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

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DISCLOSURES

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• Board Member: Senseonics, TeamType1
• Medical Advisory Board: AstraZeneca, Brightlight, Ihealth, Lexicon, Lilly USA, LLC, Mannkind Corporation, Merck, Novo Nordisk, 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 Funding: Novo Nordisk

TOPICS TO BE DISCUSSED

Unmet needs in type 1 diabetes
Historical perspective of type 1 diabetes
State of type 1 diabetes care in 2018
Continuous glucose monitoring (CGM)
Pumps versus 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), increased 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:
  - Greater Than Goal: 16%
  - Achieved Goal: 60%
  - Below Goal: 24%
- Coefficient of Variation (CV): 31.4%
- Standard Deviation (SD): 47.7 mg/dL
BANTING AND BEST
UNIVERSITY OF TORONTO 1921

Ted Ryder
5 months after starting insulin

FAST FORWARD TO T1D CARE IN 1970
- 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 adults currently have T1D\(^1\)
  – 1 million adults ≥ 20 years
• 21% increase in prevalence of T1D in people < 20 years between 2001-2009\(^2\)
• 40,000 people diagnosed each year in U.S.\(^3\)
• 5 million people in U.S. expected to have T1D by 2050\(^2\)

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

Natural Progression is months to a few years
Type 1 New and Emerging CME
You can get type 1 diabetes at any age!

**AGE AT DIAGNOSIS OF T1D**

<table>
<thead>
<tr>
<th>Age (years)</th>
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<tr>
<td>0-1</td>
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<td>1.5-2</td>
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<td>3-4</td>
<td>7829</td>
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<td>4.5-5</td>
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<td>199</td>
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<tr>
<td>13.5-14</td>
<td>333</td>
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</table>

**FAMILY HISTORY OF T1D**

- First-degree family member with T1D
  - Yes: 16%
  - No: 84%

**RISK OF DEVELOPING TYPE 1 VS TYPE 2**

- General Population: 0.3% Type 1, 8-11% Type 2
- If you have a sibling with T1D: 4% Type 1
- If your mother has T1D: 2.3% Type 1
- If your father has T1D: 6.8% Type 1
- If you have an identical twin with T1D: ~50% Type 1, 100% Type 2
Type 1 New and Emerging CME

RACE/ETHNICITY

- White Non-Hispanic: 81%
- Black Non-Hispanic: 5%
- Hispanic or Latino: 8%
- Native Hawaiian/Other Pacific Islander: 1%
- Asian: 1%
- American Indian/Alaskan Native: 1%
- More than One Race: 3%
- CAUCASION

OVERWEIGHT / OBESE

- Age (years)
  - <6: 14%
  - 6-<13: 18%
  - 13-<18: 19%
  - 18-<26: 24%
  - 26-<50: 28%
  - ≥50: 39%

- Overweight: 65%
- Obese: 66%

ONLY ~30% OF TYPE 1S REACH ADA GOAL OF AN A1C LESS THAN 7%

- A1c Goal = <7.0%
  - Age, years: 65%
  - A1c Goal = <7.5%
  - Age, years: 46%
  - A1c Goal = <8.0%
  - Age, years: 23%
  - A1c Goal = <8.5%
  - Age, years: 20%
  - ≥65: 30%
  - >65: 27%
  - 50-<65: 34%
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 when 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
Type 1 New and Emerging CME
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.

G6
- No calibration required
- 10 day sensor life
- Predictive low alerts
- No interference with acetaminophen
- Auto inserter
- Medicare Approved

EVERSENSE
Implantable Continuous Glucose Monitor
- Sensor: Sensor lasts up to 90 days, No weekly sensor insertion, No open wound
- Smart Transmitter: Removable and rechargeable, On-body vibe alerts, Gentle, daily adhesive patch
- Mobile App: No extra device to carry, iOS and Android platform, Alarm settings & reports

EVERSENSE IMPLANTABLE CGM
GUARDIAN CONNECT
- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

GUARDIAN CONNECT

FREESTYLE LIBRE FLASH
IS OR INTERMITTENT SENSING
- 12 hour warm-up time
- Lasts 10 days (approved for 2hr/12day)
- 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>Type 1</th>
<th>MDI</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>5</td>
<td>6</td>
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<td>26-40</td>
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<td>8</td>
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<tr>
<td>&gt; 50</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Source: Miller KM, et al., Diabetes Care. 2015
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

HOW CGM AND TRENDING INFORMATION CAN AFFECT OUR DECISIONS (C/I:CHO)

- Clamp:
  - Your glucose is steady, and it is not moving up or down.
- Slowly rising:
  - Your glucose is rising at 0 mg/dl each minute.
- Steady rise:
  - Your glucose is rising at >0 mg/dl each minute.
- Ramping:
  - Your glucose is rising faster than 0 mg/dl each minute.
- Rapidly rising:
  - Your glucose is rising faster than 0 mg/dl each minute.
- Slowly falling:
  - Your glucose is falling at <0 mg/dl each minute.
- Steady fall:
  - Your glucose is falling at 0 mg/dl each minute.
- Ramping fall:
  - Your glucose is falling faster than 0 mg/dl each minute.
- Rapidly falling:
  - Your glucose is falling faster than >0 mg/dl each minute.

No Blame or Change Information: The patient cannot always distinguish how fast your glucose is rising or falling.
MEAN CHANGE IN INSULIN DOSE BASEDON 2 ARROWS UP: SURVEY OF 300 CGM USERS

3.0 units 6.8 units

HOW CGM AND TRENDING INFORMATION CAN AFFECT DOSING DECISIONS

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 220mg/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
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.

Both dietary fat and protein increase post-meal glucose concentrations:

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

High fat/high protein
High fat/low protein
Low fat/high protein
Low fat/low protein

**HOW MUCH FAST ACTING INSULIN WOULD YOU RECOMMEND TO A PATIENT EATING A MEAL WITH 60 GRAMS OF CARBOHYDRATES (INSULIN TO CARB RATIO IS 3 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

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**64 YEAR OLD MALE WITH T1D FOR 30 YEARS ON A T1D REGIMEN**

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

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**SUBCUTANEOUS INSULIN HAS A VERY NARROW THERAPEUTIC WINDOW**

- Too little insulin leads to postprandial hyperglycemia
- Too much leads to hypoglycemia
- Very difficult to get it just right

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SERUM INSULIN LEVELS IN TYPE 1 DIABETES

**LisPro Regular**

**Regular**

**Time (h)**

22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00

**LisPro Regular**

**Regular**

**Time (h)**

22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00

**BLOOD GLUCOSE LEVELS**

**Lispro**

**Regular**

**Avg A1c = 6.8**

**Time (h)**

22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00

**PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION**

Liver

Pancreas

Insulin

Amylin

Glucagon

Beta Cell

Alpha Cell

Systemic Circulation

Portal Vein

Insulin

Amylin

Glucagon

Beta Cell

Alpha Cell
PHYSIOLOGIC INSULIN SECRETION AND GLUCOSE LEVELS IN HEALTHY SUBJECTS

Insulin (µU/mL)

Bolus Insulin (40 to 60% of TTD)

Basal Insulin HGO (40 to 60% of TTD)

Glucose (mg/dL)

Basal Glucose

TIME OF DAY

A.M. P.M.

1 2 3 4 5 6 7 8 9 10 11 12

GENERIC AND TRADE NAMES: INSULIN

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>Fast-Acting Insulin</td>
<td>Regular U-500, Aspart, Lispro (U-100 and U-200)</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>Intermediate-Acting NPH, Long-Acting: Detemir, Glargine (U-100, U-300), Degludec (U-100/200)</td>
</tr>
<tr>
<td>Inhaled Insulin</td>
<td>Follow-on biologic lispro, Inhaled insulin</td>
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Rapid on
Rapid off

- Better post meal glucose values
- Less delayed hypoglycemia
FASTER-ACTING ASPART (ADDICTION OF L-ARGININE AND NIAVINAMIDE 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 150U at one time

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

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

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
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.

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

BASAL/BOLUS OR MDI INSULIN REGIMEN
WITH RAPID AND LONG-ACTING ANALOGS/INHALED INSULIN

75% of Type 1s
SOFTWARE PROGRAMS AS PUMPS

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

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

TESTING A BASAL SEGMENT IN T1D:
FOUNDATION OF ANY INSULIN REGIMEN

https://mysugr.com/basal-rate-testing/
Is this basal dose right?

SAME PT. FASTING FROM 9PM UNTIL 7AM

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

PHYSIOLOGIC INSULIN, GLUCAGON AND AMYLIN SECRETION

Liver → Pancreas → Beta Cell (Insulin) → Alpha Cell (Amylin) → Glucagon → Systemic Circulation
PHYSIOLOGIC INSULIN AND AMYLIN SECRETION AFTER MEALS

Plasma insulin (pM)

<table>
<thead>
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<th>7 am</th>
<th>12 noon</th>
<th>5 pm</th>
<th>Midnight</th>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Amylin

Insulin

Plasma amylin (pM)

Koda et al, Diabetes. 1995; 44 (s1): 23BA.


REGULATION OF BLOOD GLUCOSE LEVELS AFTER MEALS BY AMYLIN

Amylin

Reduces the appetite and leads to weight loss

Stomach motility is normalized

Edelman SV, Henry RR. Diagnosis and management of type 2 diabetes. Eleventh

PRAMLINTIDE REDUCES FBG, PPG AND GLUCOSE FLUCTUATIONS

Insulin alone

Insulin plus pramlitide

Clinical Practice Study. 50 µg SYMLIN

N=166; *p-values for all data points <0.05

Data on file, Amylin Pharmaceuticals, Inc.
PRAMILTIDE + INSULIN: EFFECT ON SUSTAINED WEIGHT LOSS

Insulin alone: weight gain

insulin plus pramlintide: weight loss

49YO WOMAN WITH T1D X 33 YEARS, A1C 9%
AVG GLUCOSE 176.9 / S.D. 66.3

AFTER 3 MONTHS ON PRAMILTIDE, 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 1/2 inhibitors
- No agent is actively being studied for FDA approval in type 1 diabetes

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ADJUNCT ONE AND TWO: LIRAGLUTIDE IN T1DM – PHASE 3A TRIAL DESIGNS

Key inclusion criteria
- T1DM ≥ 12 months
- Age ≥ 18 (– 75) years
- HbA1c 7.0 – 10.0%
- BMI ≥ 20 kg/m²
- Basal - bolus insulin or CSII ≥ 6 months
- Stable insulin dose ≥ 3 months

Key endpoints
- HbA1c, insulin dose, body weight, hypoglycaemia, hyperglycaemia and adverse events

Insulin-capped
- Liraglutide 0.6 mg + insulin
- Liraglutide 1.2 mg + insulin
- Liraglutide 1.8 mg + insulin
- Liraglutide placebo + insulin
- Placebo 0.3 mL + insulin
- Placebo 0.2 mL + insulin
- Placebo 0.1 mL + insulin

Duration: 26 weeks
N=~800
Treat-to-target
- Liraglutide 0.6 mg + insulin
- Liraglutide 1.2 mg + insulin
- Liraglutide 1.8 mg + insulin

Duration: 52 weeks
N=~1400
Liraglutide placebo + insulin
- Placebo 0.3 mL + insulin
- Placebo 0.2 mL + insulin
- Placebo 0.1 mL + insulin

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CHANGE IN HbA1c FROM BASELINE TO END OF TREATMENT

<table>
<thead>
<tr>
<th>ADJUNCT ONE</th>
<th>ADJUNCT TWO</th>
</tr>
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<tbody>
<tr>
<td>Time since randomisation (week)</td>
<td>Time since randomisation (week)</td>
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<tr>
<td>HbA1c (%)</td>
<td>HbA1c (%)</td>
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<tr>
<td>Mean BL value</td>
<td>Mean BL value</td>
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<tr>
<td>0.1299</td>
<td>0.0164</td>
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<td>0.0021</td>
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<tr>
<td>&lt;0.0001</td>
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p value vs placebo | p value vs placebo
Change in Body Weight from Baseline to End of Treatment

Change in Total Insulin Dose from Baseline to End of Treatment

Subjects Achieving HbA1c <7.0% and No Severe Hypoglycaemia
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
INTESTINAL SGLT1-MEDIATED GLUCOSE ABSORPTION

RENAL SGLT2 (SGLT1) MEDIATED GLUCOSE REABSORPTION

Meal

SGLT1 Glucose Absorption

Blood Glucose

Post-meal Glucose Levels

Tissues

Glucose Filtration

SGLT1 (SGLT2) Glucose Reabsorption

No Urinary Glucose

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

Meal

SGLT1 Glucose Absorption

Blood Glucose

Post-meal Glucose Levels

Tissues

Glucose Filtration

SGLT2 (SGLT1) Glucose Reabsorption

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

Meal

SGLT1 Glucose Absorption

Blood Glucose

Post-meal Glucose Levels

Tissues

Glucose Filtration

SGLT2 (SGLT1) Glucose Reabsorption

Moderately Increased Urinary Glucose Excretion
RENAL HANDLING OF GLUCOSE

SGLT 2

S1

S3

10%

10%

NO GLUCOSE

(180 L/day) (1000 mg/L) = 180 g/day

INTANDEM STUDY DESIGN

- Week Screening
- Baseline A1C
- Primary endpoint A1C
- Week 52 endpoint A1C
- Insulin optimization
- DB core treatment
- DB extension
- Week 24 Safety Follow-up
- IdMC review / A1C masked

Optimized Insulin: Insulin adjustment to meet standard of care (SOC) glycemic targets starting 6 weeks prior to randomization and continued for entire study. An independent Insulin Dose Monitoring Committee (IDMC), assessed SOC adherence and provided feedback to PI 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%

A1C, LSM Change from Baseline ± SE (%)

Week 24 - Week Difference from PBO
-0.30% (-0.4, -0.2); P = 0.001
-0.23% (-0.30, -0.16); P = 0.001

Week 52 - Week Difference from PBO
-0.22% (-0.31, -0.13); P = 0.001
-0.20% (-0.27, -0.13); P = 0.001

Baseline = 7.5% - 7.8%

Placebo

Sotagliflozin 200 mg

Sotagliflozin 400 mg
INTANDEM1: INSULIN DOSE

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal</th>
<th>Bolus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>65.1</td>
<td>35.1</td>
<td>100.2</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>64.2</td>
<td>34.8</td>
<td>99.0</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>63.4</td>
<td>33.4</td>
<td>96.8</td>
</tr>
<tr>
<td><strong>P</strong>&lt;0.001</td>
<td></td>
<td></td>
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</tbody>
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Data presented as the change from baseline in insulin dose (95% CI), P-value.

LSM, least squares mean.

INTANDEM1: WEIGHT

<table>
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<tr>
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<th>Basal</th>
<th>Week Difference from PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>87 kg</td>
<td>-3.14 kg (-3.81, -2.46)</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>-4.32 kg (-5.00, -3.64)</td>
<td></td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>-5.53 kg (-6.59, -4.47)</td>
<td></td>
</tr>
<tr>
<td><strong>P</strong>&lt;0.001</td>
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<td></td>
</tr>
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INTANDEM 1&2 (POOLED): CONTINUOUS GLUCOSE MONITORING

"TIME IN RANGE" (70-180 MG/DL)

Week 24

-2 h, 49 min vs PBO  P<0.001
-1 h, 33 min vs PBO  P=0.055
+1 h, 17 min vs PBO  P=0.026
15 h 50 min vs PBO  P=0.70
13 h 52 min vs PBO  P=0.93
12 h 48 min vs PBO  P=0.93
10 h 48 min vs PBO  P<0.001
8 h 48 min vs PBO  P<0.001
18 min vs PBO  P=0.93

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)

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<tr>
<td>Time in Range (blinded CGM)</td>
<td>~3 hour increase</td>
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<tr>
<td>Time in Hypoglycemia (CGM)</td>
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<tr>
<td>Insulin dose</td>
<td>10-15% reduction</td>
</tr>
<tr>
<td>Weight</td>
<td>~2-3 kg reduction</td>
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<td>Systolic blood pressure</td>
<td>~3-4 mm Hg reduction</td>
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Clinically relevant adverse events include genital mycotic infections (primarily in women 12 to 15%) and DKA (3 to 4%), sometimes euglycemic DKA.

*R 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.
- If unable to drink and eat, go to the ER for fluids and further management.

APPROACH TO REDUCE DKA RISK WITH SGLTIS: STICH PROTOCOL

Walt Card - front
AN ARTIFICIAL PANCREAS IS COMING FASTER THAN WE THOUGHT POSSIBLE

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic

BG mg/dL

Time

180
60
30
15
0
Alarm – impending hypo
No response – alarm plus insulin reduction or off/glucagon on if needed
Resume preset basal rate

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

180
60
30
15
0
Alarm – impending hypo
No response – alarm plus insulin reduction or off/glucagon on if needed
Resume preset basal rate

Maximize time in "Red" zones

EXAMPLE OF AN APILET: BIONIC PANCREAS

2 ports for insulin and glucagon
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
CGM and the newer ultra rapid and basal insulins can help improve TIR
Adjunctive therapies can address some of the unmet needs.
SUPPLEMENTAL DATA SLIDES
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
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

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**

- **Dapagliflozin 5 mg:** mean baseline HbA1c was 8.52% (SD 0.72) and mean week 24 HbA1c was 8.04% (SD 0.90); adjusted mean change, –0.45% (SE 0.05).
- **Dapagliflozin 10 mg:** mean baseline HbA1c was 8.50% (SD 0.62) and mean week 24 HbA1c was 8.04% (SD 0.83); adjusted mean change, –0.47% (SE 0.05).
- **Placebo:** mean baseline HbA1c was 8.50% (SD 0.67) and mean week 24 HbA1c was 8.43% (SD 0.92); adjusted mean change, –0.03% (SE 0.05).

**DEPICT1 – WEIGHT**

- **Dapagliflozin 5 mg:** mean baseline bodyweight was 81.67 kg (SD 18.40) and mean week 24 bodyweight was 79.38 kg (SD 18.15); adjusted mean change, –2.84% (SE 0.25).
- **Dapagliflozin 10 mg:** mean baseline bodyweight was 81.70 kg (SD 16.40) and mean week 24 bodyweight was 78.72 kg (SD 15.91); adjusted mean change, –3.60% (SE 0.25).
- **Placebo:** mean baseline bodyweight was 84.36 kg (SD 18.45) and mean week 24 bodyweight was 84.50 kg (SD 18.75); adjusted mean change, 0.12% (SE 0.26).
**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 13.5): 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 13.5): 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**

- **Screening A1C**
  - Placebo run-in
- **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 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**

![A1C Graph]

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

A1C, LSM Change from Baseline ± SE (%)

Week 24 - Week Difference from PBO:
- Placebo: -0.36% (0.45, -0.27); P < 0.001
- Sotagliflozin 200 mg: -0.41% (0.50, -0.32); P < 0.001
- Sotagliflozin 400 mg: -0.31% (0.43, -0.20); P < 0.001

Week 52 - Week Difference from PBO:
- Placebo: -0.25% (0.37, -0.14); P < 0.001
- Sotagliflozin 200 mg: -0.31% (0.43, -0.20); P < 0.001
- Sotagliflozin 400 mg: -0.30% (0.43, -0.20); P < 0.001

**INTANDEM1: INSULIN DOSE**

![Insulin Dose Graph]

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

**INTANDEM1: WEIGHT**

![Weight Graph]

Baseline = 87 kg

Weight, LSM Change from Baseline ± SE (kg)

Week 24 - Week Difference from PBO:
- Placebo: -2.35 kg (2.85, -1.85); P < 0.001
- Sotagliflozin 200 mg: -3.45 kg (3.95, -2.94); P < 0.001

Week 52 - Week Difference from PBO:
- Placebo: -4.32 kg (5.00, -3.64); P < 0.001
- Sotagliflozin 200 mg: -5.53 kg (14.54, 3.48); P = 0.23
- Sotagliflozin 400 mg: -15.63 kg (24.67, 6.59); P < 0.001

-15 -10 -5 0 5 10 15

Placebo Sotagliflozin 200 mg Sotagliflozin 400 mg

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

24 h
12 h
18 h
6 h
12 h
33 min
10 h
3 min
1 h
24 min

<70 mg/dL
70–180 mg/dL
>180 mg/dL

Week 24
24 h
12 h
18 h
6 h
12 h
23 min
10 h
13 min
1 h
25 min

P = 0.70 vs PBO
P = 0.055 vs PBO
P = 0.026 vs PBO

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

Screening
6 weeks
T1D therapy
intensification
Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg

1 week
3 weeks
52 weeks
Placebo
run-in
Follow-up

Screening
T1D therapy
intensification
Placebo
Empagliflozin 2.5 mg
Empagliflozin 10 mg
Empagliflozin 25 mg

26 weeks (primary endpoint)
Placebo
run-in
Follow-up

CGM*
CGM
CGM
26 weeks
CGM*
CGM*
3 weeks

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

EASE-2: A1C

*Adjusted mean change from baseline ± standard error; 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); SE, standard error.
**EASE-3: A1C**

- **Placebo**
- Empagliflozin 2.5 mg
- 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 2.5 mg
- Empagliflozin 10 mg
- Empagliflozin 25 mg  

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

Week

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg
Empa 2.5 mg
Empa 10 mg
Empa 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-2: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME

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

EASE-3: TOTAL DAILY INSULIN DOSE REDUCTION OVER TIME

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

EASE-2: CGM RESULTS
EASE-3: SUBANALYSIS CGM RESULTS

Baseline Week 26

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
<th>Empagliflozin 2.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>6%</td>
<td>49%</td>
<td>45%</td>
<td>6%</td>
</tr>
<tr>
<td>43%</td>
<td>51%</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>5%</td>
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<td>48%</td>
</tr>
<tr>
<td>5%</td>
<td>55%</td>
<td>39%</td>
<td>48%</td>
</tr>
</tbody>
</table>

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

Empagliflozin 2.5 mg increased time in target glucose range by ~1 hr/day

SUMMARIZE FINDINGS FROM ALL SGLT -1/2 INHIBITORS
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- such as NPO, viral illness, surgery, colonoscopy, etc
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- 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.
- 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)