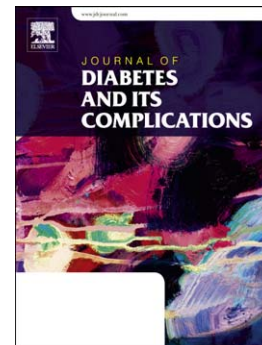# Accepted Manuscript

Towards an improved global understanding of treatment and outcomes in people with type 2 diabetes: rationale and methods of the DISCOVER observational study program

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Towards an improved global understanding of treatment and outcomes in people with type 2 diabetes: rationale and methods of the DISCOVER observational study program

Running Title: DISCOVER observational study program

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ABSTRACT

Aim: Contemporary global real-world data on the management of type 2 diabetes are scarce. The global DISCOVER study program aims to describe the disease management patterns and a broad range of associated outcomes in patients with type 2 diabetes initiating a second-line glucose-lowering therapy in routine clinical practice.

Methods: The DISCOVER program comprises two longitudinal observational studies involving more than 15 000 patients in 38 countries across six continents. Study sites have been selected to be representative of type 2 diabetes management in each country. Data will be collected at baseline (initiation of second-line therapy), at 6 months, and yearly during a 3-year follow-up period.

Results: The DISCOVER program will record patient, healthcare provider, and healthcare system characteristics, treatment patterns, and factors influencing changes in therapy. In addition, disease control (e.g. achievement of glycated hemoglobin target), management of associated risk factors (e.g. hypercholesterolemia and hypertension), and healthcare resource utilization will be recorded. Microvascular and macrovascular complications, incidence of hypoglycemic events, and patient-reported outcomes will also be captured.

Conclusions: The DISCOVER program will provide insights into the current management of patients with type 2 diabetes worldwide, which will contribute to informing future clinical guidelines and improving patient care.

ClinicalTrials.gov identifiers: NCT02322762 (DISCOVER) and NCT02226822 (J-DISCOVER).

1. Introduction

In 2015, an estimated 415 million people had diabetes and this number is predicted to increase to 642 million by 2040 (International Diabetes Federaion [IDF], 2015), with type 2 diabetes accounting for the vast majority of cases; studies in high-income countries have estimated that 87–91% of all people with diabetes have type 2 diabetes (Boyle et al., 1999; Bruno et al., 2005; Evans et al., 2000; Holman et al., 2015). Diabetes and its complications are major causes of early deaths in many countries; an estimated 5 million people worldwide aged 20–79 years died from diabetes in 2015 (IDF, 2015). Type 2 diabetes is a significant risk factor for cardiovascular disease (CVD), which is the most common cause of death in people with type 2 diabetes (Morrish et al., 2001). This high risk of CVD is explained in part by the high prevalence of other modifiable cardiovascular risk factors in people with type 2 diabetes, including hypertension, obesity, and dyslipidemia (Preis et al., 2009). The management of patients with type 2 diabetes is therefore complex and requires that issues in addition to glycemic control be addressed. The need for an individualized and patient-centered approach to diabetes care is acknowledged by current clinical guidelines, which recommend multifactorial management based on the patient characteristics (e.g. age, duration of diabetes, life expectancy, presence of comorbidities, and risk of hypoglycemia) (Chinese Diabetes Society [CDS], 2014; Garber et al., 2015; IDF, 2012; Inzucchi et al., 2015; Qaseem et al., 2012). Thus, physicians are faced with complex decision-making situations in optimizing the treatment of their patients with type 2 diabetes. For example, the importance of achieving glycemic control to reduce the risk of microvascular and macrovascular complications in patients with type 2 diabetes is well established (Holman et al., 2008; Patel et al., 2008; Ray et al., 2009; Stratton et al., 2000; UK Prospective Diabetes Study [UKPDS] Group, 1998) and current guidelines generally recommend the use of metformin, in

conjunction with lifestyle changes, as the first-line glucose-lowering therapy in patients with

no contraindications and who can tolerate it (CDS, 2014; Garber et al., 2015; IDF, 2012;

Inzucchi et al., 2015; Qaseem et al., 2012). When metformin monotherapy fails to control

glycated hemoglobin (HbA$_{1c}$) levels, guidelines recommend the timely addition of a second

glucose-lowering agent such as a sulfonylurea, a thiazolidinedione, acarbose, a dipeptidyl

peptidase-4 inhibitor, a sodium–glucose-linked transporter type 2 inhibitor, a glucagon-like

peptide-1 (GLP-1) receptor agonist, or basal insulin. However, most guidelines do not clearly

state optimal treatment pathways upon initiation of second-line therapy (CDS, 2014; IDF,

2012; Inzucchi et al., 2015; Qaseem et al., 2012); only the American Association of Clinical

Endocrinologists and American College of Endocrinology diabetes management algorithm

suggests a clear treatment hierarchy (Garber et al., 2015). This lack of guidance, combined

with the availability of numerous glucose-lowering agents, means that a wide range of

therapies is used in second and subsequent lines in clinical practice. Although recent large

cardiovascular outcomes trials suggest that some therapies can substantially reduce the risk of

major cardiovascular events such as cardiovascular death, hospitalization for heart failure,

myocardial infarction, and stroke (Marso et al., 2016; Zinman et al., 2015), little is known

about treatment pathways and their associations with outcomes after failure of first-line

therapy in routine clinical practice. Randomized clinical trials alone cannot inform treatment

decisions in clinical practice because they are restricted to specific populations based on strict

inclusion and exclusion criteria; longitudinal data on treatment pathways are therefore

essential to identify the disease, patient, and physician characteristics that are associated with

the most effective treatment decisions and optimal outcomes. A better understanding of

practice variations across and within different countries, and their determinants and

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associated patient outcomes are also key to improving public health policies and reducing the economic burden of type 2 diabetes.

We hypothesized that there is wide variability in the use of glucose-lowering agents as second-line therapy for the treatment of type 2 diabetes, and that these differences are related to various factors, including system factors (e.g. type of practice, region of the world, access to medications, and copayments), patient characteristics (e.g. medical history, comorbidities, and presence of risk factors), and physician specialty. We further hypothesized that the differences in prescribing patterns are associated with differences in disease and CVD risk factor control and evolution, occurrence of complications (microvascular and macrovascular events), quality of life, and use of healthcare resources.

1.1. Study objectives

The primary objective of the DISCOVER study program is to describe the disease management patterns and clinical evolution in patients with type 2 diabetes who are starting a second-line glucose-lowering therapy (defined as adding a glucose-lowering drug or switching between therapies) after failure of first-line oral treatment with a monotherapy, dual therapy, or triple therapy.

In addition, the study aims to describe the patient, physician, and healthcare system determinants of treatment patterns, and the associations between treatment patterns and a broad range of outcomes, including glycemic control, hypoglycemic episodes, incidence of complications (e.g. microvascular and macrovascular events), healthcare resource utilization (e.g. hospitalizations and emergency department visits), and patient-reported outcomes (PROs) (Table 1).

2. Materials and methods

2.1. Design

The multinational DISCOVER study program comprises two similar, observational, longitudinal, prospective studies conducted simultaneously: (1) DISCOVER in 37 countries (Algeria, Argentina, Australia, Austria, Bahrain, Brazil, Canada, China, Colombia, Costa Rica, Czech Republic, Denmark, Egypt, France, India, Indonesia, Italy, Jordan, Kuwait, Lebanon, Malaysia, Mexico, Netherlands, Norway, Oman, Panama, Poland, Russia, Saudi Arabia, South Africa, South Korea, Spain, Sweden, Taiwan, Tunisia, Turkey, and United Arab Emirates) and (2) J-DISCOVER in Japan (Fig. 1). Countries were selected across different continents to obtain a global assessment of the current state of type 2 diabetes treatment and to gain specific insights in countries with a high prevalence of diabetes (e.g. China, India, Brazil, and countries in the Middle East and Africa) and in regions that have never or rarely been studied (e.g. Middle East and Africa). DISCOVER recruited patients from December 2014 to June 2016; J-DISCOVER recruited patients from September 2014 to December 2015. Patients will be followed up for 3 years from initiation of second-line therapy (baseline). Baseline data should be available in the first quarter of 2017.

This is a non-interventional study; enrolled participants will undergo clinical assessments and receive standard medical care as determined by their treating physicians. Patients will not receive any investigational treatment or experimental intervention as a consequence of their participation in the study. Participation is on a voluntary basis and patients are free to withdraw from the study at any time and without prejudice to their subsequent treatment. Patients lost to follow-up will not be replaced.

The study protocol was approved by the appropriate clinical research ethics committees in each participating country and by the relevant institutional review board at each site. The protocol complies with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice, and the local regulations for clinical research (ClinicalTrials.gov identifiers: NCT02322762 for DISCOVER; NCT02226822 for J-DISCOVER). All participating patients provided signed informed consent.

2.2. Site and investigator selection

Characteristics of physicians and practices involved in the management of patients with type 2 diabetes were assessed in each participating country by combining data from peer-reviewed articles, information from reports published by organizations such as the World Health Organization, and insights from national coordinating investigators. Proportions of different types of physicians (primary care physicians, diabetologists, endocrinologists, cardiologists, and other specialists) and practices (primary care centers, specialized diabetes centers, and different types of hospitals), as well as the location of practices (urban vs rural and geographical distribution within a country), were collated. A list of prospective sites that would match these characteristics as much as possible was then established for each country, and all sites were invited to participate in the study. The number of sites in each country was commensurate with the targeted number of patients and the recruitment potential of the sites. Practical and logistical reasons (e.g. low recruitment potential or site refusal to participate) that may preclude achieving optimal representativeness were documented and will be reported and taken into account in the data analysis and/or the interpretation of results. Characteristics of the 815 participating sites are shown in Supplementary Table 2. The large

majority of sites are primary care centers (53.6%), located in urban areas (74.2%), and privately funded (58.3%)."

2.3. Study participants

Eligible patients with type 2 diabetes initiating a second-line glucose-lowering treatment (add-on or switching) after a first-line oral treatment with a monotherapy, dual therapy, or triple therapy were invited to participate in the study by their physician. Patients using an injectable agent (i.e. insulin or a GLP-1-receptor agonist) as first-line therapy were excluded from the study because they might constitute a population with a more severe disease profile, which would warrant a separate study. Patients who received short-term initial treatment with insulin followed by oral therapy were eligible if the treatment with insulin lasted no more than 2 weeks and occurred at least 6 months before initiation of second-line therapy. In such cases, insulin was considered not as a first-line treatment but as an acute course to lower glycemic levels quickly before starting regular treatment. All inclusion and exclusion criteria are shown in Supplementary Table 1. A total of 16 309 patients (14 391 in DISCOVER and 1915 in J-DISCOVER; Figure 1) were enrolled.

2.4. Data collection

2.4.1. Data collection using an electronic case report form

For all eligible patients who sign the informed consent form, data will be collected at baseline (date of initiation of the second-line therapy) and at 6, 12, 24, and 36 months (Fig. 2A). In most countries, data for all time points will be collected by investigators using an electronic case report form (eCRF) via a web-based data capture system. Data will be saved immediately to a central database, and all eCRFs will be checked to ensure that they

are completed appropriately. Where technically feasible and allowed by local regulations, the information captured in the eCRF will be linked with other sources of health information, such as existing electronic medical records (EMRs) and disease registries, to build a comprehensive data resource for research.

Baseline data will be collected at the routine visit, during which the second-line glucose-lowering therapy will be prescribed. If this is not possible (e.g. because of time constraints), the investigator will arrange for another visit to take place within 2 weeks to collect all necessary information. This will include demographic and anthropometric data, available laboratory test results, medical history of type 2 diabetes, presence of comorbidities, co-medications, level of care, previous glucose-lowering treatment (first-line therapy) and reason for change, second-line glucose-lowering drug class, HbA$_{1c}$ target, and PROs (Table 2).

During the 3-year follow-up, data will be captured at 6, 12, 24, and 36 months within a 4-month window ($\pm$ 2 months) (Fig. 2A) to increase the probability that the data collection time point coincides with a routine patient visit; the protocol does not mandate any compulsory follow-up visits in order to ensure that the study results reflect routine clinical practice as much as possible. Variables to be recorded will include physiological parameters, laboratory test results, change(s) in glucose-lowering therapy and reason(s) for change(s) (e.g. suboptimal glycemic control and adverse events), HbA$_{1c}$ level at time of change(s), occurrence of microvascular and macrovascular events, occurrence of minor and major hypoglycemic events, changes in comorbidities and co-medications, PROs, and healthcare resource utilization. In addition, information related to hospitalizations or emergency department visits during follow-up (including reason for and duration of hospitalization,

details about the ward where the patient was treated, and interventions received) will be recorded in specific fields of the eCRF (Table 2). The investigators will be asked to contact the physician(s) in charge of the patient during hospitalization to obtain the required information. Events identified through this procedure will be classified without further assessment.

In all countries except Japan, additional patients could be enrolled retrospectively to compensate for short recruitment periods in countries where protocol approval was delayed. All eligible patients who initiated their second-line glucose-lowering therapy between December 31, 2014 and the end of the recruitment period in each country could be invited to participate in the study and enroll after providing informed consent. Therefore, for countries in which recruitment was closed in June 2016, the maximal length of time between initiation of second-line therapy and enrollment could be 18 months. For these patients, data from the baseline visit and subsequent visits that occurred in the past were collected retrospectively by the investigators from medical records (Fig. 2B); PRO questionnaires were not completed for these time points.

2.4.2. Patient-reported outcomes

PROs will be collected using up to four self-administered questionnaires depending on availability in local languages: (1) the 36-item Short-form Health Survey version 2 (SF-36v2) will be used to measure general health status across eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Ware et al., 2007); (2) the revised Hypoglycemia Fear Survey (HFS-II), a 33-item survey using five-point Likert scales (score range: 0–132), will be used to assess behaviors and worries relating to fear of hypoglycemia

(Stargardt et al., 2009); (3) a seven-item questionnaire will be used to assess patients' lifestyles as 'unhealthy', 'intermediate', 'healthy', or 'very healthy', based on questions relating to smoking, alcohol intake, physical activity, and diet (Carlsson et al., 2013); and (4) a two-item questionnaire will be used to determine whether patients avoided healthcare and/or medication because of cost. In addition to the SF-36v2 questionnaire, the J-DISCOVER study will use slightly different questionnaires: (1) the Japanese version of the diabetes treatment satisfaction questionnaire (DTSQ), an 8-item survey using 7-point Likert scales, will be used to assess treatment satisfaction and measure the perceived frequency of hyperglycemia and hypoglycemia (Ishi et al., 2000); (2) the brief self-administered diet-history questionnaire (BDHQ) will be used to assess dietary habits (Kobayashi et al., 2011; Sasaki et al., 1998); and (3) the short version of the International Physical Activity Questionnaire (IPAQ-SV), a 9-item survey, will be used to estimate physical activity levels (Craig et al., 2003; Murase et al., 2002).

2.4.3. Data collection from electronic medical records

In Denmark, France, Norway, and Sweden, available study variables will be extracted automatically from existing primary care EMR databases. For all patients meeting the inclusion criteria at each participating site, EMR data will be extracted at baseline and yearly thereafter. At the time of de-identified EMR data extraction, a key code will be created that links each patient identification number to their registry data. This key code will be encrypted, password protected, and stored separately from the database used for analysis. Data not routinely captured in EMR databases (e.g. reason for treatment change) will be collected by investigators using an additional questionnaire. These data will then be linked back to the EMR to create a full dataset for each patient. In addition, in Denmark, Sweden,

and Norway, data extracted from EMRs will be merged with data from mandatory national health registries (e.g. information on hospitalizations, prescribed drugs, and cause of death) to create a de-identified study database.

A similar approach will be used in Canada. All patients were identified retrospectively, using the IMS Brogan EMR database. Eligible patients were invited to participate and enrolled after providing informed consent. Most data will be extracted from the EMR database for all time points. A short eCRF completed by the patient will also be used to collect additional data not routinely captured in the EMR database (e.g. hypoglycemic events and PROs). The eCRF was not be used at baseline because patients were enrolled retrospectively. This approach will provide a more limited dataset than in other DISCOVER countries; therefore, data from Canada will only be included in the global analysis of the DISCOVER results when appropriate.

In Canada, Denmark, France, Norway, and Sweden, it will also be possible to collect EMR data beyond the 3-year follow-up period, providing insights on longer-term disease management and outcomes. In these five countries, retrospective data will be collected from EMRs and/or national health registries for all patients with type 2 diabetes treated at each primary care site participating in the DISCOVER study (including patients not enrolled in the prospective DISCOVER study) and analyzed separately. This approach will enable a longer observation period in a large cohort and provide important data to assess the external validity of the results from the global DISCOVER study. The possibility of implementing a similar extended follow-up in other DISCOVER countries will be explored.

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2.4.4. Adverse event reporting

DISCOVER is a non-interventional study program and there is no requirement to report adverse events. Adverse drug reactions observed in patients participating in DISCOVER will be reported to health authorities as required by local regulations and/or if the investigator considers reporting to be appropriate.

2.5. Statistical analysis

Descriptive statistics will be used to summarize demographic variables, patient characteristics, treatment patterns, changes in HbA_{1c} level, blood glucose, lipid profile, body weight, body mass index, and blood pressure, incidence of complications and hypoglycemic events, PROs, and healthcare resource utilization. Data will be stratified by pharmacological drug class and/or individual agent when clinically relevant. Hierarchical multivariate regression analyses and general linear models will be used to determine potential predictors of treatment choices and clinical outcomes. When applicable, model-based point estimates of odds ratios or risk ratios, as appropriate, corresponding 95% confidence intervals, and *p* values will be reported. For analyses of clinical outcomes during follow-up, Cox models and mixed models for longitudinal data will be used, adjusted for age and sex, and using country as the indicator variable. Time-to-event analyses will be used to describe treatment patterns (e.g. initiation of third-line therapy).

The minimum sample size was estimated to be 11 100 patients, based on the following criteria: (1) the intention to have a minimum of 200 patients in any given group of patients to be analyzed (e.g. patients receiving a certain drug class or patients from one country), which would result in a precision of at least 7% for any expected qualitative variable at a frequency of 5–95%; (2) at least 200 patients meeting each of the composite endpoints of macrovascular

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complications (cardiovascular death, myocardial infarction, ischemic stroke, hospitalization for heart failure, coronary revascularization) and microvascular complications (neuropathy, retinopathy, nephropathy) at years 1, 2, and 3, based on expected yearly rates for these events (5.5% for the composite of macrovascular complications; 10.4% for the composite of microvascular complications); (3) at least 200 patients meeting each individual macrovascular and microvascular endpoint at year 3 (expected rates over 3 years: 2.4–4.6% for macrovascular complications; 3.5–15.7% for microvascular complications); and (4) an estimated attrition rate of 15% per year of follow-up.

All statistical analyses will be performed using the SAS statistical software system (SAS Institute, Inc., Cary, NC).

2.6. Funding and responsibilities

DISCOVER is funded by AstraZeneca. As it is a non-interventional study, no drugs are supplied or funded. The DISCOVER Scientific Committee comprises 12 scientists (L.J., F.B., B.C., M.B.G., M.K., K.K., A.N., S.P., W.R., M.V.S., I.S., and H.W.) and the following AstraZeneca members: the Scientific Project Leader (J.M.), the Global Medical Affairs Leader Diabetes (P.F.), the Global Medical Affairs Medical Evidence and Observational Research Diabetes Lead (N.H.), the Medical Affairs Senior Director Japan (K.H.), and former International Region Medical Directors (F.S. and G.M.).

3. Discussion

Although large, international, non-interventional studies of patients with type 2 diabetes have been conducted (Bradley et al., 2011; Echtay et al., 2013; Freemantle et al., 2012; Khunti et al., 2012; Kim et al., 2012; Li et al., 2011; Liebl et al., 2012; Mathieu et al., 2013;

Matthaei et al., 2012; Oguz et al., 2013; Rosales et al., 2015; Shah et al., 2010; Tsai et al.,

2011; Valensi et al., 2008), they only examined patients treated with insulin (Echtay et al.,

2013; Freemantle et al., 2012; Khunti et al., 2012; Liebl et al., 2012; Matthaei et al., 2012;

Oguz et al., 2013; Shah et al., 2010; Tsai et al., 2011; Valensi et al., 2008) or another specific

glucose-lowering drug class (Kim et al., 2012; Li et al., 2011; Mathieu et al., 2013; Matthaei

et al., 2012; Rosales et al., 2015), were limited to five or fewer countries (Echtay et al., 2013;

Liebl et al., 2012; Oguz et al., 2013) or included a relatively small number of patients

(< 1000) (Oguz et al., 2013), were of short duration (follow-up ≤ 6 months) (Echtay et al.,

2013; Khunti et al., 2012; Kim et al., 2012; Li et al., 2011; Rosales et al., 2015; Shah et al.,

2010; Tsai et al., 2011; Valensi et al., 2008), or were cross-sectional (Bradley et al., 2011). In

addition, many of these studies focused on drug safety and/or efficacy (Echtay et al., 2013;

Kim et al., 2012; Khunti et al., 2012; Li et al., 2011; Mathieu et al., 2013; Rosales et al.,

2015; Shah et al., 2010; Tsai et al., 2011) and few assessed quality of life (Bradley et al.,

2011; Shah et al., 2010; Valensi et al., 2008), incidence of hypoglycemic events (Echtay et

al., 2013; Khunti et al., 2012; Valensi et al., 2008), or treatment patterns (Freemantle et al.,

2012; Khunti et al., 2012; Liebl et al., 2012; Matthaei et al., 2012; Oguz et al., 2013;

Vichayanrat et al., 2013).

DISCOVER is a global, prospective, observational study of patients with type 2

diabetes, and it will be the first to report treatment patterns after initiation of second-line

therapy regardless of the agent(s) prescribed, in a large, contemporary, diverse, and

heterogeneous population. The study will provide a comprehensive overview of current

clinical practices in the treatment of patients with type 2 diabetes after failure of first-line oral

therapy across 38 countries, and will identify potential differences between practice and

clinical recommendations. The study is designed to generate sufficient data to analyze

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determinants of treatment decisions, and associations between treatment patterns and several disease-specific outcomes, including glycemic control, microvascular and macrovascular events, hypoglycemic episodes, and PROs. In addition, the large sample size will allow subanalyses to help to identify patient profiles or subgroups that respond well to specific therapeutic approaches. Importantly, the DISCOVER study program will generate real-world data on the management of type 2 diabetes and associated outcomes in countries with alarmingly high and rising prevalences of type 2 diabetes that have been under-studied to date.

DISCOVER is primarily a descriptive study, and representativeness of participating patients and physicians is key to meeting the study objectives and ensuring external validity of the results. Physicians invited to participate were therefore carefully selected across different specialties, care settings, and geographic regions in order to ensure that the findings would be representative of the management of patients with type 2 diabetes in each country. Nevertheless, physician selection bias should be considered when interpreting the results. Physicians who are more involved and/or competent in the treatment and management of diabetes may be more likely to participate and to treat patients earlier. In this case, the results of DISCOVER may slightly overestimate disease control and quality of care in day-to-day clinical practice. However, the large number of participating investigators (> 1000) across all specialties and from different clinical settings, and the inclusion of a diverse patient population, are likely to provide an accurate overview of diabetes management in each participating country or region.

DISCOVER uses PRO questionnaires and therefore relies on patients' recollection to determine the incidence of some events (e.g. minor hypoglycemic events); recall bias may therefore also influence the results of the study. However, this potential misclassification of

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outcomes is unlikely to be systematically associated with patient characteristics, risk of complications, or exposure to glucose-lowering agents. In addition, results from these questionnaires should be interpreted cautiously in light of data missing from patients enrolled retrospectively. Loss to follow-up might also be a source of bias. Patients with poorly controlled diabetes may be more likely to drop out over the 3-year follow-up than those with better outcomes, which could result in an underestimation of negative outcomes. It should also be noted that patient visits are not determined by the protocol; therefore, data collection during follow-up will rely on patients attending regular routine visits (the frequency of which may be country dependent) and on investigators being able to collect all relevant information (e.g. data about hospitalizations or emergency department visits). Finally, in common with all observational studies, confounding should be considered when interpreting the results. However, the available variables collected using the study eCRF will be used in multivariate analyses to minimize confounding when assessing associations between clinical outcomes and patient, physician, and healthcare system characteristics, and treatment patterns.

The DISCOVER study program also has major strengths in addition to the large sample size and the broad geographical representation. First, the naturalistic design of the studies, whereby the chances of protocol-induced findings and protocol-induced healthcare resource use are minimized, will help to ensure external validity of the results. In addition, the same eCRF will be used in all countries, ensuring consistent data collection. This user-friendly eCRF, combined with a relatively small target number of patients (< 20 on average) per investigator, will ensure that the time burden for investigators is minimal and that data are collected completely and accurately for all patients. The long follow-up period is also a key strength of DISCOVER and will allow the study of treatment patterns beyond initiation of second-line therapy. In some countries, prospective data collection will be complemented by

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data extracted from existing EMR databases, thus providing the opportunity to follow up some patients for longer than 3 years. Comparison of data extracted from EMRs and data collected with the eCRF may also inform the design of future observational studies. In addition, the DISCOVER study program will allow platforms for future research to be set up in countries with no previous systems for the capture of observational data from patients with type 2 diabetes.

It should be noted that, although the DISCOVER study program does not cover the USA, it has been developed in parallel with the recently launched Diabetes Collaborative Registry (DCR) (Arnold et al., 2016), which has the potential to become the largest cross-specialty clinical registry to track, evaluate, and eventually improve the quality of diabetes and metabolic care in the USA. The DCR captures similar data via EMR data extraction and will complement the DISCOVER results from 38 other countries. Studies of this type are essential to review trends in prescribing practices, diabetes management, and clinical outcomes, in order to help improve the standard of care for patients with type 2 diabetes.

4. Conclusion

The DISCOVER study program is a global initiative that will provide valuable insights into the treatment of patients with type 2 diabetes in real-world settings and will highlight differences between daily clinical practice and recommendations in current national and international guidelines. In addition, collection of patient-centric health status and healthcare resource utilization data will enable the evaluation of important outcomes beyond glycemic control and clinical events. The DISCOVER study program will also allow benchmarking of clinical practice between and within countries, help to inform future updates to clinical guidelines, and will further improve the care of patients with type 2 diabetes.

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Duality of interest

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Author contributions

The DISCOVER Scientific Committee is responsible for the design and conduct of the study and all study analyses. The authors were responsible for the preparation of this article. The first draft of the manuscript was developed by L.J., and all authors contributed to its development and approved the final version for submission. An AstraZeneca team reviewed the manuscript during its development and was allowed to make suggestions; however, the final content was determined by the authors. L.J. is the guarantor of this work.

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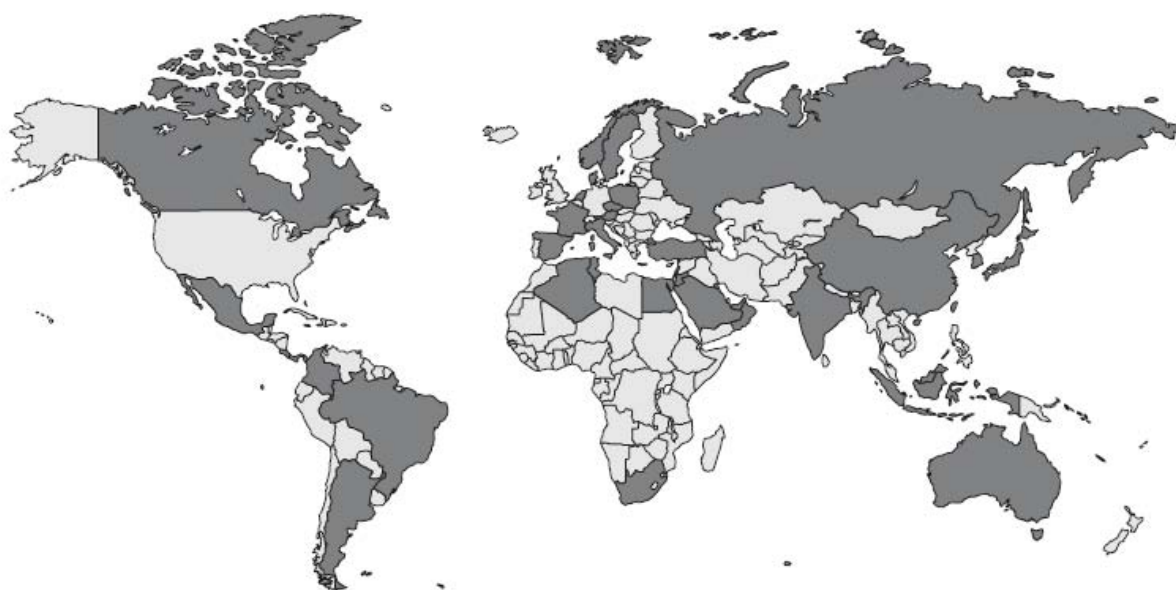
Figure legends

Fig. 1. Countries participating in the DISCOVER study program (indicated in dark gray), and number of enrolled patients in each country.

Fig. 2. Study timelines. **A.** Patients enrolled on the day of initiation of second-line glucose-lowering therapy. **B.** Patients enrolled retrospectively (after initiation of second-line glucose-lowering therapy).

Fig. 1

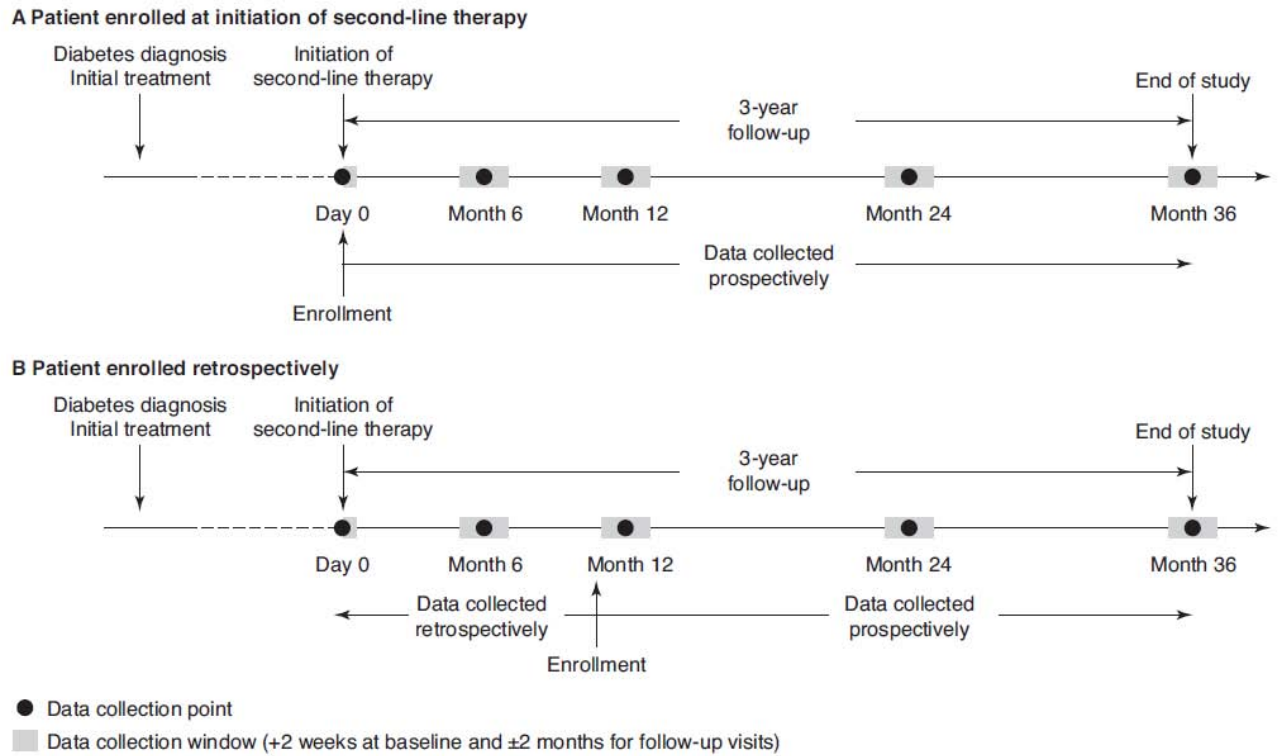|							
Algeria	294	Czech Republic	461	Lebanon	371	South Africa	518
Argentina	302	Denmark	42	Malaysia	342	South Korea	250
Australia	175	Egypt	584	Mexico	473	Spain	233
Austria	209	France	267	Netherlands	172	Sweden	237
Bahrain	70	India	3150	Norway	80	Taiwan	265
Brazil	444	Indonesia	238	Oman	31	Tunisia	218
Canada	386	Italy	378	Panama	92	Turkey	536
China	1298	Japan	1915	Poland	328	United Arab Emirates	102
Colombia	205	Jordan	275	Russia	601		
Costa Rica	128	Kuwait	51	Saudi Arabia	585		

Fig. 2

A Patient enrolled at initiation of second-line therapy

- Diabetes diagnosis / Initial treatment
- Initiation of second-line therapy
- 3-year follow-up
- End of study
- Day 0, Month 6, Month 12, Month 24, Month 36
- Enrollment
- Data collected prospectively

B Patient enrolled retrospectively

- Diabetes diagnosis / Initial treatment
- Initiation of second-line therapy
- 3-year follow-up
- End of study
- Day 0, Month 6, Month 12, Month 24, Month 36
- Data collected retrospectively
- Enrollment
- Data collected prospectively

● Data collection point

▨ Data collection window (+2 weeks at baseline and ±2 months for follow-up visits)

Table 1

Study objectives.

Primary objective

- To describe the disease clinical course and management patterns in patients with type 2 diabetes initiating a second-line glucose-lowering therapy (defined as adding a glucose-lowering drug or switching between therapies), after a first-line oral treatment with a monotherapy, dual therapy, or triple therapy

Secondary objectives

- To describe treatment response overall, by patient characteristics, and by second-line glucose-lowering medication class as assessed by:
  - changes in HbA_{1c} levels
  - changes in body weight
  - changes in blood pressure
  - changes in lipid profile
  - achievement of HbA_{1c} targets
- To describe treatment changes after initiation of second-line therapy, including:
  - addition of other glucose-lowering medications
  - initiation of insulin therapy
  - switching between glucose-lowering therapies
  - dose changes
- To determine the incidence of microvascular complications:
  - diabetic nephropathy
  - diabetic neuropathy
  - diabetic retinopathy
  - diabetes-related non-traumatic amputation
- To determine the incidence of macrovascular complications:
  - cardiovascular death
  - heart failure
  - myocardial infarction
  - stroke
  - diabetes-related revascularization
- To assess patient-reported outcomes:
  - general health status (using the SF-36v2)
  - fear of hypoglycemic events (using the Hypoglycemia Fear Survey)
  - general health status (based on smoking, diet, physical activity, and alcohol intake)
  - whether patients avoided healthcare and/or medication because of cost

- To describe healthcare resource utilization
- To determine risk factors associated with microvascular and macrovascular complications, hypoglycemic events, loss of quality of life, and increased healthcare resource utilization during follow-up:
  - patient characteristics (e.g. age, sex, comorbidities, and socioeconomic status)
  - disease characteristics (e.g. duration of diabetes)
  - treatment characteristics (e.g. second-line glucose-lowering medication class)
  - physician/practice characteristics (e.g. primary care vs specialists)
- To describe factors associated with treatment choice at baseline

HbA$_{1c}$: glycated hemoglobin, SF-36v2: 36-item Short-form Health Survey version 2.

Table 2

Data collection at baseline (initiation of second-line therapy) and 6, 12, 24, and 36 months.

	Baseline data collection	Follow-up data collection [a]
Site and investigator characteristics	✓	–
• Center type (primary care, university hospital, general hospital, specialized diabetes center)		
• Geographical setting (urban, rural)		
• Center funding (public, private, mixed)		
• Physician specialty (PCP, endocrinologist, cardiologist, internist, other specialist)		
Informed consent form	✓	–
History of diabetes	✓	–
• Date of diagnosis		
• Treatment (class of drug, duration, dose)		
• Evidence of microvascular complications (nephropathy, retinopathy, neuropathy, amputation)		
• Diabetes education received by patient		
• Risk factors (alcohol use, smoking status)		
First-line glucose-lowering drug and reason for change	✓	–
Initiation of second-line glucose-lowering treatment	✓	–
• First-line glucose-lowering drug class (specific agent if data are available)		
• Second-line glucose-lowering drug class (specific agent if data are available)		
• HbA_{1c} target		
• Reason for initiating second-line therapy		
• Reason for choice of second-line therapy		
Demographics	✓	✓
• Sex		
• Date of birth		
• Self-reported ethnic origin		
• Living status (living alone, not living alone)		
• Education level (basic, low, medium, high)		
• Employment status (employed, unemployed)		
Comorbidities	✓	✓
Co-medications	✓	✓

	Baseline data collection	Follow-up data collection [a]
Physiological and anthropometric parameters	✓	✓
• Seated blood pressure		
• Pulse rate		
• Weight		
• Height		
• Body mass index		
• Waist circumference		
Laboratory test results (most recent results available for the past 3 months)	✓	✓
• Blood test results (HbA$_{1c}$ and/or glucose level [fasting, post-prandial or casual], aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, creatinine, albumin, hematocrit, hemoglobin, total cholesterol, LDL-C, HDL-C, and triglycerides levels, white blood cell and platelet counts)		
• Urine test results (protein, albumin, creatinine)		
Healthcare resource utilization	–	✓
• Number of visits to PCP, specialist, and emergency department		
• Hospitalizations		
o Number and duration (by ward)		
o Reason (diabetes-related or not, and specific diagnosis)		
o Test and procedures		
• Tests and procedures not requiring hospitalization		
• Severe hypoglycemic events requiring medical assistance		
• Medications		
• Glucose-monitoring equipment		
• Educational resources		
• Number of days off work because of illness		
Patient-reported outcome questionnaires [b]	✓	✓
• SF-36v2		
• HFS-II		
• Lifestyle score		
• Healthcare avoidance due to cost		
Occurrence of minor hypoglycemic event(s) (past month)	✓	✓
Occurrence of major hypoglycemic event(s) (past year at baseline	✓	✓

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	Baseline data collection	Follow-up data collection [a]
and since last visit during follow-up)		
Occurrence of microvascular and macrovascular complication(s)	–	✓
Change(s) in glucose-lowering treatment and reason(s) for change(s)	–	✓

[a] Follow-up visits at 6, 12, 24, and 36 months within a 4-month window (± 2 months).

[b] Patient-reported outcomes will not be collected for baseline and for any data collection time point occurring before enrollment for patients identified retrospectively. Patients will only complete questionnaires available in their country.

HbA_{1c}: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, HFS-II: revised Hypoglycemia Fear Survey, LDL-C: low-density lipoprotein cholesterol, PCP: primary care practitioner, SF-36v2: 36-Item Short-Form Health Survey version 2.