
5 Del Prato S, Foley JE, Kothny W, Kozlovski P, Stumvoll M, Paldánius PM *et al*. Study to determine the durability of glycaemic control with early treatment with a vildagliptin-metformin combination regimen vs. standard-of-care metformin monotherapy-the VERIFY trial: a randomized double-blind trial. *Diabet Med* 2014; **31**: 1178–1184.
6 Pratley RE, Schweizer A, Rosenstock J, Foley JE, Banerji MA, Pi-Sunyer FX *et al*. Robust improvements in fasting and prandial measures of beta-cell function with vildagliptin in drug-naïve patients: analysis of pooled vildagliptin monotherapy database. *Diabetes Obes Metab* 2008; **10**: 931–938.
7 Hill NR, Levy JC, Matthews DR. Expansion of the homeostasis model assessment of beta-cell function and insulin resistance to enable clinical trial outcome modeling through the interactive adjustment of physiology and treatment effects: iHOMA2. *Diabetes Care* 2013; **36**: 2324–2330.
8 Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA *et al*. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary. *Endocr Pract* 2017; **23**: 207–238.
9 Abdul-Ghani MA, Puckett C, Triplitt C, Maggs D, Adams J, Cersosimo E *et al*. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab* 2015; **17**: 268–275.
10 Pratley RE, Fleck P, Wilson C. Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naïve patients with type 2 diabetes: a randomized, double-blind, 6-month study. *Diabetes Obes Metab* 2014; **16**: 613–621.
11 Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab* 2014; **16**: 410–417.
12 Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study. *Int J Clin Pract* 2013; **67**: 1283–1293.
13 Williams-Herman D, Xu L, Teng R, Golm GT, Johnson J, Davies MJ *et al*. Effect of initial combination therapy with sitagliptin and metformin on β-cell function in patients with type 2 diabetes. *Diabetes Obes Metab* 2012; **14**: 67–76.
14 Reasner C, Olansky L, Seck TL, Williams-Herman DE, Chen M, Terranella L *et al*. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2011; **13**: 644–652.
15 Mirasol RC, Pathan MF, Chawla M, Kim TH, Cooke K, Hours-Zesiger P *et al*. INITIAL combination therapy with vildagliptin/metformin in drug-naïve Asian T2DM patients: influence of age, BMI and co-morbidities in a real-world setting. PO-774. Poster presented at the 53rd European Association for the Study of Diabetes Annual Meeting, 11–15 September 2017, Lisbon, Portugal.
16 Viberti G, Kahn Se, Greene DA, Herman WH, Zinman B, Holman RR *et al*. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* 2002; **25**: 1737–1743.
17 Diabetes Prevention Program (DPP) Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679–686.
18 Tan VM, Lee YS, Venkataraman K, Khoo EY, Tai ES, Chong YS *et al*. Ethnic differences in insulin sensitivity and beta-cell function among Asian men. *Nutr Diabetes* 2015; **5**: e173.
19 Harris MI, Cowie CC, Gu K, Francis ME, Flegal K, Eberhardt MS. Higher fasting insulin but lower fasting C-peptide levels in African Americans in the US population. *Diabetes Metab Res Rev* 2002; **18**: 149–155.

Appendix

Table A1 Trial investigators and sites

Site number	Principal investigator	Institution
1	Silvia Gorban de Lapertosa	Centro Universitario de Investigaciones en Farmacologia Clin, Corrientes, Argentina
2	Diego Aizemberg	Centro Medico Viamonte, Buenos Aires, Argentina
3	Ines Bartolacci	Instituto Privado De Investigaciones Clinicas De Cordoba, Cordoba, Argentina
4	Silvia Orio	IMOBA, CABA, Capital Federal, Argentina
5	Federico Perez Manghi	CINME, CABA, Buenos Aires, Argentina
6	Laura Maffei	Consultorios Medicos (Investigacion Clinica Aplicada SRL), CABA, Buenos Aires, Argentina
7	Jorge Aiub	Grupo Medico Alem, San Isidro, Buenos Aires, Argentina
8	Paula Kavalieros	Woy Woy General Practice, Woy Woy, NSW, Australia
9	Hans Blom	Vale Medical Practice, Brookvale, NSW, Australia
10	Adrian Kenny	Morayfield Medical Centre, Morayfield, QLD, Australia
11	Rudolf Prager	Krankenhaus der Stadt Wien Hietzing-Lainz, Wien, Austria
12	Alexandra Kautzky-Willer	Univ. Klinik fuer Innere Medizin III, AKH Wien, Wien, Austria
13	Maria Zanella	Universidade Federal de Saeo Paulo, Sao Paulo, SP, Brazil
14	Carolina Chrisman	Núcleo de Medicina Integrada, Mogi das Cruzes, Brazil
15	Freddy Eliaschewitz	Centro de Pesquisa Clínica Ltda, Sao Paulo, SP, Brazil
16	Joao Felicio	Hospital Universitário João de Barros Barreto, Belem, PA, Brazil
17	Jorge Gross	Centro de Pesquisas em Diabetes, Porto Alegre, RS, Brazil
18	Joao Borges	Centro de Pesquisa Clinica do Brasil, Brasilia, DF, Brazil
19	Maria Jose Cerqueira	Instituto de Ensino e Pesquisa Clínica do Ceará, Fortaleza, CE, Brazil
20	Miguel Nasser Hissa	Centro de Pesquisas em Diabetes e Doenças Endrócrino-Metaból, Fortaleza, CE, Brazil
21	Sergio Cunha Vencio	Instituto de Ciências Farmacêuticas, Goiania, GO, Brazil
22	Edgard Niclewicz	Hospital Nossa Senhora das Gracas, Curitiba, PR, Brazil
23	Joao Salles	Irmandade da Santa Casa de Misericordia de Sao Paulo, Sao Paulo, SP, Brazil
24	Rosa Santos	Hospital das Clinicas da Faculdade de Medicina da USP, Sao Paulo, SP, Brazil
25	Galina Dakovska	USHATE"Akad. Ivan Penchev", Sofia, Bulgaria
26	Ivona Daskalova	MMA-MHAT- Sofia, Sofia, Bulgaria
27	Zdravko Kamenov	UMHAT Alexandrovska, Sofia, Bulgaria
28	Stefka Vladeva	UMHAT Kaspela, Plovdiv, Bulgaria
29	Nataliya Temelkova	Alexandrovska University Hospital, Dermaology & Venerology, Sofia, Bulgaria
30	Natalia Veleva	DCC XII, Sofia, Bulgaria
31	Maria Lucheva	MHAT D-r Hristo Stambolski EOOD, Kazanlak, Bulgaria
32	Emilia Apostolova	MHAT Bratan Shukerov, Smolian, Bulgaria
33	Dotska Minkova	MHAT Razgrad, Razgrad, Bulgaria
34	Rositsa Shumkova	MHAT Dr. Tota Venkova AD, Cardiology Department, Gabrovo, Bulgaria
35	Tsvetodara Kuneva	DCC 1 Russe EOOD, Ruse, Bulgaria
36	Jaime Ibarra	Centro de Diabetes Cardiovascular del Caribe, Barranquilla, Colombia
37	Hernan Yupanqui	DEXADIAB, Bogotá, Colombia
38	Arturo Orduz	Fundacion Hospital Infantil Universitario de San Jose, Bogota, Cundinamarca, Colombia
39	Fernando Manzur	Centro de Diagnostico Cardiológico, Cartagena, Bolivar, Colombia
40	Jose Luis Accini Mendoza	IPS Centro Cientifico Asistencial, Barranquilla, Colombia
41	Jan Gerle	Medica JM S.R.O., Praha, Czech Republic
42	Tomas Spousta	Diabetologicka ambulance Ostrava, Ostrava, Czech Republic
43	Jan Vorisek	Diabetologicka ambulance MUDr. Jan Vrkoc S.R.O., Moravska Ostrava, Czech Republic
44	Sarka Kopecka	DIACENTRUM Brandys n.L. s.r.o, Brandys Nad Labem, Brandys Nad Labem
45	Katarina Halciakova	Diabetologicka ambulance, Prague 5, Czech Republic
46	Miloslava Komrskova	Diabetologicka, interni ambulance, Pisek, Czech Republic
47	Casimiro Velazco	Instituto de Endocrinologia, Nutricion y Osteoporosis, Santo Domingo, Republica Dominicana
48	Dolores Mejia	Hospital General Plaza de la Salud, Santo Domingo, Republica Dominicana
49	Juan Vargas	Hospiten Santo Domingo, Santo Domingo, Republica Dominicana
50	Svea Rosenthal	Rosenthal Family Doctors Centre, Tallinn, Estonia
51	Mirjam Turkson	Pirita Family Doctor's Centre, Tallinn, Estonia
52	Kristi Otsmaa	OU Kodudoktori PAK Sinu Arst, Tallinn, Estonia
53	Kaja Martsin	Mustamae Health Centre, Tallinn, Estonia
54	Mai Stern	Saku Health Care Center, Saku, Estonia
55	Juri Linros	Keravan terveyskeskus, Kerava, Finland
56	Karita Sadeharju	Seinajoen Seudun Terveyskeskus, Seinajoki, Finland
57	Jyrki Makela	Mehilainen Lahti, Lahti, Finland
58	Paivi Matsi	Kouvolan terveysasema, Kouvola, Finland
59	Anneli Hametvaara	Terveystalo Tampere, Tampere, Finland
60	Susanna Pihlman	Pohjois-Karjala projekti-saatio, Joensuu, Finland
61	Matti Kuusela	Kokkolan Laakarikeskus,, Kokkola, Finland
62	Sirkka Keinanen-Kiukaanniemi	Oulun Diankonissalaitos, Oulu, Finland
63	Thomas Behnke	Zentrum für Klinische Forschung Neuwied (ZKSN), Neuwied, Germany

Table A1 (*Continued*)

Site number	Principal investigator	Institution
64	Michael Eggeling	Aerztehaus Schulstr. 165 Dres. Eggeling, Koch, Wollny, Kamp-Lintfort, Germany
65	Stefan Goelz	Praxis Dr. Goelz, Esslingen am Neckar, Germany
66	Hans-Peter Kempe	Gemeinschaftspraxis Dres. Stemler u. Kempe, Ludwigshafen, Germany
67	Gerhard Klausmann	Gemeinschaftspraxis Dr. Klausmann/Dr. Welslau, Aschaffenburg, Germany
68	Uwe Kleinecke-Pohl	Praxis Dr. Kleinecke-Pohl / Zentrum für Klinische Forschung, Koeln, Germany
69	Michael Morcos	Stoffwechselzentrum Rhein-Pfalz, Mannheim, Germany
70	Thorsten Rau	Praxis Dr. Rau, Essen, Germany
71	Joachim Sauter	Praxis Dr. Sauter, Wangen, Germany
72	Alexander Segner	Praxis Dr. Segner, St. Ingbert – Oberwuerzbach, Germany
73	Joerg Simon	Praxis Dr. med. Joerg Simon, Fulda, Germany
74	Marc Haeffner	Praxis Dr. Haeffner / Steinmaier, Viernheim, Germany
75	Dietrich Tews	Diabeteszentrum Dr. Tews, Gelnhausen, Germany
76	Martin Grundner	Praxis Dr. Grundner / Dr. Hintze, Hainstadt, Hainburg, Germany
77	Michael Roden	Deutsches Diabetes Zentrum / Heinrich-Heine-Universitaet, Duesseldorf, Germany
78	Tobias Ohde	Ambulantes Diabeteszentrum Essen Nord, Essen, Germany
79	Markolf Hanefeld	GWT-TUD mbH, Studienzentrum Prof. Hanefeld, Dresden, Germany
80	Sergio Bran	Clínica Dr. Sergio Bran, Guatemala City, Guatemala, Mexico
81	Clara Chang	Clinica Dra Clara Chang,, Guatemala City, Mexico
82	Lorena Garcia	Centro Clínico Reumatológico, Guatemala City, Guatemala, Mexico
83	Luis Ramirez	Clínica Dr. Luis Ramirez 2, Guatemala City, Guatemala, Mexico
84	Narda Guerrero	Centro de Investigacion Clinica, Guatemala City, Guatemala, Mexico
85	Juan Moreira	Centro de Investigacion Dr. Moreira clinica, Mexico
86	Flor Ranchos	Centro de Investigacion Dra. Flor de Maria Ranchos, Guatemala City, Guatemala, Mexico
87	Risa Ozaki	Medicine & Therapeutics,The Chinese University of Hong Kong, HongKong
88	Chiu-Chi Tsang	Alice Ho Mui Ling Netherole Hosptial, Hong Kong
89	Michelle Wong	Shau Kei Wan Jockey Club GOPC, Hong Kong
90	Robert Takacs	Szent Gyorgyi Albert Klinikai Kozpont, Szeged, Hungary
91	Albert Szocs	Szocs Depot Eu Szolg Kft, Budapest, Hungary
92	Janos Penzes	Haziorvosi Rendelo Csongrad, Csongrad, Hungary
93	Laszlo Futo	Markhot Ferenc Korhaz, Eger, Hungary
94	Zsuzsanna Kerenyi	Toth Ilona Eu Szolgalat, Budapest, Hungary
95	Tamas Oroszlan	Zala Megyei Korhaz, Zalaegerszeg, Hungary
96	Margit Mileder	Veszprém Megyei Csolnoky Ferenc Kórház Nonprofit Zrt., Veszprem, Hungary
97	Gizella Pap	Kalocsai Szent Kereszt Korhaz, Kalocsa, Hungary
98	Kasthuri Alagiasingachar Srinivasan	Bangalore Diabetes Centre, Bangalore, Karnataka, India
99	Mala Dharmalingam	Bangalore Endrocrinology Diabetes Research Center, Bangalore, Karnataka, India
100	Sudhir Bhandari	Bhandari Clinic & Research Center, Jaipur, Rajasthan, India
101	Uday Phadke	Hormones and Diabetes Care Clinic, Pune, Maharashtra, India
102	Rakesh Kumar Maliram Parikh	Diamed Clinical Research Services Pvt. Limited, Jaipur, Rajasthan, India
103	A. Ramachandran	Dr.A.Ramachandran's Diabetes Hospital, Chennai, Tamil Nadu, India
104	Anil Bhansali	Post Graduate Institute of Medical Education & Research, Chandigarh, India
105	C. S. Yajnik	KEM Hospital, Pune, Maharashtra, India
106	Vishwanathan Mohan	Dr. V. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India
107	Arun Chankramath Somasekharan	Amritha Institute of Medical Sciences (AIMS), Kochi, Kerala, India
108	Satish Agarwal	Indraprastha Apollo Hospital, New Delhi, India
109	Ganapathi Bantwal	St. John's National Academy of Health Sciences, Bangalore, Karnataka, India
110	Sunil M Jain	TOTALL Diabetes Hormone Institute, Indore, Madhya Pradesh, India
111	Julio Wainstein	The E Wolfson Medical Center, Tel Giborim, Holon, Israel
112	Mohammed Sabbah	Research Unit, Diabetes and Lipids Department, Linn MC, Heifa, Israel
113	Taiba Zornitzky	Kaplan Medical Center, Rehovot, Israel
114	Victor Vishlitzky	Meir Sapir Medical Center, Kfar-Saba, Israel
115	Anat Tsur	Clalit Health Services management, Jerusalem, Israel
116	Faiad Adawi	Ziv MC, Sefad, Israel
117	Raed Alami	Saint Joseph Hospital, Jerusalem, Israel
118	Piermarco Piatti	Ospedale San Raffaele IRCCS S R L, Milano, MI, Italy
119	Maurizio Tiziano Bevilacqua	ASST Fatebenefratelli Sacco Ospedale Luigi Sacco, Milano, MI, Italy
120	Nicola Lucio Liberato	Az.Ospedaliera della Prov.di Pavia Ospedale C. Mira, Casorate Primo, PV, Italy
121	Marianna Maranghi	A O Policlinico Umberto I Universita La Sapienza, Roma, RM, Italy
122	Antimo Aiello	Presidio Ospedaliero A. Cardarelli - ASREM Az.San.Reg.Molise, Campobasso, CB, Italy
123	Davide Lauro	Fondaz.Policlin.Tor Vergata-Univ. degli Studi Tor Vergata, Rome, RM, Italy
124	Paola Ponzani	Stab Osp La Colletta Presidio Ospedal Unico ASL 3 Genovese, Arenzano, GE, Italy
125	Paolo Desenzani	ASST degli Spedali Civili Brescia-Pres.Osped.di Montichiari, Montichiari, BS, Italy
126	Kunho Yoon	The Catholic University of Korea Seoul St Marys Hospital, Seoul, South Korea
127	Hyuksang Kwon	The Catholic University of Korea Yeouido St. Mary's Hospital, Seoul, South Korea
128	Jongmin Lee	The Catholic University of Korea Daejeon St.Mary's hospital, Daejeon, South Korea
129	Sungdae Moon	Incheon St. Mary's hospital The Catholic University of Kore, Incheon, South Korea

Table A1 (*Continued*)

Site number	Principal investigator	Institution
130	Soonjib Yoo	The Catholic University of Korea, Bucheon St.Mary Hospital, Bucheon, Gyeonggi-do, South Korea
131	Yubae Ahn	The Catholic University of Korea St. Vincent's Hospital, Suwon, Gyeonggi-do, South Korea
132	Taeseo Sohn	Catholic University of Korea Uijeongbu St. Mary's Hospital, Uijeongbu-Si, Gyeonggi-do, South Korea
133	Sangah Chang	The Catholic University of Korea St. Paul's Hospital, Seoul, South Korea
134	Jelena Sokolova	Daugavpils Regional Hospital LTD, Daugavpils, Latvia
135	Ilze Lagzdina	ap SANUS, Liepaja, Latvia
136	Dace Teterovska	Dr. Teterovska's Private Practice in Endocrinology, Ogre, Latvia
137	Valdis Pirags	P Stradina Clinical University Hospital, Riga, Latvia
138	Inga Rezgale	Pulss 5 Medical Centre, Riga, Latvia
139	Inta Leitane	SIA Rigas veselibas centrs Tornakalns branch, Riga, Latvia
140	Valda Stalte	VSV Centrs, Talsi, Latvia
141	Sigita Pastare	Zemgales Diabetes Centre, Jelgava, Latvia
142	Laila Kudule	Riga Outpatient Clinic "Dziednieciba", Riga, Latvia
143	Ruta Eglite	General Practice "R.Eglites Doktorats", Kuldiga, Latvia
144	Agne Abraitiene	Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania
145	Vaidotas Urbanavicius	Private Endocrinology Clinic, Vilnius, Lithuania
146	Jurate Lasiene	Hospital of Lithuanian University of Health Sciences Kaunas, Kaunas, Lithuania
147	Lina Radzeviciene	Kaunas Dainavos Outpatient Clinic, Kaunas, Lithuania
148	Egle Urbanaviciene	Kaunas Silainiai Outpatient Clinic, Kaunas, Lithuania
149	Kristina Baltramonaitiene (Aglinskiene)	Kristavita UAB, Jonava, Lithuania
150	Ab Aziz Al-Safi Ismail	Hospital Universiti Sains Malaysia, Kota Bahru, Kelantan, Malaysia
151	Ee Ming Khoo	University Malaya Medical Centre, Kuala Lumpur, Malaysia
152	Nor Azmi Kamaruddin	Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
153	Leobardo Sauque	Instituto de Diabetes, Obesidad y Nutricion S.C., Cuernavaca, Morelos, Mexico
154	Leobardo Sauque	Instituto de Diabetes, Obesidad y Nutricion S.C., Cuautla, Morelos, Mexico
155	Sergio Hernandez	Instituto Nacional de Ciencias Medicas y Nutricion Salvador, Distrito Federal
156	Guadalupe Morales	Centro de Diabetes Durango, Durango, Mexico
157	Enrique Morales	Centro de Investigación Cardiometabólica Ags, Aguascalientes, Mexico
158	Jorge Aldrete	Paracelsus, S.A. de C.V., México, Distrito Federal
159	Guillermo Fanghanel	Clinica integral del paciente diabetic, Ciudad De Mexico, Distrito Federal
160	Manuel Aguilera	Centro de Investigacion Biomedica y Farmaceutica, Mexico D.F, Distrito Federal
161	Juan Villagordoa	Centro de Estudios Clinicos de Queretaro S.C., Querétaro, Mexico
162	Eli Heggen	Oslo Universitetssykehus HF, Ullevål, Oslo, Norway
163	Jorn Gronert	Flattum legesenter, Hønefoss, Norway
164	Asad Uzzaman	Fet Legesenter AS, Fetsund, Norway
165	Lars-Erik Fikke	Enebakk legesenter, Enebakk, Norway
166	Rolf Johansen	Spikkestadlegene, Spikkestad, Norway
167	Marilyn Donato	CEDITER, Panama City, Panamá
168	Pablo Fletcher	Private Clinic Dr. Pablo Fletcher, Panama City, Panamá
169	Giselle Rodriguez	PAMRI Panama City, Panamá
170	Angelica Valdivia	Clinica Geriatrica del Ejercito, Chorrillos, Lima, Peru
171	Cesar Delgado	Instituto Delgado de Investigacion Medica, Arequipa, Peru
172	Jose Solis	Hospital Nacional Arzobispo Loayza, Cercado de Lima, Lima, Peru
173	Miguel Pinto	Hospital Nacional Cayetano Heredia, San Martin de Porres, Lima, Peru
174	Luis More	Consultorio de Endocrinologia, San Isidro, Lima, Peru
175	Luis Camacho	Clinica Peruano Americana, Trujillo, La Libertad, Peru
176	Luis Zapata	Casa de Diabetes & Nutricion, Magdalena, Lima, Peru
177	Ma Concepcion Marcelo	Cardinal Santos Medical Center, San Juan City, Philippines
178	Cecilia Jimeno	San Juan de Dios Educational Foundation Inc. Hospital, Pasay City, Philippines
179	Elizabeth Catindig	Institute for Studies on Diabetes Foundation Inc, Marikina, Metro Manila, Philippines
180	Tomas Lazatin, Jr	Quirino Memorial Medical Center, Quezon City, Metro Manila, Philippines
181	Roberto Mirasol	Rizal Medical Center, Pasig City, Philippines
182	Rhea Severina Comia	Amang Rodriguez Memorial Medical Center (ARMMC), Marikina City, Philippines
183	Malgorzata Rozycka-Grudniewicz	NZOZ Specjalista Sp.z.o.o, Kutno, Poland
184	Ewa Krzyzagorska	Praktyka Lekarska Ewa Krzyzagorska, Poznan, Poland
185	Maria Modzelewska	NZOZ DIABMED, Poznan, Poland
186	Janusz Gumprecht	Gabinet Prywatny Prof. Janusz Gumprecht, Zabrze, Poland
187	Piotr Napora	Centrum Badan Klinicznych Piotr Napora Lekarze Sp.p., Wroclaw, Poland
188	Dorota Pisarczyk-Wiza	GAJA Poradnie Lekarskie Maciej Wiza, Poznan, Poland
189	Amorin Popa	Emergency County Hospital Oradea, Oradea, Jud. Bihor, Romania
190	Mihaela Popoviciu	Medical Practice srl, Oradea, Jud. Bihor, Romania
191	Mihaela Voitec	Ambulatory of Institute of Nutrition Diseases and Diabetes, Bucharest, Romania
192	Adriana Dumitrescu	Medical Centre "Sanatatea ta", Bucharest, Romania

Table A1 (*Continued*)

Site number	Principal investigator	Institution
193	Cornelia Zetu	Institute of Nutrition Diseases and Diabetes "N. Paulescu", Bucharest, Romania
194	Bogdan Popa	Spitalul Judetean de Urgenta Ploiesti, Ploiesti, Jud. Prahova, Romania
195	Lavinia Ionutiu	Centrul Medical Sf. Stefan SRL, Timisoara, Romania
196	Diana Alpenidze	Out-patient City Clinic #117, St-Petersburg, Russia
197	Valeria Esip	Consultation and Diagnostic Centre #85, St-Petersburg, Russia
198	Sergey Martsevich	State Research Centre for Preventive Medicine, Moscow, Russia
199	Galina Reshedko	Smolensk State Medical Academy of Roszdrav, Smolensk, Russia
200	Ruslan Sardinov	Institute of Experimental Medicine, St- Petersburg, Russia
201	Sergey Shustov	Military Medical Academy n.a.S.M Kirov, St-Petersburg, Russia
202	Yury Shvarts	Saratov State Medical University of Roszdrav, Saratov, Russia
203	Natalia Vezikova	Baranovs Republican Hospital, Petrozavodsk, Russia
204	Sergey Yakushin	Ryazan State Medical University n.a.Pavlov, Ryazan, Russia
205	Olga Zanozina	N.A.Semashko's Regional Clinical Hospital of N.Novgorod, N.Novgorod, Russia
206	Marina Sergeeva-Kondrachenko	Penza Regional clinical hospital n/a Burdenko, Penza, Russia
207	Viera Donicova	Human-Care S.R.O., Kosice, Slovakia
208	Katarina Belesova	Lumedic S.R.O., Kosice, Slovakia
209	Maria Slovenska	Vnútorné lekárstvo, diabetológia, poruchy látkovej premeny a, Kosice, Slovakia
210	Dana Solcova	DIADAN S.R.O., Ambulancia s odborným zameraním vnút.lekarstv, Kosice, Slovakia
211	Dalibor Sosovec	DIAB S.R.O., Roznava, Slovakia
212	Dasa Skripova	ARETEUS S.R.O. Diabetologicka ambulancia, Trebisov, Slovakia
213	Marek Macko	Diabetol S.R.O., Presov, Slovakia
214	Livia Tomasova	IN-DIA S.R.O., Lucenec, Slovakia
215	Drahoslava Kanderkova	MUDr. Kanderková S.R.O., Namestovo, Slovakia
216	Ingrid Buganova	MEDIVASA s.r.o., Diabetologia, Zilina, Slovakia
217	Anna Vargova	DIA-KONTROL S.R.O., Levice, Slovakia
218	Ladislav Pavlik	DIA MEDICO S.R.O., Sala, Slovakia
219	Miriam Teplanova	FUNKYSTUFF S.R.O., Nové Zámky, Slovakia
220	Jozef Strba	Endiant S.R.O., Sered, Slovakia
221	Adriana Ilavska	MEDISPEKTRUM s r o, Bratislava, Slovakia
222	Milan Behuncik	Zeleznicne zdravotnictvo, S.R.O. Kosice, Slovakia
223	Martina Merciakova	MEDI-DIA S.R.O., Diabetologicka ambulancia, Sabinov, Slovakia
224	Denisa Spodniakova	DIASTYLE S.R.O. Interna-diabetologicka ambulancia, Banska Bystrica, Slovakia
225	Iveta Kurcova	DIA Zilina S.R.O., Diabetologicka a interna ambulancia, Zilina, Slovakia
226	Olga Benusova	BENROD S.R.O., diabetologicka ambulancia, Sturovo, Slovakia
227	Aslam Amod	Suite 215, Durban, South Africa
228	Magda Conradie	Department of Endocrinology, Cape Town, South Africa
229	Deepak Lakha	1644 Starling Street, Johannesburg, South Africa
230	J Kok	Cardiology Clinical Research, Alberton, South Africa
231	Hemant Makan	Private Practice, Gauteng, South Africa
232	S Pillay	Suite C5 Seadoon Mall, Durban, South Africa
233	Tasneem Vally	Synexus SA Watermeyer Clinical Research, Pretoria, South Africa
234	Akbar Mahomed	Dr A A Mahomed Medical Centre, Pretoria, South Africa
235	Luthando Adams	LCS Clinical Research Unit, Johannesburg, South Africa
236	Xavier Cos Claramunt	CAP Sant Marti de Provençals, Barcelona, Spain
237	Carles Brotons Cuixart	CAP SARDENYA, Barcelona, Spain
238	Jordi Ingla	CAP Santa Coloma, Santa Coloma de Gramanet, Barcelona, Spain
239	Manel Mata	CAP La Mina, Sant Adria del Besos, Barcelona, Spain
240	Wayne Huey-Herng Sheu	Taichung Veterans General Hospital, Taichung, Taiwan
241	Jui-Hung Sun	Chang Gung Memorial Hospital Linkou, Lin-Kou, Taiwan
242	Yi-Jen Hung	Tri-Service General Hospital, Taipei, Taiwan
243	Dee Pei	Cardinal Tien Hospital, Hsin-tien, Taiwan
244	Nevin Dinccag	Istanbul University Istanbul Medical Faculty, Istanbul, Turkey
245	Mehmet Buyukbese	Sutcu Imam University Medical Faculty, Kahramanmaras, Turkey
246	Muyesser Sayki Arslan	S.B. Yildirim Beyazit Training and Research Hospital, Diskapi / Ankara, Turkey
247	Ramazan Sari	Akdeniz University Medical Faculty, Antalya, Turkey
248	Fusun Saygili	Ege University Medical Faculty, Izmir, Turkey
249	Abdurrahman Comlekci	Dokuz Eylul University Medical Faculty, Izmir, Turkey
250	Senay Topsakal	Pamukkale University Medical Faculty, Kinikli / Denizli, Turkey
251	Hasan Kudat	Istanbul University Istanbul Medical Faculty, Istanbul, Turkey
252	Murat Sert	Cukurova University Medical Faculty, Adana, Turkey
253	Yagiz Uresin	Istanbul University Istanbul Medical Faculty, Istanbul, Turkey
254	Zerrin Yigit	Istanbul University Cardiology Institute, Istanbul, Turkey