Journal of Diabetes Science and Technology
Volume 2, Issue 5, September 2008

ORIGINAL ARTICLES

The DURABLE Trial Study Design: Comparing the Safety, Efficacy, and Durability of Insulin Glargine to Insulin Lispro Mix 75/25 Added to Oral Antihyperglycemic Agents in Patients with Type 2 Diabetes

Jessie Fahrbach, M.D., Scott Jacober, D.O., Honghua Jiang, Ph.D., and Sherry Martin, M.D.

Abstract

Background:

While studies have compared the safety and efficacy of starter insulin regimens in type 2 diabetes, none have evaluated regimen durability (length of time a patient can maintain glycemic control) or the safety and efficacy of subsequent intensification regimens in a large, multinational cohort.

Methods:

The DURABLE (Assessing the DURAbility of Basal vs Lispro Mix 75/25 Insulin Efficacy) trial will compare the ability of glargine once daily vs lispro mix 75/25 (75% insulin lispro protamine suspension, 25% lispro) twice daily added to oral antihyperglycemic agents to achieve and maintain hemoglobin A1c (HbA1c) goals. This randomized, open label, parallel study will enroll over 2000 insulin-naïve patients with type 2 diabetes from 11 countries, ages 30 to 80, with HbA1c >7.0% on at least two oral antihyperglycemic agents. At the completion of the 6-month initiation phase, safety and efficacy of the two regimens will be compared. Patients who achieve an HbA1c ≤7.0% at 6 months will continue into the 24-month maintenance phase to evaluate durability.

In a substudy, patients not achieving HbA1c ≤7.0% at 6 months may be randomized to one of two intensification comparisons: patients previously on glargine will receive lispro mix 75/25 twice daily or basal/bolus therapy (glargine + thrice-daily mealtime lispro) and patients previously on lispro mix 75/25 will receive lispro mix 50/50 (50% insulin lispro protamine suspension, 50% lispro) thrice daily or basal/bolus therapy.

Results:

Upon completion, this trial will provide new information about starter insulin durability, defined as the length of time patients can maintain HbA1c control (HbA1c ≤7.0%, or >7.0% but with an increase of <0.4% from the most recent HbA1c ≤7.0%). Additionally, the study will provide comparative data on HbA1c, blood glucose profiles, 1,5-anhydroglucitol, hypoglycemic episodes, weight change, and insulin dose for starter insulin regimens following 6 and 24 months of treatment, as well as intensified insulin via the 6-month substudy.

Conclusion:

This trial aims to broaden clinicians' understanding of the ability of starter insulin and insulin intensification regimens to achieve and maintain glycemic control in patients with type 2 diabetes.

J Diabetes Sci Technol 2008;2(5):831-838

Author Affiliation: Eli Lilly and Company, Indianapolis, Indiana

Abbreviations: (1,5-AG) 1,5-anhydroglucitol, (ANCOVA) analysis of covariance, (BBT) basal/bolus therapy, (DMC) data monitoring committee, (DURABLE) Assessing the DURAbility of Basal vs Lispro Mix 75/25 Insulin Efficacy, (eCRF) electronic case report form, (EDC) electronic data capture, (FPG) fasting plasma glucose, (HbA1c) hemoglobin A1c, (LM50/50) lispro mix 50/50, (LM75/25) lispro mix 75/25, (MET) metformin, (OHAs) oral antihyperglycemic agents, (SAS) Statistical Application Software, (SFU) sulfonylurea, (SMPG) self-monitored plasma glucose, (TZD) thiazolidinedione, (T2DM) type 2 diabetes mellitus, (4T) Treating to Target in Type 2 Diabetes Study

Keywords: basal bolus therapy, durable, durability, glargine, Humalog® Mix 50/50, Humalog® Mix 75/25, lispro

Corresponding Author: Jessie Fahrbach, M.D., Eli Lilly and Company, Indianapolis, IN 46285; email address *fahrbachjl@lilly.com*

Introduction

Due to progressive metabolic deterioration in patients with type 2 diabetes mellitus (T2DM), the current treatment paradigm is one of gradual regimen intensification. When lifestyle modification and oral antihyperglycemic agents (OHAs) fail to achieve adequate glycemic control, the addition of insulin is an appropriate next step.

A variety of insulin initiation treatment strategies exist. A single injection of basal may be added to OHAs.[1–5] Another option is to initiate insulin therapy with twice-daily premixed insulin. In several studies comparing a regimen of twice-daily injections of a premixed insulin analog combined with OHAs to once-daily glargine with similar OHAs, a greater hemoglobin A1c (HbA1c) reduction was noted with the use of analog mixtures.[6–8] However, these studies have been criticized because the glargine regimens were not combined with a secretagogue, and this omission may have potentially disadvantaged the glargine treatment arm.

Evidence regarding the length of time a patient is able to maintain glycemic control with a specific starter insulin regimen is lacking, as noted in the review by the Agency for Healthcare Research and Quality.[9] A better understanding of regimen durability is needed. Also, for patients who do not achieve glycemic targets on initial starter regimens, there is little randomized, controlled clinical trial evidence regarding appropriate insulin intensification.[10–12]

The DURABLE study (Assessing the DURAbility of Basal vs Lispro Mix 75/25 Insulin Efficacy) will evaluate the efficacy, safety, and durability of two common starter insulin regimens, once-daily insulin glargine [LANTUS® insulin glargine (rDNA origin)] vs twice-daily insulin lispro mix 75/25 [(LM75/25) Humalog® Mix 75/25™: 75% insulin lispro protamine suspension, 25% lispro] when added to existing OHAs [sulfonylureas (SFUs), metformin (MET), and/or thiazolidinedione (TZD)]. This study will enroll approximately 2000 insulin-naïve patients from 11 countries and is designed with a 6-month initiation phase to assess safety and efficacy and a subsequent 24-month maintenance phase to compare durability. This will be defined as the length of time a patient can maintain glycemic control with a regimen and, as such, represents a measure of the long-term effectiveness of that therapy (primary end point is duration of time for maintaining HbA1c at goal).

In addition to providing answers to questions of comparative safety, efficacy, and durability of two insulin initiation regimens, this study also has an intensification substudy to address questions about appropriate second-step insulin treatment. For patients who do not achieve the targeted HbA1c goal with glargine starter insulin therapy, an intensification comparison will evaluate basal/bolus therapy (BBT): glargine and premeal insulin lispro (Humalog®) three times daily vs LM75/25 twice daily. For patients who do not achieve the 6-month glycemic goal with twice-daily LM75/25, an additional comparison will assess intensification with either BBT or insulin lispro mix 50/50 ([LM50/50] Humalog® Mix50/50 TM: 50% insulin lispro protamine suspension, 50% lispro) three times daily.

Methods

Study Design

This 30-month, randomized, multicenter, multinational, open-label, two-arm, parallel study will be conducted in approximately 2000 patients from 269 centers in 11 countries, including Argentina, Australia, Brazil, Canada, Greece, Hungary, India, Romania, Spain, The Netherlands, and the United States (**Figure 1**). All patients will participate in the 6-month initiation phase, during which insulin doses will be optimized. Following the initiation phase, patients who achieve glycemic control (HbA1c ≤7.0%) will continue into a 24-month maintenance phase. No change in OHA therapy will be allowed during the initiation or maintenance phases. Because rescue therapy with the addition of another insulin formulation is not allowed, maintenance phase patients will discontinue from the trial if HbA1c rises above 7.5%. Additionally, at initiation phase completion, patients who did not achieve glycemic control (HbA1c ≤7.0%) will have the opportunity to proceed into a 6-month intensification substudy to evaluate second step insulin advancement. At this point, SFUs will be discontinued and all other prestudy OHAs (MET and TZD) will be continued.

The protocol will be approved by the ethics review committee/institutional review board affiliated with each investigative center and will be conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All participants will provide written informed consent. An independent external data monitoring committee (DMC) will review safety, initiation

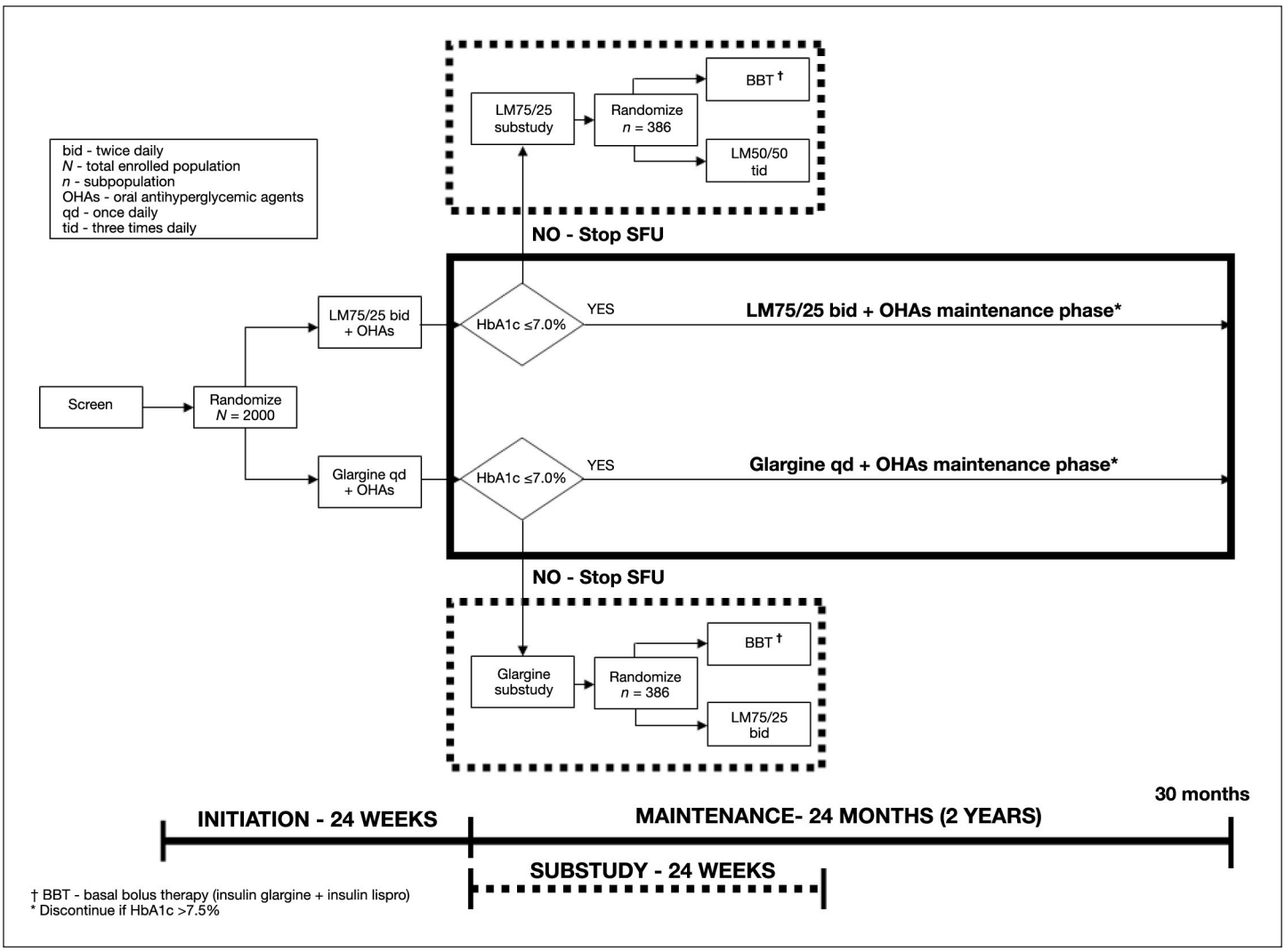

Figure 1. DURABLE study design. Solid lines identify design and timing of the initiation and maintenance phases of the primary study. Dotted lines identify design and timing of the two substudy arms.

phase insulin dose adjustments, and maintenance phase interim analysis data, which are designed to evaluate if the trial can be stopped early due to demonstration of efficacy.

Outcomes

The primary efficacy measure for the initiation phase and substudy evaluating intensification is end point HbA1c adjusted for baseline HbA1c for each treatment group. The primary efficacy measure for the maintenance phase is the duration of time from when patients first achieve HbA1c ≤7.0% within 6 months of initiating insulin therapy to when the HbA1c is >7.0% and has increased ≥0.4% from last HbA1c ≤7.0%.

Secondary outcome measures for the initiation phase, maintenance phase, and intensification substudy include percentage of patients with HbA1c ≤7.0%, <7.0%, ≤6.5%, change in HbA1c from baseline to end point, HbA1c at each visit, comparison of seven-point self-monitored plasma glucose (SMPG) parameters, 1,5-anhydroglucitol (1,5-AG) values, incidence and rate of self-reported hypoglycemic episodes, absolute weight and incremental weight change, and total daily insulin dose. For the maintenance phase only, the rate of increase of HbA1c is a secondary outcome measure.

Sample Size

The sample size calculation is based on the primary objective for the maintenance phase of the study: time to failure after patients have been brought into glycemic control. Approximately 1000 patients will be randomized to each initiation phase treatment arm. Assuming a 10% dropout rate within the first 6 months, an estimated 900

patients per treatment arm will reach the 6-month time point. This will provide approximately 97% power to detect a difference of 0.2% in end point HbA1c between treatment groups with two sided $\alpha = 0.05$ assuming a standard deviation of 1.1%. At 6 months, it is estimated that 30% of the patients in the glargine arm and 45% of the patients in the LM75/25 arm will achieve the HbA1c goal.[4–8,13] With this sample size for the maintenance phase, it should be possible to detect a difference in durability of 11 to 15% between arms at the end of the 30-month time period with approximately 81 to 94% power and a two-sided $\alpha = 0.05$ (including adjustment for interim analysis).

For the substudy, approximately 386 patients with an HbA1c >7.0% at 6 months from each starter insulin group will be eligible to enroll into an intensification arm ($n = 386$ from glargine and $n = 386$ from LM75/25); each intensification arm has two comparator treatment groups. The sample size of the intensification arms was originally powered for superiority of BBT; however, new published evidence has since suggested that a noninferiority analysis would be appropriate.[11,14–16] This change in hypothesis from superiority to noninferiority of BBT was made in the statistical analysis plan prior to data analysis. A sample size of 163 patients per treatment group completing the study will provide 85% power to demonstrate that premix therapies are noninferior to BBT with a margin of 0.4% in end point HbA1c with a two-sided t test ($\alpha = 0.05$), assuming a standard deviation of 1.2%.

Statistical Analysis

In the main trial, randomization will be stratified based on country, TZD, and SFU use through an interactive voice-response system. All analyses will be conducted on an intent-to-treat basis using the last observation carried forward method unless otherwise specified. All randomly assigned patients who receive the study drug (excluding screen failures based on visit 2 central laboratory HbA1c value) will be included in every safety analysis unless otherwise specified, whereas all randomly assigned patients with at least one postbaseline follow-up will be included in the efficacy analyses. All tests of treatment effects will be conducted at a two-sided α level of 0.05 unless otherwise stated. When an analysis of variance (type III sums of squares) model is used to analyze a continuous variable, the model will contain the terms of treatment, baseline information, and stratification variables. For analysis of proportions, the Cochran–Mantel–Haenszel statistic test or Fisher's exact test will be used. The stratification variables are country, TZD use, and use of SFU. Statistical Application Software (SAS, Version 8.02) will be used to perform all statistical analyses.

The primary analysis for the initiation phase will be a comparison between treatment groups of the HbA1c at end point (last observed value up to 6 months). Treatment groups will be compared using analysis of covariance (ANCOVA) with the following terms in the model: treatment group, baseline HbA1c, and stratification variables (country, TZD use, and SFU use). A similar approach will be used for other continuous outcome measures.

The primary analysis for the maintenance phase of the study is a survival analysis of time to failure after the patients have achieved glycemic control (HbA1c ≤7.0%). Failure is defined by HbA1c of >7.0% with a change of at least 0.4% from the most recent HbA1c that was ≤7.0%. This twofold definition will incorporate both the concept of a threshold and also define a clinically significant excursion for patients who are close to that threshold. Use of a higher threshold for discontinuation (HbA1c >7.5%) allows for testing different definitions of failure and thus allows assessment of treatment group differences to the definition of failure. Treatment groups will be compared using a stratified log-rank test. The time at which a patient achieved control will be the starting point of the analysis; either 3 or 6 months postrandomization. Strata to be included in the model are country, TZD use, and SFU use and will be done using Kaplan–Meier estimates in Proc Lifetest in SAS.

One interim analysis of the maintenance phase of the study will occur after 25% of the subjects continuing in this phase have completed the 2-year follow-up period. The interim analysis will be conducted under the auspices of the external DMC to minimize operational and statistical bias that may result from performing interim analyses. The purpose of the DMC is to evaluate whether the trial should be continued or if the trial may be stopped early due to efficacy. Only the DMC is authorized to review the unblinded interim analysis.

For each intensification arm of the substudy, randomization will be stratified based on country and TZD use. The primary analysis for the intensification arms is to show that LM75/25 twice daily or LM50/50 thrice daily is noninferior to BBT (four injections daily) based on HbA1c at week 24. The ANCOVA model will be used with the following terms in the model: treatment group, baseline HbA1c, and stratification variables (country, TZD use). A similar approach will be used for other continuous outcome measures.

Study Population

Men and women, ages 30 to 80, with T2DM (World Health Organization classification), taking at least two OHAs for 90 days (minimum dose: MET 1500 mg/day, SFU one-half maximum daily dose, pioglitazone 30 mg/day, or rosiglitazone 4 mg/day), with a local laboratory HbA1c of 1.2 to 2.0 times upper limit of normal will be eligible for the study. Patients who meet local laboratory HbA1c criterion but subsequently have a baseline central laboratory HbA1c of ≤7.0% will not be included in the study.

Patients will be excluded if they have a history of recent scheduled long-term insulin use; recent use of acarbose, miglitol, pramlintide, exenatide, repaglinide, or nateglinide; body mass index >45 kg/m^2; recent history of severe hypoglycemic episodes; significant concomitant hematologic, oncologic, renal, cardiac, hepatic, or gastrointestinal disease; recent systemic steroid use; or pregnant or breastfeeding.

Study Procedures

During the initiation phase, in addition to office visits every 6 weeks, patients will be contacted weekly for the first 6 weeks and then biweekly for the next 6 weeks to facilitate insulin dose optimization with an electronic review of dose adjustments by the DMC. During the maintenance phase, patients will have scheduled office visits every 3 months. The intensification arms are set up in a similar fashion with office visits at baseline, 6 weeks, 3 months, and 6 months, as well as telephone visits following initiation of the intensified regimen.

At screening, patients will have HbA1c, alanine aminotransferase, creatinine, and a pregnancy test (females) performed by a local laboratory. At baseline and every 3 months, HbA1c will be analyzed (Bio-Rad Variant HbA1c assay) by a central laboratory (analyzed regionally by Covance: Geneva, Switzerland; Sydney, Australia; Indianapolis, Indiana; Singapore). Fasting insulin (Access® Ultrasensitive Insulin chemiluminescent immunoassay on Beckman Coulter Access® 2 and Unicel® DxIAccess® immunoassay systems), fasting glucose (hexokinase enzymatic method on Roche Modular analyzer), adiponectin (enzyme immunoassay produced by R & D Systems), and 1,5-AG (Glycomark® assay manufactured by Tomen America Inc.) will be collected at baseline and every 6 months and analyzed by the central laboratory (adiponectin and 1,5-AG samples all analyzed at Covance, Indianapolis, IN; fasting insulin and glucose samples analyzed regionally by Covance). Additionally, insulin doses, hypoglycemic events, and SMPG profiles will be recorded in patient diaries. Safety, including serious adverse events, and tolerability will be assessed throughout the study. A subset of patients (United States and Puerto Rico participants) will receive questionnaires to assess generic and diabetes-specific health-related quality of life. Similar laboratory tests, clinical monitoring, and diary collection will occur in the intensification arms.

Insulin Dosing, Algorithms and Blood Glucose Targets

The minimum starting dose for insulin glargine is 10 units once daily[17] and for LM75/25 is 10 units twice daily.[18] Insulin doses will be adjusted to achieve a goal HbA1c ≤6.5% and SMPG targets based on regimen-specific minimum insulin dose adjustment algorithms[13,18] (**Table 1**). As the frequency of self-monitoring of glucose could influence glycemic control and hypoglycemia, both treatment groups will monitor their glucose at least twice a day: fasting (prior to breakfast) and prior to evening meal.

During the initiation phase, utilizing an electronic data capture (EDC) system, dose adjustments will be

Table 1.
Initiation and Maintenance Phase Minimum Dosing Titration Algorithms

Insulin glargine[a,b]			Insulin lispro mix 75/25[c,d]		
Plasma-equivalent glucose values[d,e]		Dose change	Plasma-equivalent glucose values[e,f]		Dose change[e]
mg/dl	mmol/liter		mg/dl	mmol/liter	
<80	<4.4	–2 units	<80	<4.4	–2 units
80–100	4.4–5.5	0	80–109	4.4–6.0	0
101–120	5.6–6.7	+2 units	110–139	6.1–7.7	+2 units
121–140	6.8–7.8	+4 units	140–179	7.8–9.9	+4 units
141–160	7.9–8.9	+6 units	≥180	≥10.0	+6 units
>160	>8.9	+8 units	—	—	—

[a] Adapted from Fritsche *et al.*[13]
[b] The insulin dose should not be increased if hypoglycemia is present.
[c] From Hirsch *et al.*[18]
[d] Fasting glucose values should be considered for glargine.
[e] Based on most values during the last 3–7 days.
[f] Fasting and pre-evening meal glucose values should be considered for LM75/25. For LM75/25, the first daily dose will be adjusted based on the glucose measurement prior to the evening meal, and the second daily dose will be adjusted based on the fasting glucose measurement. Only one of the two LM75/25 doses should be increased at a time. If both glucose measurements meet criteria for an increase, the dose corresponding to the highest glucose measurements should be increased.

monitored by the DMC to ensure patient safety and that investigators are appropriately utilizing the dosing algorithms to adjust insulin regimens. Using patients' SMPG values and hypoglycemic event data, the EDC system will calculate a recommended new dose based on the regimen-specific dosing algorithms. Investigators will then enter the patients' actual prescribed new dose into the electronic case report (eCRF) form and have an opportunity to explain any discrepancies between the recommended and the actual prescribed dose. Prescribed insulin doses that are less than recommended by the algorithm will be reviewed by the DMC. When the majority of DMC members disagree with the investigator, this information will be communicated to the investigative physician and there will be an opportunity to reevaluate the clinical situation. However, because insulin adjustment is an individualized procedure for each patient, dosing changes will be ultimately controlled by the judgment of the investigator.

During the intensification substudy, blood glucose goals for all insulin regimens will be a premeal blood glucose level of <110 mg/dl with no hypoglycemia. A dose adjustment algorithm is not specified, as at this point, investigators will have gained significant clinical experience with patients on insulin therapy. For patients in the LM50/50 arm, if fasting plasma glucose (FPG) targets cannot be achieved, the evening premeal dose of LM50/50 may be changed to LM75/25.[11,12]

Patients will be instructed to record a hypoglycemic episode anytime they feel, or another person observes, that the patient is experiencing a sign or symptom that he or she would associate with hypoglycemia or a plasma glucose measurement ≤70 mg/dl. Additionally, all eCRFs with recorded SMPG values ≤70 mg/dl will be considered hypoglycemic events, regardless of whether the patient felt that it was an event and specifically captured it as such within the patient diary. Events will be considered severe if a patient requires assistance from another individual. Hypoglycemic episode data will also be evaluated utilizing the American Diabetes Association definition of hypoglycemia.[19]

Discussion

The DURABLE trial aims to provide new information about safety, efficacy, and durability of two common starter insulin regimens in a large, diverse population.

As it is evaluating two distinct starter insulin regimens, starting doses and titration algorithms are specific to each regimen. The glargine treatment is expected to provide basal insulin coverage throughout 24 hours after a single injection. In contrast, LM75/25 will provide not only basal insulin coverage through the action of the lispro protamine suspension component of the fixed mixture, but also mealtime coverage through the lispro component. The starting doses used in this study are considered to be appropriate for each specific insulin regimen. The 10-unit starting dose for glargine is included in the glargine US Prescribing Information.[17] Although LM75/25 US Prescribing Information does not recommend a specific starting dose, a recent publication recommended 10 units twice daily as a safe starting dosage for premixed insulin.[18] While the inequality of starting doses could be perceived to favor LM75/25, a study conducted by Raskin and associates[8] found that, even with similar starting doses, when both were added to existing OHAs of MET and/or TZD (secretagogues were discontinued), the end point dose was likely to be higher with the premixed insulin analog compared to glargine. In that study, both insulins were started at a total daily dose of 10 to 12 units, administered as a single daily glargine injection or two 5- to 6-unit doses of biphasic insulin aspart 70/30 (NovoLog® Mix 70/30). Nevertheless, by the end of the study, the total daily insulin dose was significantly greater for patients treated with the premixed insulin analog. The difference in the final total daily insulin doses could be attributed to the fact that premixed insulin contains both basal and prandial insulin and can be administered twice daily. This may permit some increased flexibility, thereby allowing patients to tolerate higher insulin doses. Of note, despite the lesser once-daily total daily glargine dose, glargine treatment was associated with lower fasting blood glucose.[8]

The dosing algorithms recommended in the DURABLE study are also specific to each insulin regimen. For LM75/25, the algorithm was proposed in recent dosing guidance[18] and is similar to the algorithm used to adjust premixed insulin analog dosing in the Raskin *et al*. study discussed earlier.[8] The algorithm for glargine adjustment is similar to the one used in glargine treat-to-target studies[4,13] and enables investigators to increase the glargine dose more rapidly. Additionally, it targets a lower FPG level than the LM75/25 algorithm.

Another ongoing trial, The Treating to Target in Type 2 Diabetes (4T) study, is evaluating three different starter insulin regimens and the individualized requirement for insulin intensification among those regimens. The 4T study compares the safety and efficacy of once- or twice-daily basal analog insulin, thrice-daily prandial rapid-

acting analog insulin, and twice-daily premixed analog insulin in the context of continued dual OHA therapy (SFU and MET) in over 700 insulin-naïve patients with T2DM from the United Kingdom and Ireland.[10] **Table 2** presents key features of the 4T and DURABLE trial designs.

Table 2.
Key Features of 4T and DURABLE Trial Designs

	4T[10,20]	DURABLE
Number of patients	700	2000
Number of countries	2	11
Inclusion OHAs	SFU, MET	SFU, MET, TZD[a]
Length of first phase	12 months	6 months
Allow rescue therapy in first phase (additional type of insulin)	Yes	No[b]
Length of second phase	24 months	24 months
Allow rescue therapy in second phase	Yes, required for HbA1c >6.5%	No[c]
Total duration of trial	36 months	30 months
Primary end point First phase Second phase	 End point HbA1c End point HbA1c	 End point HbA1c Length of time HbA1c maintained at goal
Hypoglycemia definitions	Grade 1: symptoms, SMPG >56 mg/dl Grade 2 (minor): SMPG ≤56 mg/dl Grade 3 (major): requires assistance	Symptoms or SMPG ≤70 mg/dl Severe: requires assistance

[a] Required at least dual OHA therapy.
[b] At the end of the initiation phase, subjects who do not achieve HbA1c goals have the opportunity to proceed into a randomized assessment of intensified insulin in a 6-month substudy.
[c] Patients will discontinue if HbA1c rises above 7.5.

Through a novel design, the DURABLE trial aims to produce additional information on the capabilities of two common insulin initiation regimens in the context of continued OHAs, without the option for additional insulin as rescue therapy in the initiation or maintenance phases of the trial. In the 6-month initiation phase, this study will provide a comparison of starter insulin regimen safety and efficacy in a large ethnically diverse population. Because the study is powered based on the maintenance phase primary objective of durability, the initiation phase will have a significant number of patients in excess of the number required to address the initiation phase primary efficacy objective. As such, this will allow for significant subgroup analysis of initiation phase end points, including safety and efficacy outcomes by ethnic/racial groups, as well as exploratory predictive modeling. The study design will also provide a subset of patients that can participate in the intensification substudy to gain insight into insulin progression for those who are not controlled with starter insulin therapy. In addition, the maintenance phase will evaluate the length of time each starter insulin regimen is able to maintain HbA1c goals, an end point that has not yet been evaluated in a clinical trial setting. As a new end point, a definition for both "durability" and a way to evaluate failure of durability had to be created for this study. Characterizing durability as the length of time patients remain at HbA1c goal (or within HbA1c target range) is clinically relevant, and defining durability failure as HbA1c exceeding the target range by >0.4% from the previous measurement ensures that patients are not discontinued based on known fluctuations of HbA1c assay capabilities. These definitions provide an important framework from which to evaluate the various therapeutic regimens.

Conclusions

This trial will provide important efficacy, safety, and durability data about both initiation and progression of insulin therapy in a large, ethnically diverse population. This information should help clinicians better understand factors influencing the ability of specific regimens to achieve and maintain glycemic control.

Funding:

This study was sponsored by Eli Lilly and Company.

Acknowledgements:

The authors acknowledge John B. Buse, Chapel Hill, NC; William H. Herman, Ann Arbor, MI; and David M. Kendall, Minneapolis, MN for significant contributions to the study design, and members of the DMC committee John B. Buse (Chair) Chapel Hill, NC; William H. Herman, Ann Arbor, MI; and Bruce H. R. Wolffenbuttel, Groningen, The Netherlands.

The authors thank all of the investigators, study staff at all of the sites, and, most importantly, the patients who will make this study possible.

Disclosure:

All authors are employees and shareholders of Eli Lilly and Company.

References:

1. Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, Rajala S, Ryysy L, Salo S, Seppälä P, et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med. 1992;327(20):1426-33.
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.

3. Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care. 2001;24(4):631-6.
4. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomised addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26(11):3080-6.
5. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care. 2005;28(2):254-9.
6. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH; Lispro Mixture-Glargine Study Group. Combined therapy with insulin lispro mix75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther. 2004;26(12):2034-44.
7. Malone JK, Bai S, Campaigne BN, Reviriego J, Augendre-Ferrante B. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with type 2 diabetes. Diabet Med. 2005;22(4):374-81.
8. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A; INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care. 2005;28(2):260-265.
9. Qayyum R, Wilson LM, Bolen S, Maruther N, Marinopoulos SS, Feldman L, Ranasinghe P, Amer M, Bass EB. Comparative effectiveness, safety, and indications of insulin analogues in premixed formulations for adults with type 2 diabetes. Rockville, MD: Agency for Healthcare Research and Quality, Johns Hopkins University Evidence-based Practice Center; 2008. Comparative Effectiveness Review No. [XX]. Contract No.: 290-02-0018. In Press 2008. Available from: http://effectivehealthcare.ahrq.gov/repFiles/InsulinAnaloguesDraft2008_0229.pdf.
10. Holman RH, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC; 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med. 2007;357(17):1716-30.
11. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents. Diabetes Care. 2008;31(1):20-5.
12. Robbins DC, Beisswenger PJ, Ceriello A, Goldberg RB, Moses RG, Pagkalos EM, Milicevic Z, Jones CA, Sarwat S, Tan MH. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel group comparison. Clin Ther. 2007;29(11):2349-64.
13. Fritsche A, Schweitzer MA, Häring HU; 4001 Study Group. Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med. 2003;138(12):952-9.
14. Ligthelm RJ, Mouritzen U, Lynggaard H, Landin-Olsson M, Fox C, le Devehat C, Romero E, Liebl A. Biphasic insulin aspart given thrice daily is as efficacious as a basal-bolus insulin regimen with four daily injections. Exp Clin Endocrinol Diabetes. 2006;114(9):511-9.
15. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006;29(6):1269-74.
16. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab. 2005;7(1):56-64.
17. Lantus prescribing information. sanofi-aventis U.S. LCC; 2007.
18. Hirsch IB, Bergenstal RM, Parkin CG, Wright E Jr, Buse JB. A real-world approach to insulin therapy in primary care practice. Clin Diabetes. 2005;23:78-86.
19. American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245-9.
20. Diabetes Trials Unit: The Oxford Centre for Diabetes, Endocrinology & Metabolism [homepage on the Internet]. Oxford: Diabetes Trials Unit [updated 2008 Apr; cited 2008 Jul 3]. Treating to Target in Type 2 Diabetes. Available from: http://www.dtu.ox.ac.uk.