TYPES 1 DIABETES: NEW AND EMERGING THERAPEUTIC STRATEGIES TO ADDRESS UNMET NEEDS

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DISCLOSURES

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• Medical Advisory Board: AstraZeneca, Companion Medical, Lexicon, Lilly USA, LLC, Mannkind Corporation, Merck, Sanofi-aventis U.S. Inc.
• Speaker’s Bureau: AstraZeneca, Lilly USA, LLC, Mannkind Corporation, Merck, Sanofi-aventis U.S. Inc.

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• Research Support: Novo Nordisk, Sanofi-aventis U.S. Inc., vTv Therapeutics
• Stock Shareholder: Stability Health, Malitus Health, Phasedio
• Other/Royalty (Contracted fees paid to the University of North Carolina for advisory services): AstraZeneca, Eli Lilly, Mannkind, NovaTarg, Novo Nordisk, Senseonics, and vTv Therapeutics

TOPICS TO BE DISCUSSED

Unmet needs in type 1 diabetes
Historical perspective of type 1 diabetes
State of type 1 diabetes care in 2019
Continuous glucose monitoring (CGM)
Pumps verses multiple daily injections
Modern basal and ultra-fast acting insulins
Other adjunctive therapies for type 1 diabetes
What does the future hold?
UNMET NEEDS IN TYPE 1 DIABETES

- Unpredictable glycemic variability (GV), decreased time in range (TIR)
- Reaching A1c goal without hypoglycemia
- Controlling blood pressure
- Preventing and controlling weight gain
- Emotional burden of living with type 1 diabetes for the individual and his/her family

INDICES OF GLYCEMIC VARIABILITY: TIME IN RANGE (TIR), COEFFICIENT OF VARIATION (CV), STANDARD DEVIATION (SD), TIME SPENT IN HYPER- (>180) AND HYPOGLYCEMIA (<70)

Summary

Average Glucose: 152 mg/dL

- Time in Range: 16%
- Coefficient of Variation (CV): 31.4%
- Standard Deviation (SD): 47.7%
- Time spent in Hyper- (>180): 60%
- Time spent in Hypo- (<70): 4%
Ted Ryder 5 months after starting insulin

- NPH and regular insulins used only once or twice a day.
- Urine testing only
- No A1c test
- No pumps or pens
- No insulin analogs
- No CGM
- No Apps

PREVALENCE OF T1D INCREASING IN US

- 1.3 million people in U.S. currently have T1D¹
  - 1 million adults ≥ 20 years
- 21% increase in prevalence of T1D in people < 20 years between 2001-2009²
- 40,000 people diagnosed each year in U.S.²
- 5 million people in U.S. expected to have T1D by 2050²

TYPE 1 IS AN AUTOIMMUNE DISEASE: THE IMMUNE SYSTEM ATTACKS HEALTHY BETA CELLS

Natural Progression is months to a few years
**Natural History and Cause of Type 1 Diabetes**

- Genetic predisposition to damage the cells of the pancreas.
- Immune system dysfunction.
- Circulating auto antibodies (ICA, GAD).

**Time = months to a few years**

**Latent Autoimmune Diabetes in Adults (LADA)**

- The most missed diagnosis in diabetes.
- Type 1 diabetes can occur at any age.
- Slower beta-cell destruction (may respond briefly to oral agents).
- Typically does not have features of the metabolic syndrome.
- Blood test positive for type 1 diabetes (GAD auto antibodies).
You can get type 1 diabetes at any age!

FAMILY HISTORY OF T1D

First-degree family member with T1D

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>16%</td>
<td>84%</td>
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RISK OF DEVELOPING TYPE 1 VS TYPE 2

<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>If you have a sibling with T1D</th>
<th>If your mother has T1D</th>
<th>If your father has T1D</th>
<th>If you have an identical twin with T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3%</td>
<td>4%</td>
<td>2-3%</td>
<td>6-8%</td>
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<tr>
<td></td>
<td>8-11%</td>
<td>~30%</td>
<td>~30%</td>
<td>~30%</td>
<td>100%</td>
</tr>
</tbody>
</table>
CONSEQUENCES OF WEIGHT GAIN

- Excess weight gain associated with risk factors for cardiovascular disease, including increased
  - Lipid levels
  - Blood pressure levels
  - Waist circumference
  - Metabolic syndrome
CASE 1: PHIL

- 46 year old male with the diagnosis of type 1 diabetes at age 6 (Classic presentation of DKA)
- He has been on an insulin pump for many years
- Over the last 8 years he has developed central obesity and his insulin requirements doubled
- He also developed high blood pressure and dyslipidemia (triglycerides went up and his HDL went down).
- Family history is that his father and both paternal uncles have type 2 diabetes.

WHAT IS THE MOST LIKELY EXPLANATION OF WHY PHIL'S INSULIN REQUIREMENTS DOUBLED LATER IN LIFE?

A He developed central obesity
B He has both type 1 and type 2 diabetes
C His A1c kept rising
D He has high triglycerides
VARIABLES THAT AFFECT GLUCOSE LEVELS

Simple Carbs
Complex Carbs
Fatty Meal
French Meal

Blood Glucose Levels

Brain function

Insomnia
Exposure to cold
Menstruation
Illness
Medication
Emotion
Stress
Sex
Time change
Caffeine
Smoking

Fast
Gastroparesis
Very slow
Stomach

Gastroentery
Slow
Sustained
Exercise
Rapid

Very slow
Very slow

THE A1C REPRESENTS ONLY THE AVERAGE BLOOD GLUCOSE OVER TIME
(ALL TREATED WITH FAST-ACTING ANALOGUES)

Mean A1C=6.7%

Glucose Concentration (mg/dL)

1. Unexpected highs
2. Unexpected lows
3. Carb:Insulin ratio not working consistently
4. Correction Factor not working consistently
5. Not responding to insulin and exercise consistently

DESPITE FOLLOWING ALL OF THE RULES

IT IS ALL ABOUT “TIME IN RANGE”
KEEPING THE GLUCOSE LEVELS BETWEEN 70 AND 180 MG/DL

1. 1st priority is getting a CGM and educate your patients to respond to the trend arrows.
2. Bolus calculations are more than just the carbohydrates and static glucose readings
3. In addition to getting the A1c below 7%, try to reduce the daily glucose fluctuations in your patients (hyper- and hypoglycemia)
4. The insulin regimen should mimic what happens in a non-diabetic state

GUARDIAN CONNECT

- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

FREESTYLE LIBRE FLASH IS OR INTERMITTENT SENSING

- 2 hour warm-up time
- Lasts 2 weeks
- Swipe to get a number
- Trend arrows
- No calibration
- No alerts or alarms
- No sharing features

SEVERE HYPOGLYCEMIA – SERIOUS AE IN T1D DUE TO TOO MUCH INSULIN

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>% of Patients Reporting ≥ 1 Severe Hypoglycemic Event Over Prior 3 Months</th>
<th>Overall</th>
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<tbody>
<tr>
<td>18-25</td>
<td>4 8 6 6 8 9 7 10 8</td>
<td></td>
</tr>
<tr>
<td>26-40</td>
<td>4 8 6 6 8 9 7 10 8</td>
<td></td>
</tr>
<tr>
<td>&gt; 50</td>
<td>4 8 6 6 8 9 7 10 8</td>
<td></td>
</tr>
</tbody>
</table>

A SINGLE BG AT ONE POINT IN TIME LACKS IMPORTANT INFORMATION

No insulin
Watch and maybe get some carbs
Take a larger than usual dose

Pump and meter software suggests the same either way
**MEAN CHANGE IN INSULIN DOSE BASED ON 2 ARROWS UP: SURVEY OF 300 CGM USERS**

- **3.0 units**
- **6.8 units**


**HOW CGM AND TRENDING INFORMATION CAN AFFECT DOSING DECISIONS**

- **3.0 units**
  - No change in calculation
- **6.8 units**
  - 140% Mean Increase
- **1.5 units**
  - 48% Mean Decrease

**CASE 2: JEREMY**

- 35 year old male with type 1 diabetes for 20 years
- CHO to insulin ratio 10:1
- CF 1:30 goal 120 mg/dl

Post “Snack” BS of 220 mg/dL at 4:00 p.m.
(snack at 3:30 p.m., no insulin given with snack)
CASE 2: JEREMY (CONTINUED)

- Jeremy’s CGM Guidelines
  - Correction factor 1:30
  - Target glucose 120 mg/dL
  - 220-120/30 = 3.3 units

Note: A blood sugar of 220 does not lead to any symptoms

WHICH OPTION BELOW IS THE BEST SUGGESTION FOR JEREMY TO FOLLOW AT 4:00 PM?

A. Watch and wait (give no additional insulin)
B. Walk for an hour at a brisk pace
C. Give a correction dose of 3.3 units
D. Give a correction dose greater than 3.3 units

ADJUST INSULIN DOSE BASED ON ANTICIPATED GLUCOSE IN 30 MINUTES

- Add 50 mg/dL
- Add 75 mg/dL
- Add 100 mg/dL

Wait until trend arrow becomes horizontal
BLOOD GLUCOSE AFTER A MEAL WHEN BOLUS GIVEN 20 MINUTES BEFORE, AT START, OR 20 MIN AFTER THE MEAL.

Low fat/low protein
Four test breakfasts with identical carbohydrate content, but varying protein and fat quantities: same insulin dose.

High fat/high protein
Low fat/low protein

BOTH DIETARY FAT AND PROTEIN INCREASE POST MEAL GLUCOSE CONCENTRATIONS

How much fast acting insulin would you recommend to a patient eating a meal with 60 grams of carbohydrate (insulin to carb ratio is 1 to 10), an 8 oz filet and a salad with olives and avocado slices?

A. 3 units
B. 6 units
C. 12 units
D. More than 6 units

Type 1 New and Emerging CME
What is/are the possible causes of this patient's glucose profiles overnight?

A. Needs more basal insulin
B. Needs to be more consistent in his dinner meals/times
C. He has gastroparesis
D. All of the above

**PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION**

Liver → Portal Vein → Pancreas

- Insulin
- Amylin
- Glucagon

**PHYSIOLOGIC INSULIN SECRETION AND GLUCOSE LEVELS IN HEALTHY SUBJECTS**

- Basal Insulin (40% of TDD)
- Bolus Insulin (60% of TDD)
- Basal Glucose (40% of TDD)

**References:**
**Generic and Trade Names: Insulin**

<table>
<thead>
<tr>
<th>Fast-Acting Insulin</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>Humulin R, Novolin R</td>
<td>Humulin R U-500</td>
</tr>
<tr>
<td>Aspart</td>
<td>Novolog</td>
<td>Fiasp</td>
</tr>
<tr>
<td>Glulisine (U-100 and U-200)</td>
<td>Humalog</td>
<td>Afrezza</td>
</tr>
<tr>
<td>Follow-on biologic lispro</td>
<td>Inhaled insulin</td>
<td>Almazza</td>
</tr>
</tbody>
</table>

| Basal Insulin | Intermediate-Acting: NPH | Long-Acting: Detemir Levemir Novolin NPH Lantus Toujeo Tresiba |
|--------------|--------------------------|------------------|-----------------|-----------------|
|              | Humulin N                | Novolin NPH      | Levemir         | Levemir         |
|              | NovoLog Fiasp            | Apidra           | Humalog         | Admelog         |
|              | Akinra                   | NovoLog Fiasp    | Humalog         | Afrezza         |
|              | Basaglar                 | Tresiba          | Afrezza         | Afrezza         |

**Inhaled Insulin**

- Better post meal glucose values
- Less delayed hypoglycemia

**Faster-Acting Aspart (Addition of L-Arginine and Niacinamide for Faster Absorption)**

- 2 hour PG levels in T1D on pump therapy after a standardized meal comparing Aspart with Faster Aspart
### SHORTCOMINGS OF BASAL INSULINS INCLUDE:

- Hypoglycemia resulting in:
  - Insulin under-dosing
  - Insufficient glycemic control
- Weight gain
- Inconsistent insulin action...leading to inconsistent blood glucose levels
- Not enough flexibility with timing of injections
- Insufficient duration of action...therefore, requiring a minimum of 1 and, sometimes, 2 injections/day
- Large volume injections required for some patients

### TWO NEW BASAL INSULINS RECENTLY ADDED TO LIST OF OPTIONS

**BOTH APPROVED BY THE FDA AND NOW AVAILABLE FOR PATIENTS**

1. **U-300 glargine** a long-acting basal insulin
2. **U-100 and U-200 degludec** a long-acting basal insulin

### U-300 GLARGINE

- A more concentrated (300 units/ml) form of traditional glargine insulin (100 units/ml)
- Compared to U-100 glargine, U-300 glargine has less intra-subject variability, less hypoglycemia and less weight gain.
- Flat, stable and prolonged action up to 30 hours *(needs 5 days to equilibrate...tell your patients!)*
- In the clinical trials patients on U-300 glargine with type 1 and type 2 diabetes may require a dose 12 to 18% higher than previous U-100 glargine (still with less hypo and less weight gain).
- Pen holds 450 units
- New Pen holds 900 units and can give 160 units at one time
**Type 1 New and Emerging CME**

**U-100 AND U-200 INSULIN DEGLUDEC**

- Available as either 100 units/ml ("detemir") or 200 units/ml
- Long duration of action up to 42 hours (needs 5 days to equilibrate...tell your patients!)
- Peakless
- Low intra-subject variability
- Less hypoglycemia and variability compared to U-100 glargine
- Disposable pens hold a maximum of 300 (U-100) and 600 (units)
- 160 units can be given at one time.

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**GLUCOSE INFUSION RATE IN SUBJECTS WITH TYPE 1 DIABETES INSULIN GLARGINE U-300**

50 T1D subjects underwent two euglycemic clamp studies after six days of receiving insulin glargine U-300

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**PK/PD PROFILE WITH GLAR U-300 VS GLAR U-100**

U-300 glargine has a more even and prolonged PK/PD profile

May need 13 to 17% more than previous dose of glargine

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**GLUCOSE INFUSION RATE IN SUBJECTS**

**TIME CONCENTRATION PROFILE WITH GLAR U-300 VS GLAR U-100**

U-300 glargine has a more even and prolonged PK/PD profile

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PHARMACODYNAMICS OF INSULIN DEGLUDEC
U-100 AND U-200
IN PATIENTS WITH T2DM: SAME TIME COURSE OF ACTION

U-100 Formulation

U-200 Formulation


GIR, mg/kg/min

0 1 2 3 4 5

Time, hours

0 4 8 12 16 20 24

0.8 U/kg

0.6 U/kg

0.4 U/kg

0.2 U/kg

0.0 U/kg

Basal/Bolus or MDI Insulin Regimen
With Rapid and Long-Acting Analogs/Inhaled Insulin


Nathan DM.

SOFTWARE PROGRAMS AS PUMPS

- Carb ratio
- Correction factor
- Insulin log
- Cloud based

75% of Type 1s
LET YOUR PATIENTS PICK THE PUMP

- Animas Vibe G4 (Discontinued)
- t:slim G6/X2
- 630/670G/530G
- Omnipod

INSULIN PUMPS: ADVANTAGES

- Improved glycemic control
  - More precise, physiologic insulin delivery
  - Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements
  - "Smart features" help to estimate insulin doses and reduce errors, i.e. stacking insulin
- In some situations (but not all) freedom and flexibility in lifestyle
  - Eliminate multiple daily injections (1 stick every 3 days)
  - Very easy to respond to CGM results
  - Reduce restrictions on eating, exercise and sleeping patterns; could have the same benefits with MDI
  - Greater flexibility with sports, travel, work schedule and other activities (not with water sports)

PUMP VS. MULTIPLE DAILY INJECTIONS?

It comes down to personal choice!
**TESTING THE BASAL RATE IN TYPE 1**

**Testing Overnight**
1. Ask the patient have an early dinner, make sure the post prandial BS is between 140 and 180mg/dl (may need a correction dose) with a horizontal trend arrow
2. Fast until the next morning
3. If not on a CGM then he/she needs to test the BS every few hours

**Testing During The Day (different day than testing pm)**
1. Ask the patient if he/she can skip breakfast and fast as long as possible.
2. If patient wants to eat a small breakfast then make sure the post breakfast BS is between 140-180mg/dl with a horizontal trend arrow

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**TESTING A BASAL SEGMENT IN T1D:**

**FOUNDATION OF ANY INSULIN REGIMEN**

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**Is this basal dose right?**

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32yo Male using MDI: Glargine U100 and fast acting analog

What is the best treatment option to help this patient with his overnight values?

A. Decrease the basal insulin
B. Switch the U-100 glargine for U-300 glargine or degludec
C. Have a larger bedtime snack
D. Do not exercise after 7pm

ADJUNCTIVE THERAPIES FOR PEOPLE WITH TYPE 1 DIABETES

- Amylin Analog (Pramlintide)
- Incretins (GLP-1 RA) *
- SGLT-2 Inhibitors*
- DPP4 Inhibitors*
- Metformin*

*Medications FDA approved only in type 2 diabetes at the current time
DPP-4 INHIBITORS IN T1D
- No statistically significant differences compared to placebo

METFORMIN IN T1D
- No statistically significant differences compared to placebo in A1c, hypoglycemia and DKA
- Slight reduction in weight and insulin dose

PETRIE ET AL. LANCET DE 2017; 5:597 -609
GARG ET AL. ENDOCRINE PRACTICE, 2013

PHYSIOLGIC INSULIN, GLUCAGON AND AMYLIN SECRETION

PHYSIOLOGIC INSULIN AND AMYLIN SECRETION AFTER MEALS

KODA ET AL, DIABETES. 1995; 44 (s1): 238A.
WEYER ET AL. CURR PHARM DES. 2001; 7:1353 -1373
REGULATION OF BLOOD GLUCOSE LEVELS AFTER MEALS BY AMYLIN

- Amylin is co-released with insulin after ingestion of food
- Stomach motility is normalized
- Reduces the appetite and leads to weight loss
- Suppression of glucagon levels from the alpha cells of the pancreas
- The reduced glucagon levels help to control excessive glucose production by the liver

PRAMlintide reduces FBG, PPG and glucose fluctuations

- Clinical Practice Study, 120 µg SYMLIN
- Study vs. insulin alone
- Data on file, Amylin Pharmaceuticals, Inc.
- *p-values for all data points <0.05

PRAMlintide + insulin: effect on sustained weight loss

- Insulin alone: weight gain
- Insulin plus pramlintide: weight loss
- Data on file, Amylin Pharmaceuticals, Inc.
49YO WOMAN WITH T1D X 33 YEARS, A1C 9%
AVG GLUCOSE 176.9 / S.D. 66.3

AFTER 3 MONTHS ON PRAMINTIDE, A1C 7.4%, LOST 12 LBS.
AVG GLUCOSE 122.4 / S.D. 30.4

GLP-1 RECEPTOR AGONIST IN T1D
- There were small very early studies with exenatide
- One large well controlled study looking at liraglutide
- Many of the clinical effects in type 1 are similar to what is seen with SGLT ½ inhibitors
- No agent is actively being studied for FDA approval in type 1 diabetes
### Recap of Key Results of Liraglutide in T1DM

<table>
<thead>
<tr>
<th></th>
<th>Adjunct One</th>
<th>Adjunct Two</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c change (placebo-adjusted)</td>
<td>Mean decrease up to 0.2%</td>
<td>Mean decrease up to 0.35%</td>
</tr>
<tr>
<td>Insulin dose change (placebo-adjusted)</td>
<td>Mean decrease up to 9%</td>
<td>Mean decrease up to 10%</td>
</tr>
<tr>
<td>Body weight loss (placebo-adjusted)</td>
<td>Mean decrease up to 5 kg</td>
<td>Mean decrease up to 5 kg</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>Numerically lower in Lira vs placebo</td>
<td>No apparent difference</td>
</tr>
<tr>
<td>Symptomatic hypoglycaemia</td>
<td>Lira 1.8 mg higher vs placebo</td>
<td>Lira 1.2 mg higher vs placebo</td>
</tr>
<tr>
<td>Hyperglycaemia with ketosis</td>
<td>Lira 3.8 mg higher vs placebo</td>
<td>Lira 1.8 mg higher vs placebo</td>
</tr>
</tbody>
</table>

Liraglutide is not approved for the management of type 1 diabetes.

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**WEEKLY CGM RECORD FOR ONE PATIENT PRIOR TO LIRAGLUTIDE**

**WEEKLY CGM RECORD FOR ONE PATIENT FOLLOWING LIRAGLUTIDE**
SGLT 1/2 INHIBITORS IN T1D

- There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin)
- Sotagliflozin has filed with the FDA and is the furthest alone in development and will review the clinical trial data for Sotagliflozin in detail and summarize the other studies and also shown in the supplemental slide PDF
- If any are approved it would be the first oral agent for type 1 diabetes

RENAL HANDLING OF GLUCOSE

GLUCOSE ABSORPTION AND REABSORPTION IN PATIENTS WITH DIABETES TREATED WITH A SELECTIVE SGLT2 INHIBITOR: CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN, ERUUGLIFLOZIN

- Increased Urinary Glucose Excretion
- Meal
- SGLT1 Glucose Absorption
- Blood Glucose
- SGLT2 (SGLT1) Glucose Reabsorption
- Post-meal Glucose Levels
- Tissues
- Glucose Fibration
- Increased Urinary Glucose Excretion
GLUCOSE ABSORPTION/REABSORPTION IN PATIENTS TREATED WITH A DUAL SGLT1 & SGLT2 INHIBITOR (SOTAGLIFLOZIN):
INHIBITS SGLT1 LOCALLY IN THE GI TRACT AND SGLT2 SYSTEMICALLY IN THE KIDNEY

INTANDEM STUDY DESIGN

INTANDEM1: A1C
### INTANDEM1: INSULIN DOSE

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Basal</th>
<th>Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>66.8</td>
<td>35.1</td>
<td>31.7</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>65.1</td>
<td>34.8</td>
<td>30.3</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>64.2</td>
<td>33.4</td>
<td>30.8</td>
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</tbody>
</table>

LSM: least squares mean. Data presented as the change from baseline in insulin dose (95% CI), P-value.

### INTANDEM1: WEIGHT

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sotagliflozin 200 mg</th>
<th>Sotagliflozin 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-6.0</td>
<td>-3.9</td>
<td>-8.5</td>
</tr>
<tr>
<td>LS 24 h</td>
<td>-11.87</td>
<td>-11.28</td>
<td>-15.71</td>
</tr>
<tr>
<td>LS 48 h</td>
<td>-5.53</td>
<td>-5.9</td>
<td>-8.6</td>
</tr>
<tr>
<td>LS 72 h</td>
<td>-15.63</td>
<td>-14.54</td>
<td>-24.67</td>
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</table>

LSM, least squares mean. Data presented as the mean change from baseline weight (95% CI), P-value.

### INTANDEM 1&2 (POOLED): CONTINUOUS GLUCOSE MONITORING

"TIME IN RANGE" (70-180 mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sotagliflozin 200 mg</th>
<th>Sotagliflozin 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>+1 h, 17 min</td>
<td>P = 0.026</td>
<td>vs PBO</td>
</tr>
<tr>
<td></td>
<td>+1 h, 19 min</td>
<td>P = 0.055</td>
<td>vs PBO</td>
</tr>
<tr>
<td></td>
<td>-2 h, 49 min</td>
<td>P &lt; 0.001</td>
<td>vs PBO</td>
</tr>
<tr>
<td></td>
<td>+2 h, 49 min</td>
<td>P &lt; 0.001</td>
<td>vs PBO</td>
</tr>
</tbody>
</table>

**Type 1 New and Emerging CME**
SUMMARIZE FINDINGS FROM ALL SGLT-1/2 INHIBITORS

(DIFFICULT TO MAKE PRECISE EFFICACY COMPARISONS ACROSS TRIALS DUE TO DESIGN AND ANALYSIS DIFFERENCES)

<table>
<thead>
<tr>
<th>Efficacy (placebo adjusted)</th>
<th>Highest dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction</td>
<td>~0.4%</td>
</tr>
<tr>
<td>Time in Range (blinded CGM)</td>
<td>~3 hour increase</td>
</tr>
<tr>
<td>Time in Hypoglycemia (CGM)</td>
<td>No change or some reduction</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>10-15% reduction</td>
</tr>
<tr>
<td>Weight</td>
<td>~2-3 kg reduction</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>~3-4 mm Hg reduction</td>
</tr>
<tr>
<td>Patient reported outcomes</td>
<td>Improved</td>
</tr>
</tbody>
</table>

Clinically relevant adverse events include genital mycotic infections (primarily in women 12 to 15%) and DKA (3 to 4%), sometimes euglycemic DKA

* Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure.

RISK MITIGATION OF DKA WITH SGLT INHIBITORS

- If unable to eat or drink, hold the SGLT inhibitor - such as NPO, viral illness, surgery, colonoscopy, etc.
- If on a SGLT inhibitor, avoid the keto diets and drink adequate fluids
- Do not prescribe in poorly adherent patients and use with caution if A1c above 9% or frequent episodes of DKA
- If nauseous or sick in any way, hold the SGLT inhibitor and troubleshoot their insulin delivery and check blood or urine ketones. If ketones are positive, take insulin per protocol along with carbs and fluids (your glucose may be normal!)
- If unable to drink and eat, go to the ER for fluids and further management.

APPROACH TO REDUCE DKA RISK WITH SGLTIS: STICH PROTOCOL

- Stop SGLT inhibitor
- Inject bolus insulin
- Consume 30g Carbohydrates
- Hydrate (drink water)

Please use this card if you are on any SGLT inhibitor with diabetes. Consult your physician before stopping any medications.
AN ARTIFICIAL PANCREAS IS COMING FASTER THAN WE THOUGHT POSSIBLE

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic

BG mg/dL

Time

Alarm – impending hypo
/ No response – alarm plus insulin reduction or off/glucagon on if needed

Alarm – impending hyper
/ No response – alarm plus automated insulin push to bring level below threshold (glucagon off)

Resume preset basal rate

Minimize time in "Red" zones

EXAMPLE OF AN APILET: BIONIC PANCREAS

2 ports for insulin and glucagon

AN ARTIFICIAL PANCREAS WILL BRIDGE THE GAP UNTIL THERE IS A CURE

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic • DIY Loop

BG mg/dL

Time

Alarm – impending hypo
/ No response – alarm plus insulin reduction or off/glucagon on if needed

Alarm – impending hyper
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Resume preset basal rate

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Alarm – impending hyper
/ No response – alarm plus automated insulin push to bring level below threshold (glucagon off)

Resume preset basal rate

Minimize time in "Red" zones
The important unmet needs in T1D include improved glycemic variability (GV), increased time in range (TIR), reaching A1c goal without hypoglycemia, controlling blood pressure and weight gain, addressing the emotional burden of living, and using CGM and the newer ultra rapid and basal insulins to help improve TIR. Adjunctive therapies can address some of the unmet needs.
SUPPLEMENTAL DATA
SLIDES
There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin)

- Sotagliflozin has filed with the FDA and is the furthest alone in development and will review the clinical trial data for Sotagliflozin in detail and summarize the other studies and also shown in the supplemental slide PDF

- If any are approved it would be the first oral agent for type 1 diabetes
GLUCOSE ABSORPTION/REABSORPTION IN PATIENTS TREATED WITH A DUAL SGLT1 & SGLT2 INHIBITOR (SOTAGLIFLOZIN):
INHIBITS SGLT1 LOCALLY IN THE GI TRACT AND SGLT2 SYSTEMICALLY IN THE KIDNEY

Post-meal Glucose Levels

GLUCOSE ABSORPTION/REABSORPTION IN PATIENTS TREATED WITH A DUAL SGLT1 & SGLT2 INHIBITOR (SOTAGLIFLOZIN):
INHIBITS SGLT1 LOCALLY IN THE GI TRACT AND SGLT2 SYSTEMICALLY IN THE KIDNEY

RENAL HANDLING OF GLUCOSE

THREE SGLT DEVELOPMENT PROGRAMS HAVE COMPLETED PHASE III: DEPICT, INTANDEM, EASE

<table>
<thead>
<tr>
<th>Study</th>
<th>DEPICT1,2</th>
<th>inTandem3,5</th>
<th>EASE6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug, dose</td>
<td>Dapagliflozin • 5 mg • 10 mg • Placebo</td>
<td>Sotagliflozin • 200 mg • 400 mg • Placebo</td>
<td>Empagliflozin • 2.5 mg • 10 mg • 25 mg • Placebo</td>
</tr>
</tbody>
</table>

DEPICT STUDIES (DAPAGLIFLOZIN): DESIGN

Insulin dose reduced 20% at randomization.

DEPICT1 – A1C

Mean baseline A1C and change over 24 weeks for Dapagliflozin 5 and 10 mg, and Placebo.

DEPICT1 - WEIGHT

Mean baseline bodyweight and change over 24 weeks for Dapagliflozin 5 and 10 mg, and Placebo.
**DEPICT1 – TOTAL DAILY DOSE (TDD) INSULIN**

- **Dapagliflozin 5 mg:** Increased from 43.2% (SD 12.4) at baseline to 52.3% (SD 14.8) at week 24.
  - An absolute increase of 9.1% (SD 14.5): 2.2 hours per day
- **Dapagliflozin 10 mg:** Increased from 44.6% (SD 12.4) to 54.6% (SD 13.1) at week 24.
  - An absolute increase of 10.1% (SD 14.2): 2.4 hours per day
- **Placebo group:** Essentially unchanged
  - An absolute decrease of 0.6%: -0.14 hours a day

**DEPICT1 – CONTINUOUS GLUCOSE MONITORING “TIME IN RANGE” (70-180 MG/DL)**

- **Dapagliflozin 5 mg:** Increased from 43.2% (SD 12.4) at baseline to 52.3% (SD 14.8) at week 24.
  - An absolute increase of 9.1% (SD 14.5): 2.2 hours per day
- **Dapagliflozin 10 mg:** Increased from 44.6% (SD 12.4) to 54.6% (SD 13.1) at week 24.
  - An absolute increase of 10.1% (SD 14.2): 2.4 hours per day
- **Placebo group:** Essentially unchanged
  - An absolute decrease of 0.6%: -0.14 hours a day

**INTANDEM STUDY DESIGN**

- **8-Week Screening**
- **6-20 Week Follow-up**
- **Sotagliflozin 400 mg (n=262)**
- **Sotagliflozin 200 mg (n=263)**
- **Placebo (n=268)**

- **30-Day Safety Follow-up**
- **Screening A1C**
- **Baseline A1C**
- **Primary endpoint A1C**
- **Week 52 endpoint A1C**
- **Insulin optimization**
- **IDMC review / A1C masked**
- **DB core treatment**
- **DB extension**

Optimized insulin: Insulin adjustment to meet standard of care (SOC) glycemic targets starting 6 weeks prior to randomization and continued for the entire study. An independent Insulin Dose Monitoring Committee (IDMC) assessed SOC adherence and provided feedback to PI if deviations from SOC observed prior to Week 24.

DB, double-blind; R, randomized.
**INTANDEM1: A1C**

Screening: 8.2% - 8.3%
Baseline: 7.5% - 7.6%

- **Placebo**
- **Sotagliflozin 200 mg**
- **Sotagliflozin 400 mg**

A1C, LSM Change from Baseline

<table>
<thead>
<tr>
<th>Week</th>
<th>24-Week Difference from PBO</th>
<th>52-Week Difference from PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.36% (0.45, 0.27)</td>
<td>0.41% (0.50, 0.32)</td>
</tr>
<tr>
<td></td>
<td>0.25% (0.37, 0.14)</td>
<td>0.31% (0.43, 0.20)</td>
</tr>
</tbody>
</table>

**INTANDEM1: INSULIN DOSE**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Basal</th>
<th>Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>66.8</td>
<td>65.1</td>
<td>64.2</td>
</tr>
<tr>
<td></td>
<td>54.6</td>
<td>33.4</td>
<td>31.7</td>
</tr>
<tr>
<td></td>
<td>32.3</td>
<td>30.8</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as the mean change from baseline in insulin dose (95% CI), P-value.

**INTANDEM1: WEIGHT**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Basal</th>
<th>Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24-Week Difference from PBO</td>
<td>24-Week Difference from PBO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-2.35 kg (-2.85, -1.85)</td>
<td>-2.35 kg (-2.85, -1.85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-3.45 kg (-3.95, -2.94)</td>
<td>-3.45 kg (-3.95, -2.94)</td>
<td></td>
</tr>
</tbody>
</table>

**INTANDEM1: DB CT**

- IDMC, A1C masked
- No IDMC, A1C not masked

**INTANDEM1: DB EXT**

- Total
  - Basal: 66.8
  - Bolus: 32.3

**LSM, least squares mean.**
INTANDEM 1&2 (POOLED): CONTINUOUS GLUCOSE MONITORING
“TIME IN RANGE” (70-180 MG/DL)

Placebo
Sotagliflozin 200 mg
Baseline
Sotagliflozin 400 mg

Baseline
Placebo
Empagliflozin 10 mg
Baseline
Placebo
Empagliflozin 25 mg

EASE-2 AND EASE-3 (EMPAGLIFLOZIN): TRIAL DESIGN

EASE-2

EASE-3

*CGM performed as sub-study in ~10% patients; R, randomisation

EASE-2: A1C

Mean (SE) HbA1c (%)

*Adjusted mean change from baseline vs placebo. Screening and week 0: descriptive data in full analysis set. Week 4–52: adjusted data based on mixed model repeated measures in full analysis set (intent-to-treat). SE, standard error
Empagliflozin 10 mg
Empagliflozin 2.5 mg
6-week intensification
2-week run-in

EASE-3: A1C

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg

*Adjusted mean change from baseline vs placebo; Screening and week 0: descriptive data in full analysis set. Week 4–26: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

EASE-3: WEIGHT

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg

*Adjusted mean change from baseline vs placebo; Screening and week 0: descriptive data in full analysis set. Week 4–26: adjusted data based on mixed model repeated measures in full analysis set (observed cases).
Type 1 New and Emerging CME – Supplemental Slides

**EASE-2: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME**

(Half the reduction in basal dose and half in bolus dose)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Empa 2.5 mg</th>
<th>Empa 10 mg</th>
<th>Empa 25 mg</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>223</td>
<td>219</td>
<td>214</td>
<td>225</td>
<td>204</td>
<td>188</td>
</tr>
<tr>
<td></td>
<td>217</td>
<td>207</td>
<td>212</td>
<td>221</td>
<td>201</td>
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<td></td>
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<td>4</td>
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<td>184</td>
<td>196</td>
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<td>12</td>
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<td>160</td>
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<td>191</td>
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<td>26</td>
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<td>130</td>
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<td>161</td>
<td>142</td>
<td>142</td>
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<tr>
<td>52</td>
<td>98</td>
<td>108</td>
<td>128</td>
<td>139</td>
<td>119</td>
<td>119</td>
</tr>
</tbody>
</table>

Adjusted mean (SE) change from baseline in total daily insulin dose (U/kg)

*Adjusted mean change from baseline vs placebo. Screening and week 0: descriptive data in full analysis set. Week 4–52: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

**EASE-3: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME**

(Half the reduction in basal dose and half in bolus dose)

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<td>108</td>
<td>128</td>
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</table>

Adjusted mean (SE) change from baseline in total daily insulin dose (U/kg)

*Adjusted mean change from baseline vs placebo. Screening and week 0: descriptive data in full analysis set. Week 4–52: adjusted data based on mixed model repeated measures in full analysis set (observed cases).

**EASE-2: CGM RESULTS**

Full analysis set (screening set – excluding data after paracetamol intake).

- Glucose ≤70 mg/dl
- Glucose >70–≤180 mg/dl
- Glucose >180 mg/dl

Empagliflozin increased time in target glucose range by ~3 hrs/day.
**EASE-3: SUBANALYSIS CGM RESULTS**

<table>
<thead>
<tr>
<th>Baseline Week 26</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
<th>Empagliflozin 2.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose ≤70 mg/dl</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Glucose &gt;70 –≤180 mg/dl</td>
<td>49%</td>
<td>43%</td>
<td>51%</td>
<td>48%</td>
</tr>
<tr>
<td>Glucose &gt;180 mg/dl</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**SUMMARIZE FINDINGS FROM ALL SGLT-1/2 INHIBITORS**

(DIFFICULT TO MAKE PRECISE EFFICACY COMPARISONS ACROSS TRIALS DUE TO DESIGN AND ANALYSIS DIFFERENCES)

<table>
<thead>
<tr>
<th>Efficacy (placebo adjusted)</th>
<th>Highest dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction</td>
<td>~0.4%</td>
</tr>
<tr>
<td>Time in Range (blinded CGM)</td>
<td>~3 hour increase</td>
</tr>
<tr>
<td>Time in Hypoglycemia (CGM)</td>
<td>No change or some reduction</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>10-15% reduction</td>
</tr>
<tr>
<td>Weight</td>
<td>~2-3 kg reduction</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>~3-4 mm Hg reduction</td>
</tr>
<tr>
<td>Patient reported outcomes</td>
<td>Improved</td>
</tr>
</tbody>
</table>

* Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure

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- If unable to eat or drink, hold the SGLT inhibitor
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- If unable to drink and eat, go to the ER for fluids and further management.
APPROACH TO REDUCE DKA RISK WITH SGLTIS: STICH PROTOCOL

S
Stop SGLT inhibitor

I
Inject bolus insulin

C
Consume 30 g Carbohydrates

H
Hydrate (drink water)