New Insulin and Insulin+GLP-1 Receptor Agonist Combinations in Development: Application and Therapeutic Efficacy

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Disclosures

John Buse has been an investigator and/or consultant without any direct financial benefit under contracts between his employer (the University of North Carolina) and the following companies: Amylin Pharmaceuticals, Inc., Andromeda, AstraZeneca, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Dance Biopharm, Elcelyx Therapeutics Inc., Eli Lilly and Company, GI Dynamics, GlaxoSmithKline, Halozyme Therapeutics, F. Hoffmann-La Roche Ltd., Intarcia Therapeutics, Johnson & Johnson, Lexicon, LipoScience, Medtronic, Merck, Metavention, Novo Nordisk, Orexigen Therapeutics Inc., Osiris Therapeutics Inc., Pfizer Inc., PhaseBio Pharmaceuticals Inc, Quest Diagnostics, Sanofi, Santarus, Scion NeuroStim, Takeda, ToleRx and TransTech Pharma.

John Buse is a consultant to PhaseBio Pharmaceuticals, Inc. and will receive payments, reimbursement for travel and stock options for that effort.

New Insulins

Ultra-rapid Insulin: Inhaled Technosphere Insulin

- Regular human insulin loaded in fumaryl diketopeperazine microparticples
- Peak levels in ~20 mins
- Peak activity in 1 hour
- Terminal ½-life 1 hour

- Contraindications, Warnings, Precautions, and Adverse Effects:
  - Spirometry before initiation, at 6 months, and annually.
  - Contraindicated in patients with asthma and COPD.
  - Precaution for active lung cancer and smokers.
  - Most common adverse reactions include hypoglycemia, cough, throat irritation, and throat pain.
- Limited to 4, 8 and 12 unit doses.

Kugler AJ, et al. *Pharmacotherapy*. 2015; 35:298-314. Affreza Prescribing Information, accessed 5/4/2015

Ultra-rapid Insulin: Not Yet Available.

- Micro-needles
- Hyaluronidase co-administration
- Citrate/zinc-ion chelator
- Excipients, nicotinamide and arginine
- “BioChaperones”

Pandyarajan V, Weiss MA. *Curr Diab Rep.* 2012; 12:697-704. Heise T, et al. Diabetes Obes Metab. 2015 Apr 1. doi: 10.1111/dom.12468. [Epub ahead of print]. http://www.adocia.fr/WP/

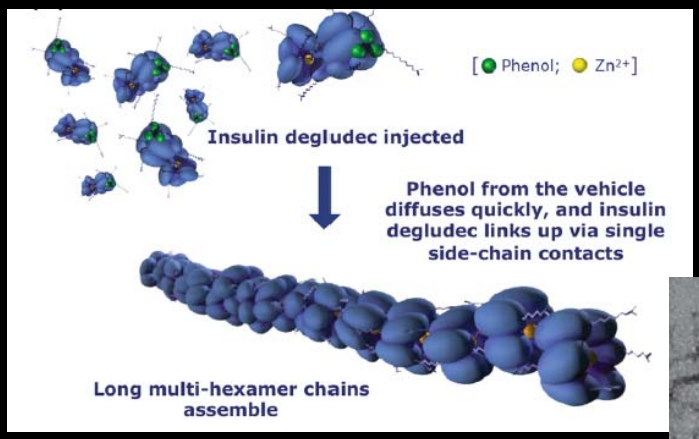
Novel Basal Insulin: Glargine U-300

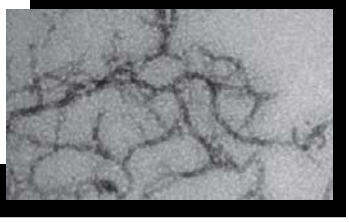
- Smaller volume results in more consistent and prolonged PK/PD profile, lower glycemic variability and stable blood glucose control beyond 24 hours
- In head to head trials with the current glargine U-100 formulation
  - Comparable HbA1c reduction
  - Lower risk of confirmed hypoglycemia
  - Modestly lower potency
  - Flexibility to adapt the timing of injections when needed with a 24 ± 3 hours interval
  - Slightly lower or similar weight gain
- Identical amino acid sequence and metabolism as glargine U-100, suggesting safety

Sutton G, et al. *Expert Opin Biol Ther. 2014*; 14:1849-60. Steinstraesser A, et al. Diabetes Obes Metab. 2014; 16:873-6.

Novel Basal Insulins: Not Yet Available in US

- Lilly: insulin glargine ("biosimilar" in EU)
- Novo: insulin degludec





Haahr H and Heise T. *Clin Pharmacokinet*. 2014; 53: 787–800.

Insulin + GLP-1 Receptor Agonist

Overview: Basal Insulin

- Excellent improvement in A1C
  - Lowers fasting glucose; glucose tends to rise during the day
- Adverse effects
  - Moderate weight gain (dose related)
  - Hypoglycemia is modest compared to premixed and prandial insulin and generally lower with analogs than human NPH
- Titration allows optimized dosing for safety and efficacy

A1C, glycosylated hemoglobin; GLP-1, glucagon-like peptide-1.

Overview: GLP-1 Receptor Agonists

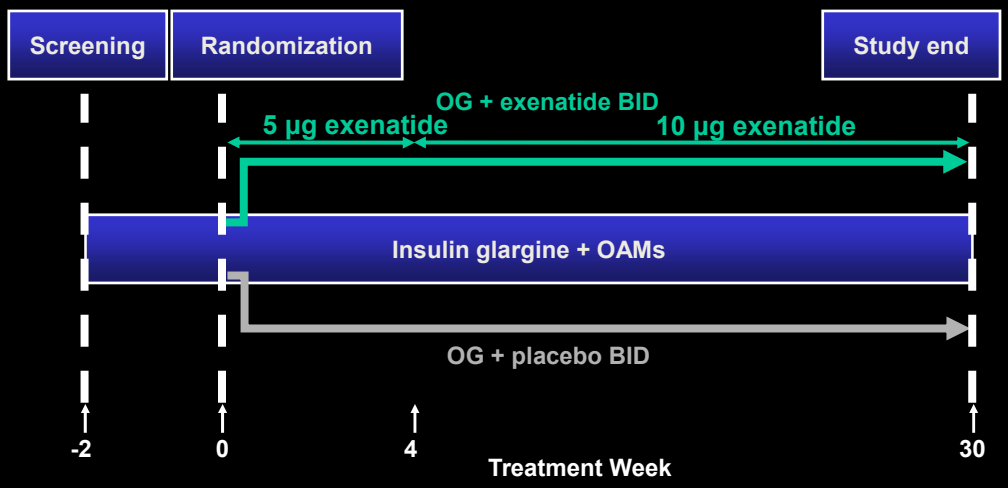
- Excellent improvement in A1C
  - Lowers fasting and postprandial glucose
- Moderate weight loss
- Modest improvement in blood pressure
- Adverse events largely gastrointestinal (dose related)
- Safety concerns (e.g., renal failure, pancreatitis, cancer)

A1C, glycosylated hemoglobin; GLP-1, glucagon-like peptide-1.

Rationale for Combining GLP-1 Receptor Agonists (GLP-1RA) and Basal Insulin Analogs (BIA)

- Combined glycemic effects of GLP-1RA (increase portal insulin delivery and decreased glucagon secretion to reduce postprandial glucose) and basal insulin (unparalleled efficacy to reduce fasting glucose) provide theoretical synergy in A1C reduction
- Potential to minimize dose-related adverse effects (nausea and weight gain)
- However, there was uncertainty regarding hypoglycemia risk of the combination

GWCO: Study Design

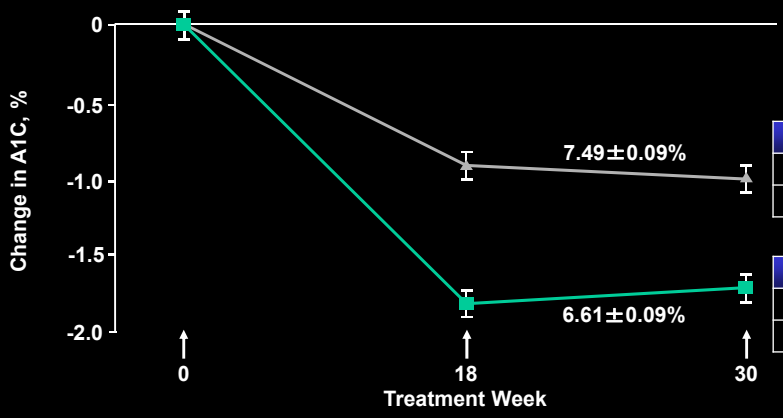


A Randomized Trial Comparing Exenatide With Placebo in Subjects With Type 2 Diabetes on Insulin Glargine With or Without Oral Antihyperglycemic Medications (study H80-US-GWCO).

OAM, oral antihyperglycemic medication; OG, optimized glargine.

Buse JB et al. *Ann Intern Med.* 2011;154(2):103-112.

GWCO: Change in A1C From Baseline



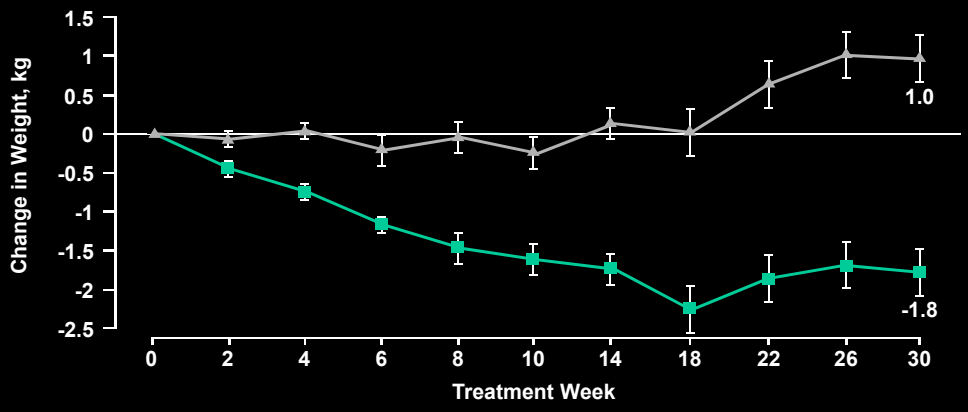
A1C, %		CI, %
≤7	35%	25-45
≤6.5	12%	6-17

A1C, %		CI, %
≤7	60%	51-69
≤6.5	40%	30-49

■ OG + exenatide BID (baseline, 8.3±0.1%)
▲ OG + placebo BID (baseline, 8.5±0.1%)

Data are least-squares mean ± SE.
A1C, glycosylated hemoglobin; OG, optimized glargine.
Adapted from Buse JB et al. *Ann Intern Med.* 2011;154(2):103-112.

GWCO: Change in Weight From Baseline



■ OG + exenatide BID (baseline, 8.3±0.1%)
▲ OG + placebo BID (baseline, 8.5±0.1%)

Data are least-squares mean ± SE.
P<.001, between-group comparison.
OG, optimized glargine.
Buse JB et al. *Ann Intern Med.* 2011;154(2):103-112.

GWCO: Safety and Adverse Events

	Exenatide BID, n (%)	Placebo BID, n (%)
Minor hypoglycemic events[a]		
Overall incidence	34 (25)	35 (29)
Rate, episodes/patient-year	1.4	1.2
Adverse events[b]		
Nausea	56 (41)	10 (8)
Diarrhea	25 (18)	10 (8)
Vomiting	25 (18)	5 (4)
Headache	19 (14)	5 (4)
Constipation	14 (10)	2 (2)

One patient in placebo group experienced 2 episodes of major hypoglycemia.

[a]No significant differences between groups.

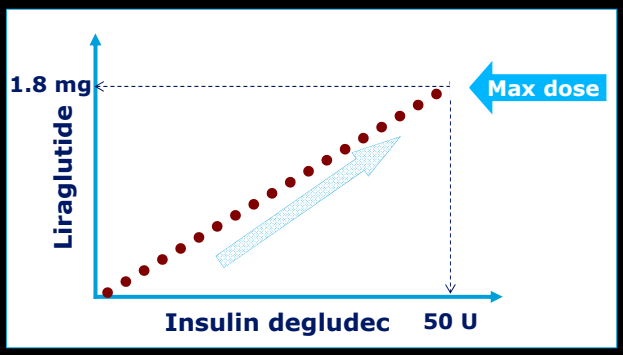
[b]$P<.05$, between-group comparison.

A Randomized Trial Comparing Exenatide With Placebo in Subjects With Type 2 Diabetes on Insulin Glargine With or Without Oral Antihyperglycemic Medications (study H80-US-GWCO).

Buse JB et al. *Ann Intern Med.* 2011;154(2):103-112.

IDegLira*

Fixed-ratio Combination of Insulin Degludec* and Liraglutide

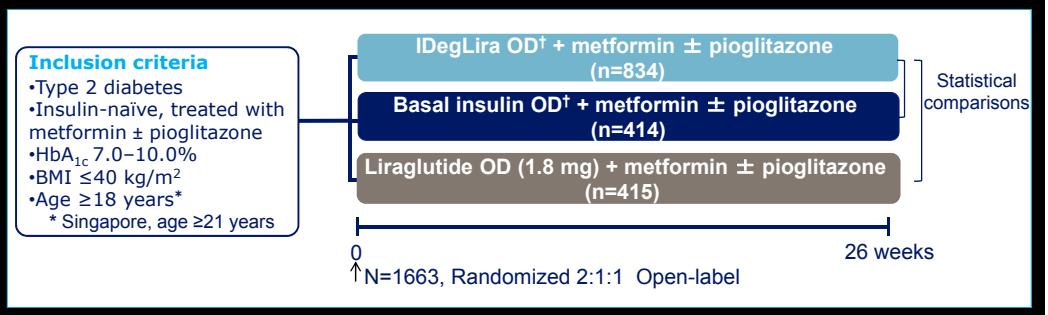


One dose step = 1 U insulin degludec and 0.036 mg liraglutide

Buse JB, et al. *Diabetes Care.* 2014; 37:2926-33.

*Not FDA approved

DUAL-1: Study Design



	Start dose	Max. dose
IDeg	10 units	Not specified
Lira	0.6 mg	1.8 mg
IDegLira	10 dose steps (10 units IDeg/ 0.36 mg Lira)	50 dose steps (50 units IDeg/ 1.8 mg Lira)

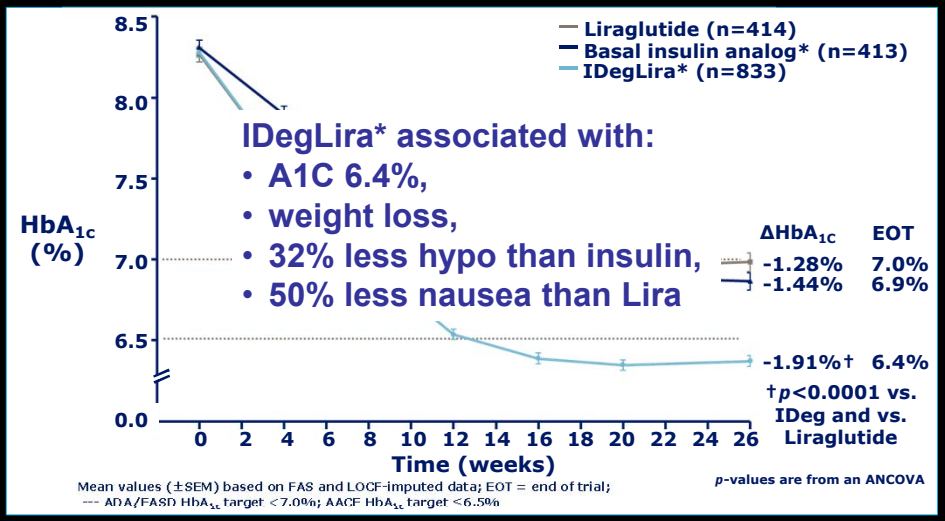
Titration algorithm: IDegLira and Basal Insulin

Mean fasting PG		Dose change
mg/dL	mmol/L	dose steps or U
<72	<4.0	-2
72–90	4.0–5.0	0
>90	>5.0	+2

Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014; 2:885-93.

†Not FDA approved

DUAL-1: Study Results



Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014; 2:885-93.

*Not FDA approved

DUAL-2: Study Design

Inclusion criteria

- Type 2 diabetes
- HbA_{1c} 7.5–10.0%
- BMI ≥27 kg/m²
- Age ≥18 years
- basal insulin (20-40U) + metformin +/- SU or glinides

IDegLira + metformin (n=199)

IDeg + metformin (n=199)

0 — 26 weeks

N=413, Randomized 1:1 Masked

	Start dose	Max. dose
IDeg	16 units	50 units
IDegLira	10 dose steps (16 units IDeg/ 0.6 mg Lira)	50 dose steps (50 units IDeg/ 1.8 mg Lira)

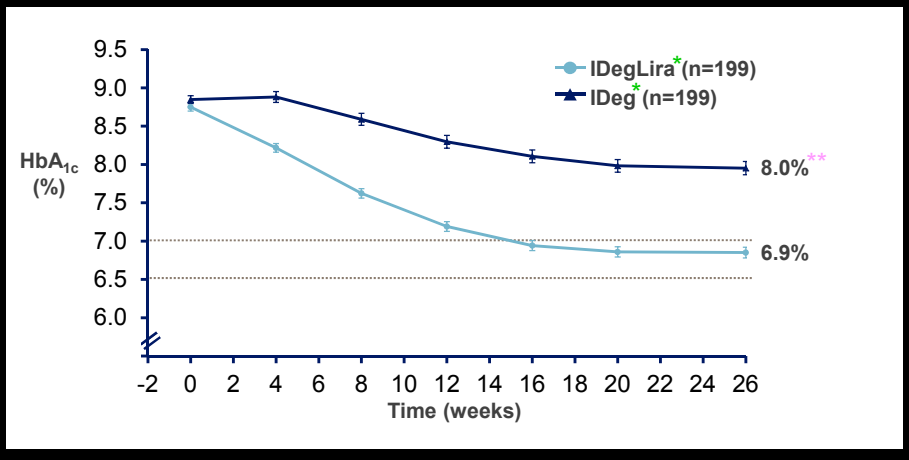
Titration algorithm: IDegLira and Basal Insulin

Mean fasting PG		Dose change
mg/dL	mmol/L	dose steps or U
<72	<4.0	-2
72–90	4.0–5.0	0
>90	>5.0	+2

†Not FDA approved

Buse JB, et al. *Diabetes Care.* 2014; 37:2926-33.

DUAL-2: A1C

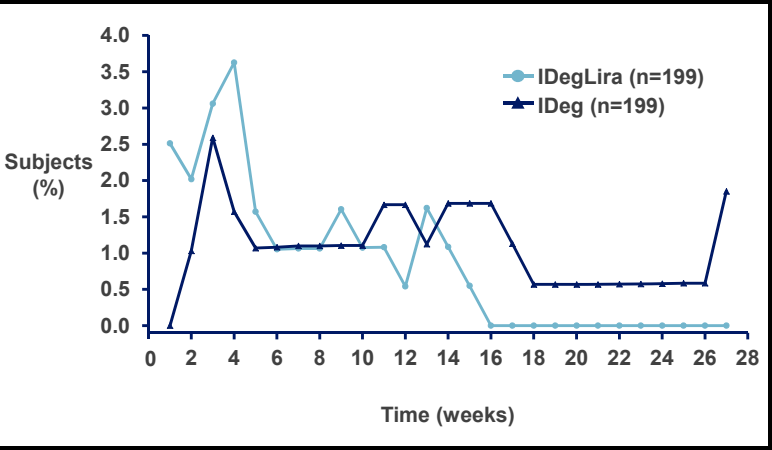


*Not FDA approved

** Capped at 50 units

Buse JB, et al. *Diabetes Care.* 2014; 37:2926-33.

DUAL-2: Nausea



Buse JB, et al. *Diabetes Care.* 2014; 37:2926-33.

*Not FDA approved

LixiLan POC: Study design

Inclusion criteria
- Type 2 DM
- Metformin ≥1500 mg/day
- A1C ≥7% and ≤10%
- BMI >20 and ≤40 kg/m²

R

- Insulin glargine + metformin (n=162)
- LixiLan + metformin (n=161)

0 — Randomized 1:1 Open label — 24 weeks

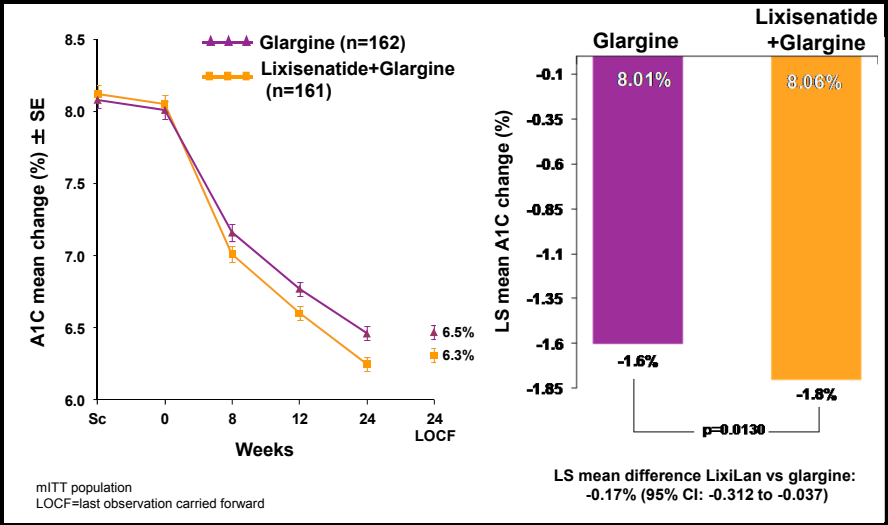
LixiLan	Glargine	Lixisenatide
Fixed ratio	2 U	1 µg
Initial dose	10 U	5 µg
Max dose	60 U	30 µg

Titration target: FPG 80–100 mg/dL
- Insulin glargine dose no upper limit
- LixiLan capped at 60 U / 30 µg

Lixisenatide+Glargine

Rosenstock, J. et al. *Benefits of a fixed-ratio formulation of once-daily insulin glargine/lixisenatide (LixiLan) vs glargine in type 2 diabetes inadequately controlled on metformin.* Oral Presentation, EASD 50th Annual Meeting, Vienna, 2014

Lixisenatide+Glargine*: A1C



*Investigational agent. Not FDA approved.

Rosenstock, J. et al. *Benefits of a fixed-ratio formulation of once-daily insulin glargine/lixisenatide (LixiLan) vs glargine in type 2 diabetes inadequately controlled on metformin.* Oral Presentation, EASD 50th Annual Meeting, Vienna, 2014

LixiLan POC: Other

- Meal tolerance test: 2-hr postprandial glucose excursion reduced 58 mg/dL (95% CI: -70 to -47) with LixiLan vs. glargine
- With LixiLan, 84% achieved an A1C target of <7% vs. 78% with glargine
- LixiLan with 1kg weight loss vs. glargine with 0.5 kg weight gain
- Documented symptomatic hypoglycemic events ≤70 mg/dL: 21.7 events/pt/year w LixiLan vs. 22.8 with glargine
- GI adverse events occurred in 15% of LixiLan treated participants versus 9% of glargine treated.

Rosenstock, J. et al. *Benefits of a fixed-ratio formulation of once-daily insulin glargine/lixisenatide (LixiLan) vs glargine in type 2 diabetes inadequately controlled on metformin.* Oral Presentation, EASD 50th Annual Meeting, Vienna, 2014

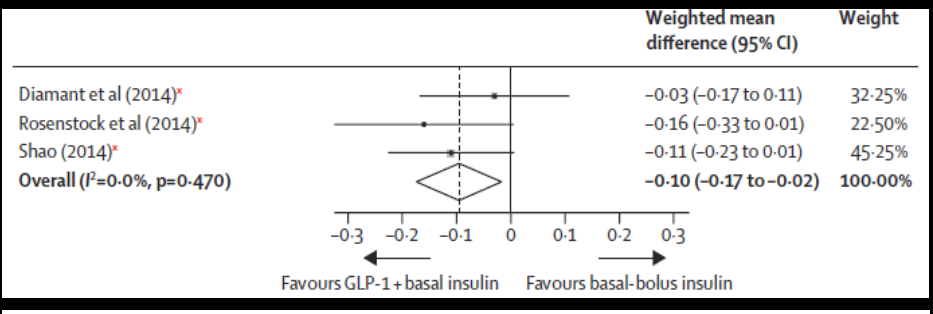
LixiLan: Further Studies

- LixiLan-O
  - Participants uncontrolled on OAD's
  - Open-label three arm comparison (lixisenatide, glargine, LixiLan)
- LixiLan-L
  - Participants uncontrolled on glargine
  - Open label two arm comparison (glargine, LixiLan)

Clinicaltrials.gov, accessed 4/4/2015

Metanalysis of GLP-1RA + Basal Insulin vs. Basal-Bolus Insulin

Author	Year	Background	Comparison
Diamant, et al	2014	Glargine plus metformin	Exenatide vs lispro (with each meal)
Rosenstock, et al	2014	Glargine ± metformin, pioglitazone, or both	Albiglutide weekly vs lispro (with each meal)
Shao, et al	2014	Glargine	Exenatide vs insulin aspart (with each meal)



Plus benefits of GLP-1RA + basal insulin on weight and hypoglycemia.

Eng C, et al. *Lancet*. 2014; 384 (9961): 2228-2234.

Summary: Clear Benefits for Combining GLP-1 Receptor Agonist (GLP-1RA) and Basal Insulin Analogs (BIA)

- Combined glycemic effects of GLP-1RA and basal insulin provides greater glycemic efficacy than either of its component parts.
- Dose related adverse effects of each component (nausea and weight gain) are minimized.
- No increased risk of hypoglycemia in the setting of improved glycemic control as compared to basal insulin alone.
- In the setting of inadequate control on basal insulin, adding a GLP-1RA is associated with greater benefits than adding prandial insulin.

Summary: Where Do the Combination GLP-1RA + BIA Products Fit

- The question is: Will combined GLP-1RA+BIA supplant both in treatment algorithms?
  - Should we think of them as enhanced insulin or enhanced GLP-1RA?
  - To avoid "treat to failure", should they be used early?
  - Or, should they be reserved for those failing either component alone?
- For today, the headlines are:
  - FDA approved combinations are basal insulin plus
    - exenatide BID, liraglutide or albiglutide
  - Prandial insulin is not approved for combination with GLP-1RA
  - Exenatide OW and dulaglutide are not approved for combination with insulin
  - IDegLira and Lixisenatide+Glargine are currently investigational in the US; they show promise for additional convenience, efficacy and tolerability.

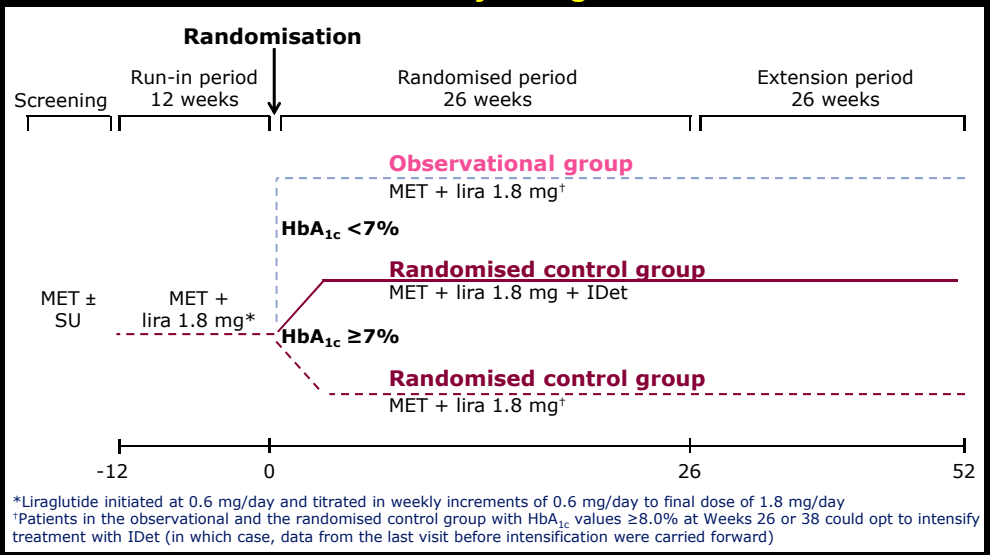
GLP-1RA = GLP-1 receptor agonist; BIA = Basal Insulin Analog; QD = once daily; BID = twice daily;
Byetta, Bydureon, Victoza, Tanzeum and Trulicity Prescribing Information, accessed 4/11/2015

Unresolved Issues

Does adding basal insulin in the setting of "failed" GLP-1RA therapy work as well as adding GLP-1RA in the setting of "failed" basal insulin therapy?

Addition of Insulin Detemir to Liraglutide

Study Design

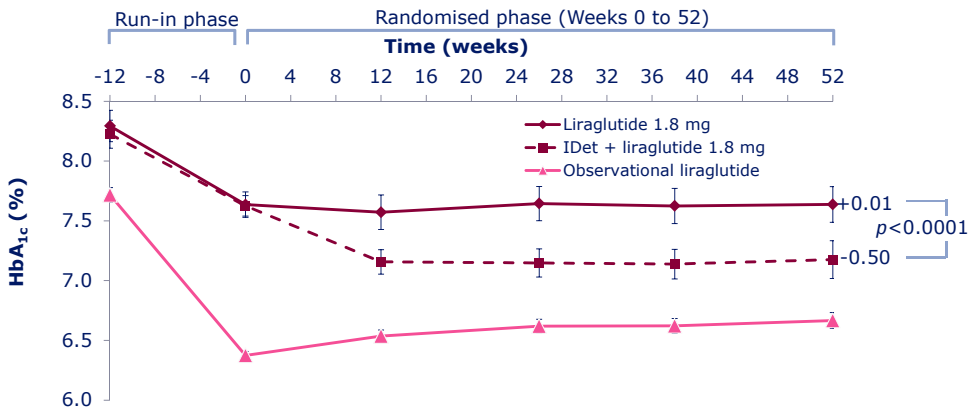


*Liraglutide initiated at 0.6 mg/day and titrated in weekly increments of 0.6 mg/day to final dose of 1.8 mg/day
†Patients in the observational and the randomised control group with HbA_{1c} values ≥8.0% at Weeks 26 or 38 could opt to intensify treatment with IDet (in which case, data from the last visit before intensification were carried forward)

DeVries JH et al. *Diabetes Care* 2012;35:1446–1454
Rosenstock, et al. *J Diabetes Complications.* 2013 Sep-Oct;27(5):492-500.

Addition of Insulin Detemir to Liraglutide

Mean HbA_{1c} By Week



Mean (2SE); data are LOCF. Last observation before intensification is included as LOCF in the initial treatment group.
ANCOVA on FAS LOCF for difference in randomised phase
ANCOVA, analysis of covariance

DeVries JH et al. *Diabetes Care* 2012;35:1446–1454
Rosenstock, et al. *J Diabetes Complications.* 2013 Sep-Oct;27(5):492-500.

Unresolved Issues

How in the setting of prandial insulin therapy how does "basal" GLP-1 receptor agonist compare to basal analog insulin?

AWARD-4: Dulaglutide vs Glargine

(on background of premeal lispro ± metformin)

- T2 diabetes. Age >18y. A1C 7-11%. BMI 23-45. On 1-2 shots of any kind of insulin at baseline.
  - Mean: age 59; duration 13; total insulin 56 units; A1C 8.5%.
- 9 week run-in to stop OADs except metformin and adjust prandial insulin. Randomized to glargine at bedtime or one of two doses of dulaglutide once weekly (0.75 mg or 1.5 mg)
- At randomization, lispro insulin at total dose of 50% of end of run-in total (and in glargine arm, 50% as glargine)

	@	DULA 1.5	DULA 0.75	Glargine
A1C change (%)	26 wk	-1.6*	-1.6*	-1.4*
Lispro dose (units)	26 wk	93	97	68
Glargine dose (units)	26 wk	0	0	65
Weight change (kg)	52 wk	-0.35	0.9	2.9
Symptomatic hypo (events/p-y)	52 wk	31	35	40
Severe hypo (N)	52 wk	11	15	22
Nausea (%)	52 wk	26	18	3

Jendle et al. EASD abstract #42. Available on-line at http://www.easdvirtualmeeting.org/resources/15089. *Not FDA approved