Kinexum ADA 2021 report

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Synthesis – main topics of the conference

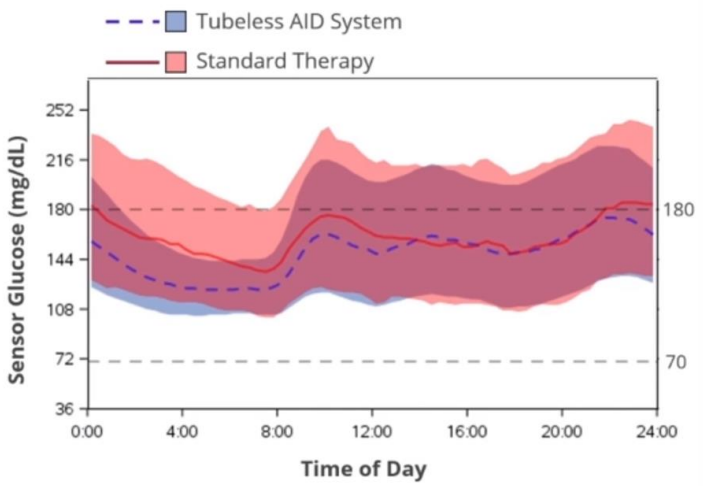
- As during ATTD, **Covid-19 was an important topic**, with its impact on diabetes management, the use of digital health and remote medical visits, and the **presentation of the safety trial DARE-19** testing dapagliflozin in patients with Covid-19. This subject was not treated in this report as it would require a full additional report.
- In drug therapies, the main focus was around the **Phase 3 results of tirzepatide in T2D with impressive results versus semaglutide**, but also **Phase 3 results of efpeglenatide** (weekly GLP-1 of Hanmi), including their CV trial showing positive CV effect of an exendin-based GLP-1. A few drugs in earlier development were presented, including the weekly basal insulin of Lilly, new data of Adocia's pramlintide insulin combination, and dual/triple GLP-1s agonists.
- In device technologies, Insulet presented positive new data concerning their **Omnipod 5 hybrid-closed loop** (in 2-6 years, the extension of their pivotal and quality of life data) comforting the positive results presented in past months. **Real-world data** were also presented, including the **770G** (similar results as with the 670G), the **780G,** and the **Control-IQ systems**, with results coherent with pivotal clinical trials. **CamAPS** (Camdiab/Hovorka's artificial pancreas) algorithm also presented first results in **T2D with end stage renal disease**. Medtronic presented their US pivotal trial with their **EWIS 7 days wear infusion set**, while **Capillary Bio** presented similar proof of concept results with their own 7 days wear technology.
- Interesting device technologies include those presented by Medtronic from the **InPen** (smart pen) with slight improved in time in range **real-world data.**
- CGM was another hot topic, with a strong interest on where and when to use them (T2D, clinical care, pregnancy, etc.) with, for instance, compelling **Dexcom G6 data in T2D patients using OAD or basal insulin**. The IDC also presented new integration of the first CGM data (from Libre Freestyle) in the Electronic Health Record.
- In the **beta-cell therapies**, the JDRF presented a good review on current projects and challenges in this field, with still some important milestones to reach. Viacyte presented promising preliminary data of their current human trial with their technology.
- Some presentations and discussions tackles the inequality in treatment access in the US and in the world, an important topic that is getting more and more attention.

INSULIN PUMPS AND ARTIFICIAL PANCREAS

Insulet – Omnipod 5 in 2-6 years T1D

- Insulet presented the results of their pivotal trial in **T1D** aged **2 to 5.9 years**. Single-arm open-label trial in **n=80 T1D** during **3 months.**
  - Inclusion criteria: ≥ 2 years, < 6 years, A1c < 10%, CSII or MDI, no history of severe hypoglycemia in the past 6 months
  - Baseline: **4.7 years**, weight = 19.7kg, **A1c = 7.4%**, total daily insulin = 13.7UI (between 5.3 & 27.1UI), **15% where MDI users**
  - Results:
    - **A1c reduced from 7.4% to 6.9%** (p<0.05)
    - 54% had A1c < 7.0% compared to 31% at baseline
    - **TIR (70-180mg/dL) increased from 57.2% to 68.1% (p<0.05)**
    - Reduced time < 70mg/dL from 2.2% to 1.9% (p<0.05), no differences for time < 54 mg/dL
    - **Sleep quality of the parents where significant improved** (measured by the Pittsburgh Sleep Quality Index)
    - 65% reached more than 60% of TIR and less than 4% of TBR
    - No severe hypoglycemia and DKA

Daily Glucose Profile with AID System vs. Standard Therapy

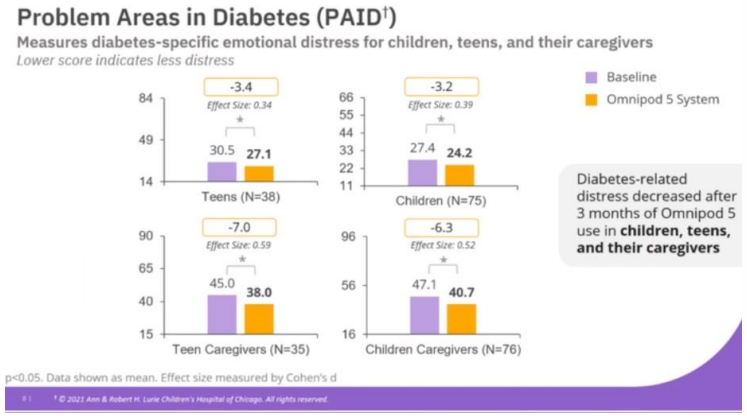


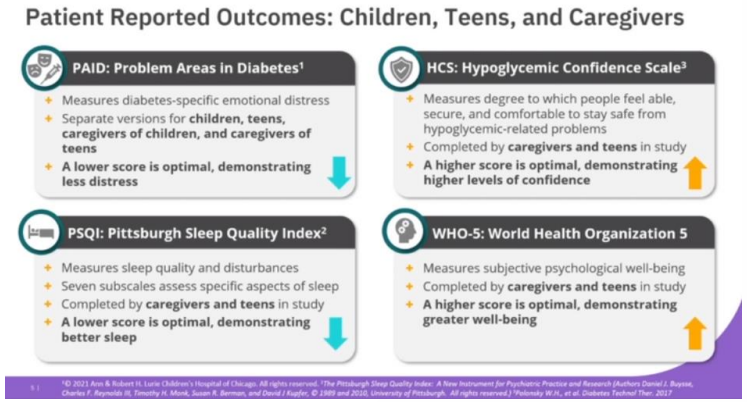
- System remained in **Automated Mode** for median **97.8%** of total AID phase duration
- Most participants selected the **120 mg/dL** target (**42%** of cumulative study time) or **110 mg/dL** target (**33%** of study time)
- Prominent improvements were seen in the overnight period, the morning, and into the afternoon
- Coefficient of variation overnight reduced from **34.7%** to **32.1%** (p<0.01)

Insulet confirms results observed in older populations with still good TIR improvement with low hypo. Similar results as Control-IQ in the same population (ADA 2020).

Insulet – Quality of life of Omnipod 5 in Youth

- **Quality of life reported outcomes of children** (6-11.9 years), **teens** (12-17.9 years), and their caregivers using **Omnipod 5** during the pivotal trial (glycemic results presented at ENDO 2021)
- Single-arm, open label trial in **T1D during 3 months**, A1c < 10%, no history of severe hypoglycemia in the past 6 months
- Baselines: **Children**: **n=83, 9.4 years**, weight = 34kg, A1c = 7.5%, 9.6% where MDI users
- Baselines: **Teens**: **n=42, 14 years**, weight = 57kg, A1c = 7.9%, 16.7% where MDI users
- Results (4 index studied):
  - **Problem Areas in Diabetes** (PAID): **Significantly decreased** in all categories
  - **Hypoglycemic Confidence Scale** (HCS): **Significantly improved for children caregivers**, trend toward improvement for the others
  - **Pittsburgh Sleep Quality Index** (PSQI): Trend toward decrease for all categories, some subscales (sleep disturbance, duration of sleep and overall sleep quality) where significantly improved in caregivers of children
  - **World Health Organization Well-Being Index** (WHO-5): **Significantly improved in children caregivers**, trend toward improvement for the others

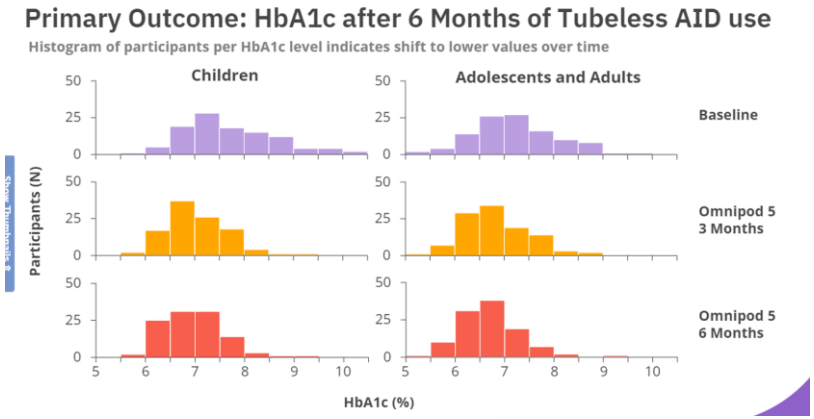




Use of diabetes specified index and more classical index (as WHO-5). Improvement of quality of life especially visible in children and their caregivers.

Insulet – Omnipod 5 – Extension of the pivotal trial

- Insulet presented the results of the extension phase of the pivotal trial testing their hybrid-closed loop Omnipod 5 (Pivotal results previously presented at ENDO 2021 and reported in my Q1 2021 report)
- Single-arm, open label pivotal trial **in n=241 T1D** testing **Omnipod 5 during 3+3 months**
- Inclusion criteria: **6-70 years old**, T1D for at least 6 months, **A1c < 10%**, without history of severe hypoglycemia in the past 6 months, **CSII or MDI**
- Pause of 3 months in the middle of the trial (median after 44 days) where patients would use Omnipod dash or another system.
- Baselines:
  - **Children** (6-13.9 years): **n=112**, **10 years**, **A1c = 7.7** ± 0.9%, 39kg, 0.85 UI/kg/day, 11.6% MDI
  - **Adults** (14-70 years): **n=128**, **37 years**, **A1c = 7.2** ± 0.9%, 79kg, 0.61 UI/kg/day, 18% MDI
- Main results of the extension compared to the results after 3 months:
  - **A1c** numerically improved in children (6.9% vs 7.0%), and **significantly improved in adolescents/adults** (6.7% vs 6.8%, $p < 0.05$)
  - **No significative change in TIR and TBR**



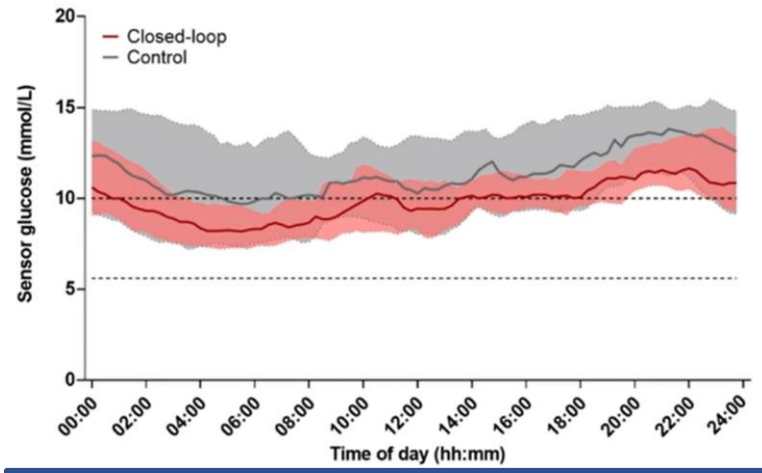
Data that confirms good results obtained during their pivotal at 6 months. 1st time they share this histogram of A1c.

CLIO – Real world quality of life observations with Control-IQ

- **Observational** post-approval, single-arm study in **n=700 T1D aged 6 years or more**, **initiating Tandem Control-IQ** system in the US (sub-population of the ongoing trial). Measures at **3 months.**
- Baselines: **80.1% were already using an insulin pump**, 89% a CGM, 81.3% had a HbA1c < 8.5%
- Results:
  - **Dawn Impact of Diabetes Profile** (DIDP) **significantly decreased** from 4.79 to 4.41
  - **Diabetes Impact** (DI) **significantly decreased** from 4.79 to 3.26
  - **Diabetes satisfaction** increased from 7.06 to 8.77
  - **Sleep quality highly improved**
- Data yet to be published

CamAPS – Full closed-loop – Fiasp – T2D with end stage renal disease (dialysis)

- Results of a cross-over, open-label AP-RENAL trial in UK/Swizerland testing the **CampAPS fully closed-loop system** with **Fiasp** vs standard insulin therapy during **20 days** in **adults T2D** using insulin (A1c < 11%) and **with end-stage renal disease requiring dialysis**
- System: **CamAPS** algorithm with **Dana** insulin pump and Dexcom **G6** CGM and Glooko/Diasend to upload CGM data. **Standard insulin therapy is MDI** with masked Dexcom G6 CGM.
- Baselines: **68.3 years**, **A1c = 7.2%,** BMI = 30.4 kg/m², on dialysis for 1.5 years
- Main results:
  - Time in range (100-180mg/dL): 52.8% vs 37.7%, p<0.001
  - **Time in range (70-180mg/dL): 57.1% vs 42.5%, p=0.002**
  - Time < 70mg/dL: 0.12% vs 0.17, p=0.040
  - **Time in range during dialysis days (100-180mg/dL): 53.9% vs 37.2%**
  - 1 severe hypoglycemia in the closed-loop arm
  - Improvement of quality of life ->



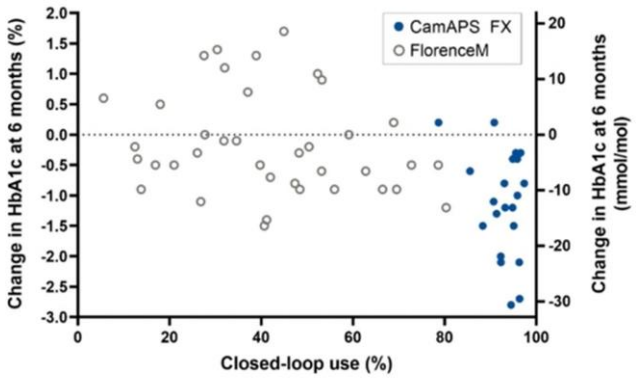
Good results obtained with a full closed-loop system in this population.
The control being MDI, it is difficult to estimate how the system will compare with other insulin pump technologies.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Q1. I was happy to have my glucose levels controlled automatically by the system	22 (92)	2 (8)	0 (0)	0 (0)	0 (0)
Q2. I spent less time to manage my diabetes (glucose testing, adjusting insulin therapy, keeping a diary, data review…)	19 (79)	3 (13)	2 (8)	0 (0)	0 (0)
Q3. I was less worried about my glucose control	20 (83)	1 (4)	3 (13)	0 (0)	0 (0)
Q4. I slept better during the nights	11 (46)	1 (4)	10 (42)	1 (4)	1 (4)
Q5. I would recommend Closed-Loop to others	23 (96)	1 (4)	0 (0)	0 (0)	0 (0)

CamAPS – Hybrid closed-loop in Youth – DAN05

- Results of the DAN05 trial testing **CamAPS hybrid closed-loop** system in **young people with T1D**
- Open-label trial testing FlorenceM system in the US and **CampAPS FX system in the UK vs insulin pump** treatment in **T1D aged 6-<19 years**, **already using an insulin pump**, A1c between 7 & 10%, using between 2 & 15 UI of insulin per day, during **6 months**
- FlorenceM: Cambridge algorithm on a phone with Medtronic 640G insulin pump and Guardian 3 CGM sensor
- **CamAPS FX: Cambridge algorithm on a phone with Dana Diabecare RS insulin pump and Dexcom G6 CGM sensor**
- Baselines: **13.1-12.8** years, **A1c: 8.2-8.3%,** 69-65% using a CGM
- Main results:
  - A1c improvement: 7.6% vs 8.1%, p=0.020
  - Time in range (3.9-10.0mmol/L): 54% vs 47%, p=0.004
  - Time < 3.9mmol/L: 6.1% vs 5.4%
  - US patients using FlorenceM had a low usage of closed-loop mode (less than 60% during the 1st month, less than 40% during the last month, due to calibration of the sensor and hardware failures), while the closed-loop mode was high with CamAPS (more than 90%)
  - **A1c improvement in the CamAPS cohort: 6.8% vs 7.9%, p<0.001**
  - **TIR in the CampAPS cohort: 63% vs 49%, p<0.001**
  - Time < 3.9 mmol/L in the CampAPS cohort: 10.8% vs 6.3%, p=0.15

Closed-loop use and change in HbA1c

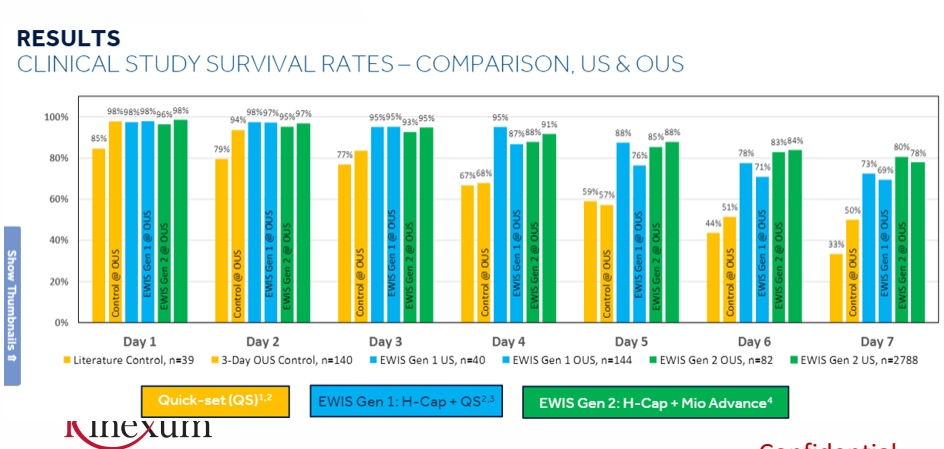


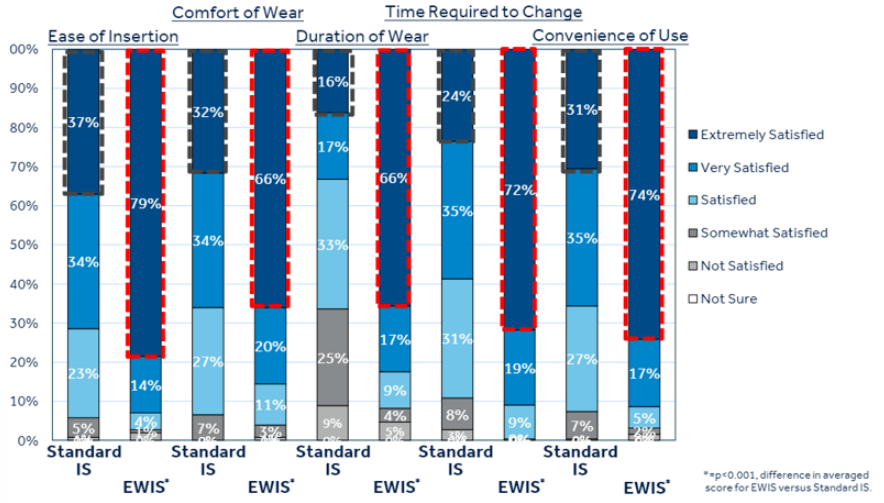
US system using Medtronic pump and CGM seems to not work very well, with really low time in auto-mode (as or more than observed with the 670G). Better results in EU.
High time in hypoglycemia, higher than the control.

Medtronic – EWIS – Pivotal trial

- Medtronic presented in two posters the results of their **US** **pivotal trial** testing their **extended wear infusion site** (EWIS)
- Open label, single arm trial testing the EWIS system in **n=259 adults T1D** using their **670G pump** with **Humalog or Novolog**. All patients used 12 EWIS sets during 174h or until set failure.
- Baselines: **45 years**, weight 85.6kg, Diabetes duration = 27 years, A1c = 7.2%, 92.7% are white
- Main results:
  - 0.13% of rate of infusion set failure at 7 days with Humalog, 0.41% with Novolog
  - No change in A1c, +2.8% of time in range in the first 3 days compared to 3 days infusion sets (p<0.001)
  - Increased satisfaction compared to 3 days wear infusion set

Good survival rate as observed in Europe, similar to better than 3 days wearing infusion sites currently used. The product was recently launced in Europe. This trial was the last one before submission in the US.





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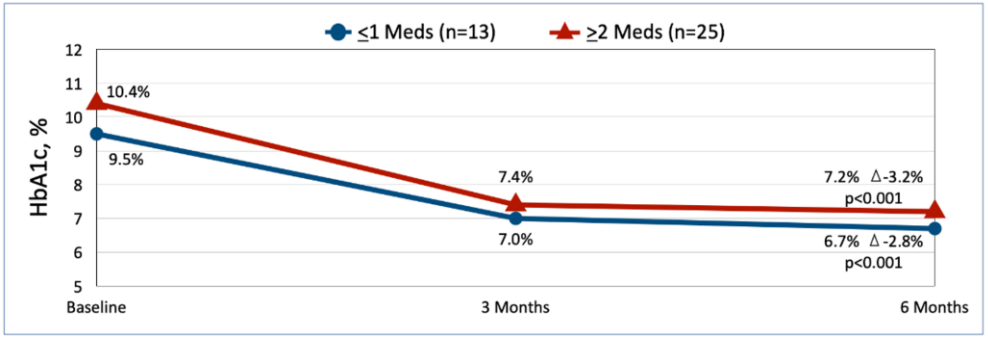
CGM AND DIGITAL HEALTH

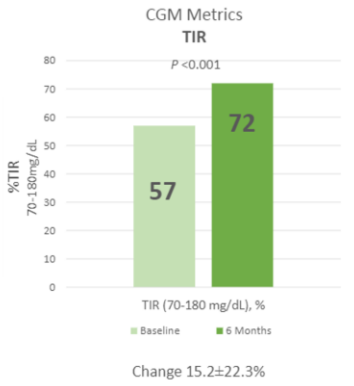
Dexcom – Use of CGM in T2D treated with less intensive therapy

- Among numerous presentations and posters supporting the use of CGMs in different populations including T2D, Dexcom presented a convincing, single-arm trial testing their **G6 CGM in n=38 T2D using basal insulin only or non-insulin therapies**
- Baselines: **54.7 years, A1c = 10.1%**, BMI = 35.6 kg/m², Time in range (70-180mg/dL) = 57.0%
- Main results:



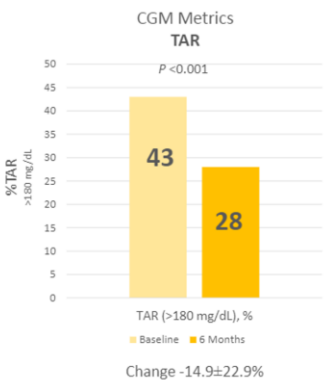
Very good glucose improvement, or even better than observed, in T1D. It brings additional support to the use of CGM in T2D, main current target of market expension.

Time in Range



Change 15.2±22.3%

Time Above Range



Change -14.9±22.9%

Change -8.4±16.7%

Eversense – PROMISE – US pivotal 180 days

- Senseonics presented the results of their **US pivotal trial**, PROMISE, open-label, single-arm, testing 2 versions of their **180 days wear implantable CGM** in **n=181 adults** diabetes patients. Eversense sensor with **2 calibrations/day to day 21 and 1 calibration/day after.**
- Baselines: **48.6 years**, 22.0 years duration of diabetes, 69.6% of T1D, A1c = 7.6%
- Main results:
  - Primary sensor: Overall MARD of 9.1% with higher MARD at day 1 (11.0%) and day 180 (10.4%). 92.9% of the CGM readings within 20/20% of YSI values. 65% of survival at day 180.
  - **SBA sensor** (**new sensor** with specific chemistry modifications): Overall **MARD of 8.5%**, 11.2% at day 1 and **7.4% at day 180**. **93.9%** of the CGM readings **within 20/20%** of YSI values. **90% of survival at day 180.**
  - **A1c improved from 7.6**% to 7.2% at day 90 and **7.3% at day 180**
  - **No failure to remove the sensor on first attempt**
  - 2 mild skin infections

Good accuracy in results supporting potential future approval of a 180 days device in the US. Senseonics is also targeting 1 year in the future.

CGM data integration into the Electronic Health Record

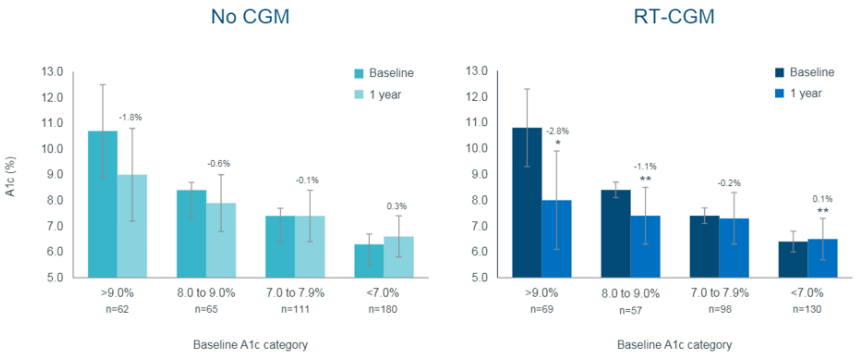
- Dr. Criego, from the International Diabetes Center (IDC), presented their recent work allowing **integration of CGM data into the Electronic Health Record** (EHR).
- Currently, in the US, each device that produces electronical data (CGMs, smart-pens, insulin pumps) use their own application/software to synthetise these data and share them with HCPs; each of them being different, sharing sometimes the way to present data (as with the AGP). But, none communicate directly with the EHR.
- **The IDC managed to first integrate data of Abbot Libre Freestyle CGM into the EHR facilitating the access to data by the HCP.**
- The IDC is **currently working on integrating other data.**
- The IDC published during the conference a press release on this topic.

It is an important step towards standardization of diabetes data. Integrating diabetes data will facilitate the work of HCPs, especially for HCPs that doesn't have a team of diabetes experts behind them. It may benefit patients in the end and possibly have an impact on diabetes technology use.

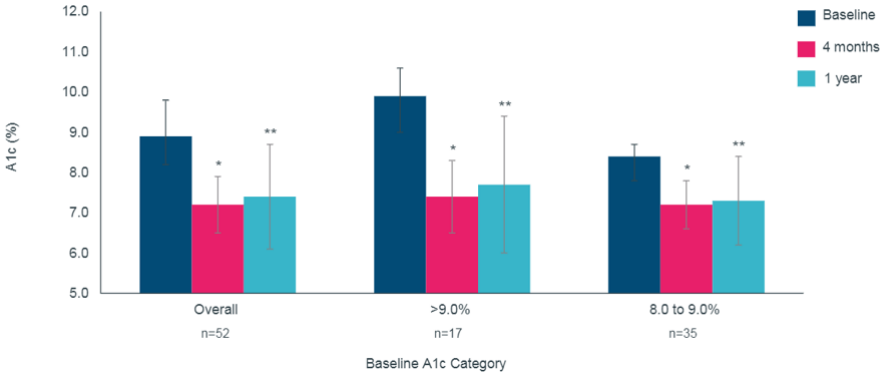
Onduo – Real-world data

- 2 posters on real-world data analysis:
- Analysis 1: **1 year of use of Onduo** virtual care program in **n=772 adults T2D**, without CGM, or initiating CGM
  - Baselines: **54.3 years, A1c=7.7%,** BMI=35.9 kg/m², 32% are using insulin
- Analysis 2: Looking at patients that were previously involve in a 4 month trial with active Onduo program intervention. Looking at these patients **7 months after, without the active Onduo program. N=52 adults T2D patients.**
  - Baselines: **57.9 years**, **A1c = 8.9%**, BMI = 33.5 kg/m²

Analysis 1



Analysis 2

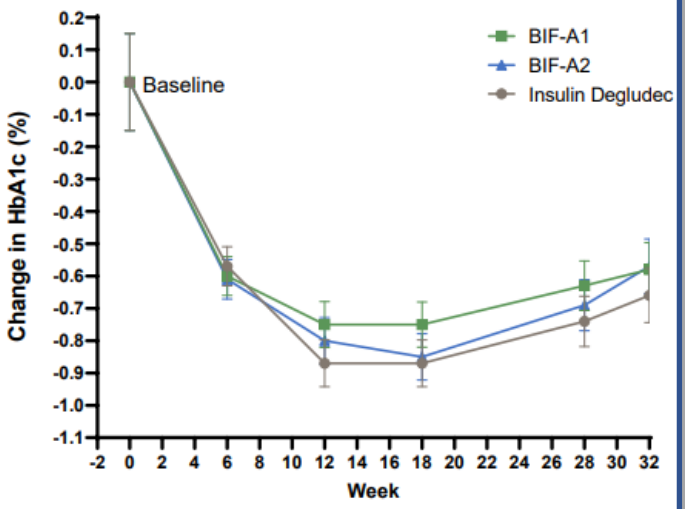


Clear glucose improvement in patients with high A1c. It seems that this glucose improvement can be maintained once the active Onduo program is stopped, possibly due to an education effect.

INSULIN THERAPIES

Eli Lilly – Basal Insulin Fc – Phase 2 results

- Eli Lilly presented results of a Phase 2 testing their **weekly insulin in adults T2D**. Some of the results were previously presented at ENDO 2021 and results details are available on ct.gov
- Open-label Phase 2 trial comparing **BIF** with 2 different dosing algorithms to **daily insulin degludec** in **n=399 adults** with **T2D** already using basal insulin and up to 3 oral antidiabetes medications during **32 weeks**. A1c between 6.5 & 10%, BMI between 20 & 45 kg/m².
- Baselines: **60.2 years, A1c = 8.1%,** BMI = 32.2 kg/m²
- **BIF was non-inferior to insulin degludec as measured by A1c change**
- No important differences in adverse events with slightly less number of hypoglycemia with BIF (significant difference for the 1st algorithm vs degludec)
- Slides



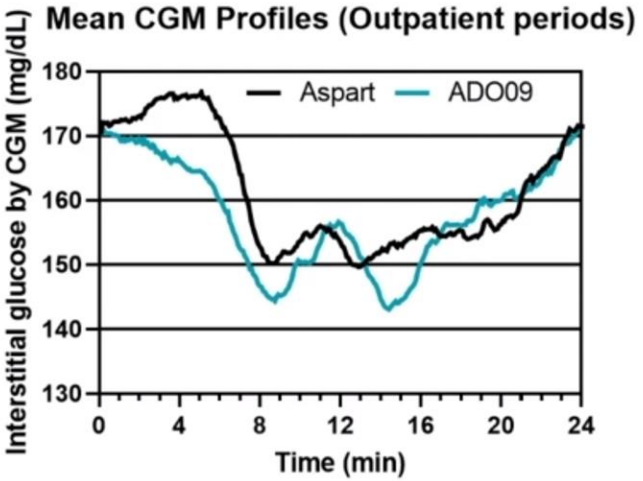
Similar results as observed with insulin Icodec from Novo with quite good results on the hypo side (they found a good algorithm to use it). They used degludec insulin as comparator, while Novo used glargine, degludec being known to have less hypos.

n (%)	Insulin Degludec (N=132)	BIF-A1 (N=135)	BIF-A2 (N=131)
Treatment-emergent adverse events	74 (56.1)	79 (58.5)	87 (66.4)
Serious adverse event	10 (7.6)	7 (5.2)	8 (6.1)
Hypoglycemia ≤70 mg/dL (3.9 mmol/L)			
Number of subjects	117 (88.6)	124 (91.9)	117 (89.3)
Number of episodes	2494	1671	1632
Hypoglycemia <54 mg/dL (3.0 mmol/L)			
Number of subjects	76 (57.6)	66 (48.9)	68 (51.9)
Number of episodes	240	174	155
Severe hypoglycemia	0	0	2 (1.5)
Treatment-emergent anti-drug antibodies	1 (0.9)	2 (1.5)	3 (2.3)

Abbreviations: N, number of subjects in the analysis population; n, number of subjects in the specified category.

Adocia – ADO09 (insulin + pramlintide) – Phase 2 in T1D

- 2nd part of a Phase 2 trial, double-blind, cross-over, testing **MDI ADO09** (prandial fixed ratio of **pramlintide and human insulin** A21G) **vs insulin aspart**, in **n=15 adults T1D** requiring between **40 & 75 UI/day**, during **24 days**
- Inclusion criteria: 18-64 years, A1c ≤ 9.0%, without gastroparesis
- Baselines: **46.5 years, A1c = 7.4%**, **Weight = 101.2kg**
- Main results:
  - Improvement of post prandial glucose, slowing down of gastric emptying and post prandial glucagonemia reduction after a meal test similar to what was observed in previous trials
  - **Improvement of time in range (70-180 mg/dL) = +58min = +4%, p=0.0432**
  - **Increase time < 70 mg/dL = +13min = +0.9%, p=0.1486**
  - Increase time < 54 mg/dL = +4min = +0.3%, p=0.0766
  - Decrease total daily insulin: 66.0 UI/day vs 77.8 UI, -15.2%, p=0.0027
  - **Weight reduction: -1.6kg vs +0.4kg, (-2% vs aspart), p=0.0065**
  - **20% increase number of hypoglycemia with ADO09**
  - Expected adverse events (gastrointestinal disorders)



Similar results as in part 1, glucose control and weight loss similar to what is known with Symlin.
Increased number of hypoglycemia that could be decreased with a better insulin titration protocol.
TIR baselines were not disclosed, which doesn't allow a good idea on the efficacy of the drug.

INCRETIN BASED THERAPIES

ELI Lilly - Tirzepatide Phase 3 results (1/5)

- In multiple presentations, Eli Lilly showed results of their SURPASS Phase 3 program testing tirzepatide in adults T2D.
- Double-blind or open label depending on the comparator, testing **3 doses of tirzepatide (5, 10 & 15mg**) vs placebo or an active comparator during **40 weeks**

Link to ct.gov	SUPRASS-1	SURPASS-2	SURPASS-3	SURPASS-5
Link to the slides	**SURPASS-1**	**SURPASS-2**	**SURPASS-3**	**SURPASS-5**
Comparator	**Placebo**	**Semaglutide 1mg**	**Insulin degludec**	**Placebo**
Add-on therapies	None	Metformin	Metformin +/- SGLT-2 & SUs	Insulin glargine +/- metformin
A1c inclusion	7-9.5%	7-10.5%	7-10.5%	7-10.5%
BMI inclusion	≥ 23 kg/mg	≥ 25 kg/mg	≥ 25 kg/mg	≥ 23 kg/mg
Number of patients	478	1,878	1,437	475
Age	54.1 ± 11.9 years	56.6 ± 10.4 years	57.4 ± 10.0 years	60-61.5 years
A1c baseline	**7.94 ± 0.87%**	**8.28 ± 1.03%**	**8.17 ± 0.91%**	**8.3%**
Baseline weight	**85.9 ± 19.8kg**	**93.7 ± 21.9kg**	**94.3 ± 20.1kg**	**95.2kg**

ELI Lilly - Tirzepatide Phase 3 results (2/5)

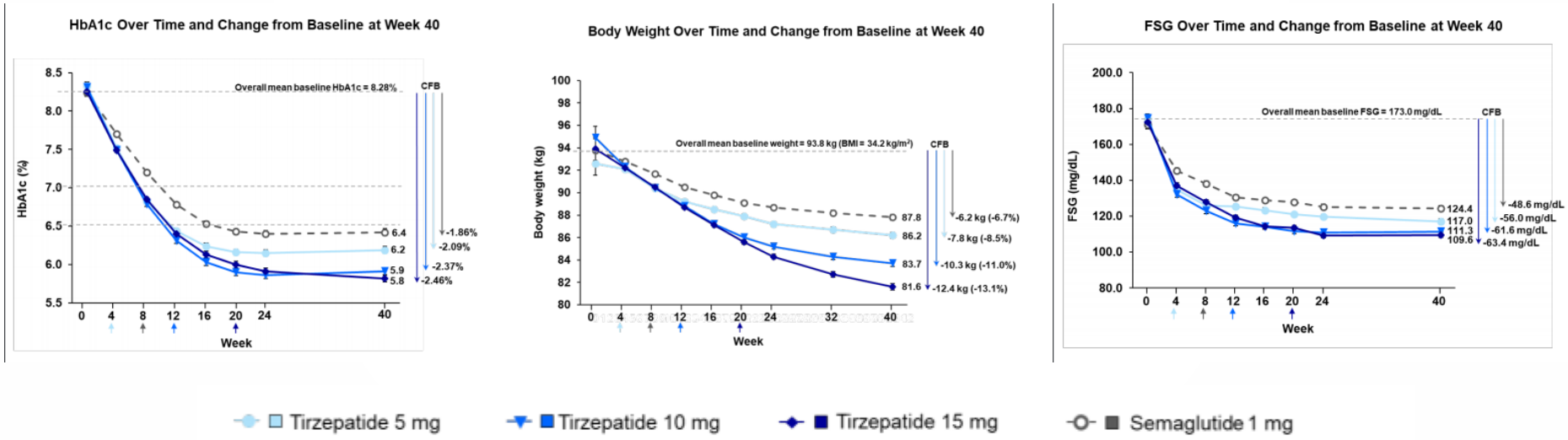
- Main results (efficacy-estimand):

	SUPRASS-1			SURPASS-2			SURPASS-3			SURPASS-5		
Dose	**5mg**	**15mg**	**Pl.**	**5mg**	**15mg**	**Sema**	**5mg**	**15mg**	**iDeg**	**5mg**	**15mg**	**Pl.**
A1c decrease	**-1.87%***	**-2.07%***	**+0.04%**	**-2.09%***	**-2.46%***	**-1.86%**	**-1.93%***	**-2.37%***	**-1.34%**	**-2.23%***	**-2.59%***	**-0.93%**
A1c < 5.7%	34%*	52%*	1%	29.3%*	51%*	20%	26%*	48%*	5%	26%*	62%*	3%
Weight loss	-7kg*	-9.5kg*	-0.7kg	-7.8kg*	-12.4kg*	-6.2kg	-7.5kg*	-12.9kg*	+2.3kg	-6.2kg*	-10.9kg*	+1.7kg
Weight loss ≥ 10%	31%*	47%*	1%	36%*	65%*	25%	37%*	69%*	3%	23%*	51%*	1%
Nausea	11.6%	18.2%	6.1%	17.4%	22.1%	17.9%	11.5%	23.7%	1.7%	12.9%	18.3%	2.5%
Decrease appetite	4.1%	8.3%	0.9%	7.4%	8.9%	5.3%	6.1%	12.0%	0.6%	6.9%	14.2%	1.7%
Injection site reaction	3.3%	1.7%	0%	1.9%	4.5%	0.2%	0.3%	2.2%	1.7%	3.4%	6.7%	0.8%
Treatment disc. Due to AE	3.3%	6.6%	1.7%	6.0%	8.5%	4.1%	7.0%	10.9%	1.4%	6.0%	10.8%	2.5%

* p<0.001 vs comparator

ELI Lilly - Tirzepatide Phase 3 results – SURPASS-2 (3/5)

- Here are selected graphs from SURPASS-2 trial (vs semaglutide 1mg):



ELI Lilly - Tirzepatide Phase 3 results – SURPASS-1 – patient reported outcomes (4/5)

- Eli Lilly presented in a separate presentation **patient reported outcomes** of SURPASS-1 (vs placebo) on **n=375**. Increased scores indicate better outcomes. Here are reported differences with the placebo arm (slides of the presentation):

Index	5mg	10mg	15mg
EQ-5D-5L (overall health status: mobility, self-care, usual activities, pain/discomfort & anxiety/depression)	+0.03 (b. 0.84)	+0.0.3 (b.0.88)	+0.04 (b. 0.88)
EQ VAS (health-related quality of life reported on a vertical visual scale)	+4.0* (b. 80.4)	+5.1* (b.82.8)	+6.2* (b.83.8)
IW-SP (self perception relating to their body weight)	+4.7 (b.65.7)	+8.6* (b.67.6)	+7.9* (b.68.2)
APPADL (self-reported ability to perform tasks of daily living)	+2.7 (b. 70.7)	+3.0 (b. 79.4)	+4.0 (b.79.7)

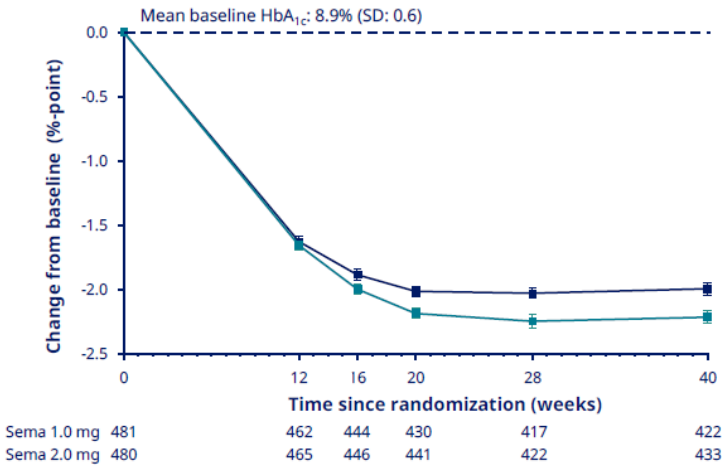
* $p<0.05$ vs placebo

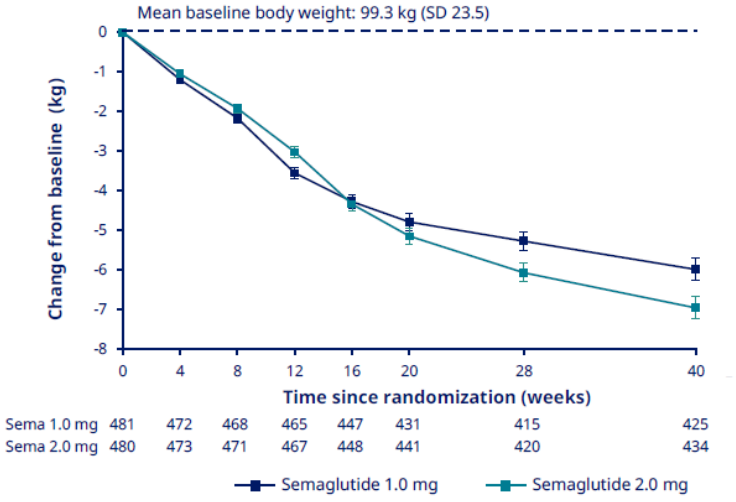
ELI Lilly - Tirzepatide Phase 3 results – Comments (5/5)

- One of the most anticipated results of this conference. They presented consistent results between their different trials with very good glucose control and weight loss data.
- Their trial comparing tirzepatide with semaglutide shows a clear benefit for tirzepatide, both in glucose control and weight loss.
- They manage to reduce gastrointestinal disorders compared to what was observed in their Phase 2 with a slower doses escalation protocol. Even with this protocol, they got a faster glucose improvement and weight loss than with semaglutide. But, they still have more gastrointestinal disorders and more discontinuations than with semaglutide, that may have an impact on patient adherence to the treatment.
- This drug is also studied in various indications including obesity, NASH, and CV diseases.

Novo Nordisk - SUSTAIN FORTE – Semaglutide 2mg vs 1mg in T2D

- Novo Nordisk presented detailed results of their **Phase 3 SUSTAIN FORTE** testing **semaglutide 2mg vs 1mg in adults T2D**:
  - Double-blind trial, in **n=961 adults T2D**, A1c between 8.0 & 10.0%, with stable dose of metformin w/o SU, with eGFR ≥ 30 mL/min/1.73m², during **40 weeks**
  - Baselines: **57.9-58.2 years, A1c = 8.8-8.9%, Weight = 98.6-100.1 kg**
  - Main results (trial product estimand):
    - **-0.23% A1c** (p=0.0003, -1.9% vs -2.2%)
    - **-0.93kg weight loss** (p=0.0155, -6.0 vs -6.9kg)
    - 57.5% of patients with A1c < 7% with 1mg vs 67.6% with 2mg
    - 22.6% of patients with weight loss ≥ 10% with 1mg vs 28.4% with 2mg
    - Difference in weight reduction is more important in patients with lower A1c (< 9%) and in patients with lower BMI (< 35kg/m²)
    - **Slightly higher patients with gastrointestinal adverse events (30.8% with 1mg vs 34.0% with 2mg)**
    - Stronger decreased appetite (3.8% with 1 mg vs 6.1% vs 2mg)
- Slides

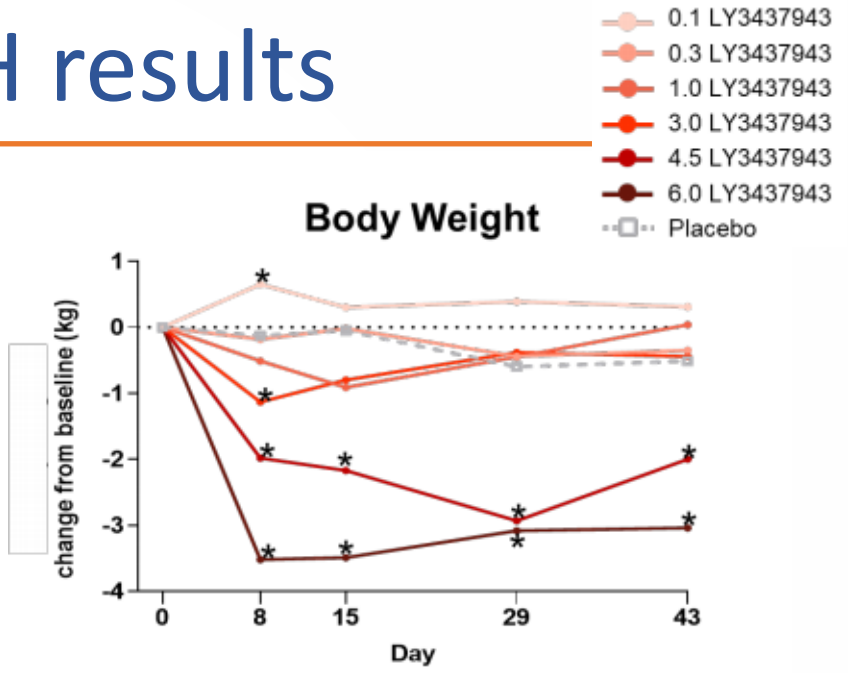




Small improvement, but with almost no increase in adverse events. In a similar strategy with dulaglutide, Lilly showed better difference, but possibly due to the low first dose of dulaglutide approved.

ELI-LILLY – GIP/GLP-1/Glucagon co-agonist – FIH results

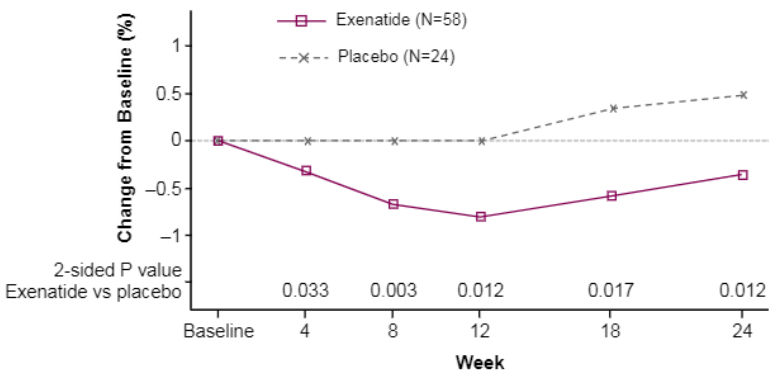
- Eli Lilly presented the results of their **first in human** testing their **triple agonist** (LY3437943) in a double-blinded, placebo-controlled, single-ascending dose study in **n=45 healthy adults**
- Dose tested: 0.1mg, 0.3mg, 1mg, 3mg, 4.5mg & 6mg
- Baselines: **22-61 years, 48-105kg**
- **Single dose were well tolerated up to 3mg.** Higher doses were associated with increased incidence of classical gastro-intestinal adverse events.
- PK data support a **once-weekly dosing** and confirms dose-proportion
- **Single dose of 4.5 & 6mg already shows significant decrease in body weight**
- Slides of the presentation
- Lilly also presented encouraging pre-clinical data showing better weight loss than tirzepatide or cotadutide in DIO mice (slides)
- Lilly also presented results of a similar study with their **GLP-1/glucagon** agonist with good safety data, **PK data that support once weekly dosing, but less strong weight reduction** (slides)

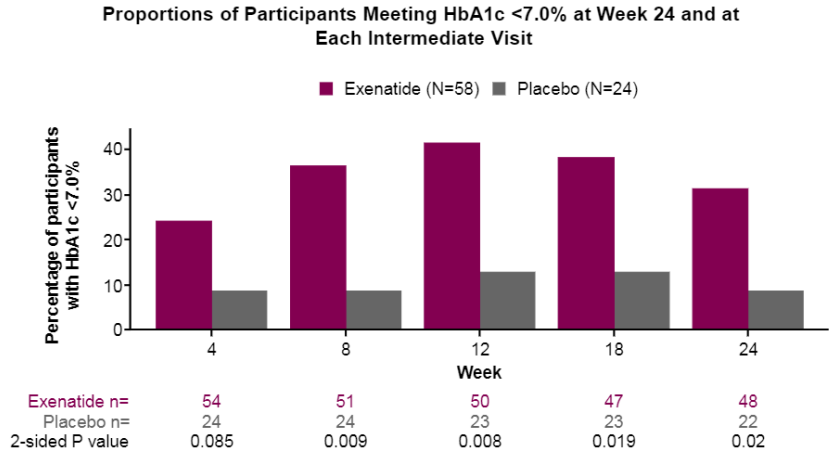


Very good weight loss results after a single dose of the drug, but associated with high adverse events. Longer data needed to see how future dose escalation protocol will allow the finding of a good balance between weight loss and AE.

Astrazeneca – Bydureon in Youth

- Phase 3 trial, double-blind, placebo-controlled testing **Bydureon 2mg in n=83 T2D aged between 10 and 18 years** with A1c between 6.5 & 11% if they are not taking insulin or SU or between 6.5% & 12% otherwise, during **12 weeks**
- Baselines: 15.1 years, no A1c or weight baselines disclosed
- Main results:
  - **A1c reduction of -0.36% vs +0.49 %, p=0.012**
  - **Weight loss of -0.59kg vs + 0.63kg, p=0.307**
  - No increase in gastrointestinal disorders, but increased in the number of hypoglycemia (8 vs 1)
- Results published on ct.gov

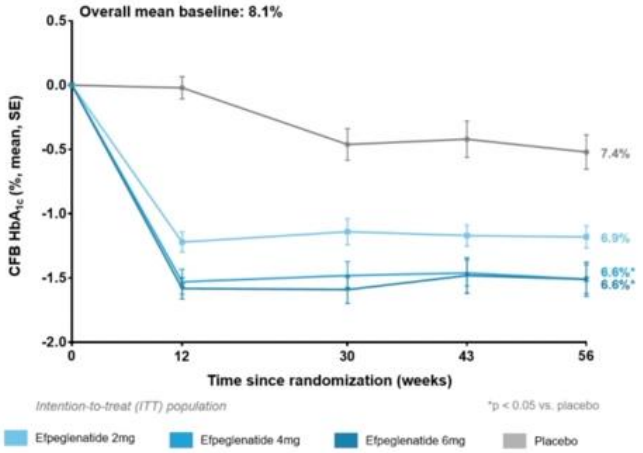




Coherent results with what is observed in adults, but lower than with semaglutide or tirzepatide than should be approved at some point for adolescent. Currently, only liraglutide is approved in the US for adolescents.

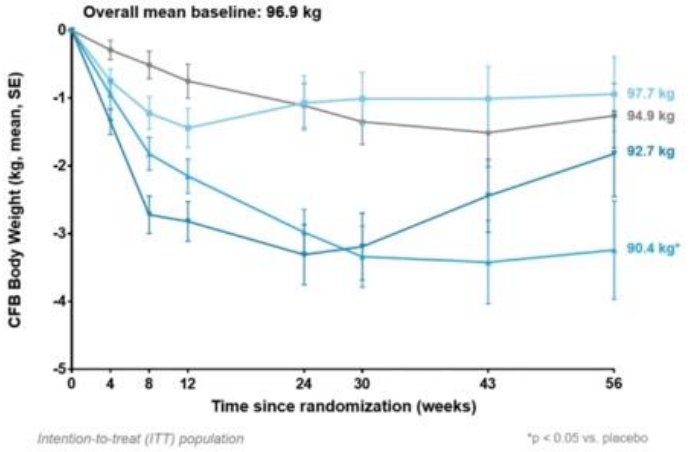
Hanmi – Efpeglenatide – AMPLITUDE-M Phase 3

- Hanmi presented the results of the Phase 3 AMPLITUDE-M with their **weekly GLP-1** previously licensed to Sanofi
  - Double-blind, placebo-controlled Phase 3 trial testing **3 doses of efpeglenatide** (2, 4 & 6mg) during **56 weeks in n=406 adults T2D**
  - Inclusion criteria: adults T2D, treated with diet and exercice, A1c between 7.0 & 10.0% with different exclusion criteria to avoid comorbidities (no BMI/weight restriction)
  - Baselines: **56.3-59.6 years, A1c = 7.97-8.09%, Weight = 95.2-98.0kg**
  - Main results (intend to treat):



Good glucose control, but small weight loss compared to other GLP-1s.

Results at 56 weeks	2mg	4mg	6mg	Placebo
A1c	6.9%	6.6%*	6.6*	7.4%
Fasting plasma glucose	7.5mmol/L*	7.0mmol/L**	7.0mmol/L**	8.2mmol/L
Weight	97.7kg	90.4kg*	97.7kg	94.9kg
Gastrointestinal disorders	36.3%	46.6%	60.6%	26.5%
Discontinuation due to adverse events	8.8%	9.7%	17.2%	4.9%



*p<0.05, **p<0.001 vs placebo

Hanmi – Efpeglenatide – AMPLITUDE-O CV trial

- Hanmi presented the results of the Phase 3 **AMPLITUDE-O** **Cardiovascular** trial with their weekly GLP-1. Results were also published during the conference
  - Double-blind, placebo-controlled Phase 3 trial testing **efpeglenatide** (4 & 6mg) in **n=4,076 adults T2D** during a **median time of 1.81 years** on top of standard of care
  - Inclusion criteria: adults T2D, A1c > 7%, with **established CV disease**, **or aged 50+ (male) or 55+ (female), or with eGFR between 25 & 60 mL/min/1.73m² and at least one CV risk factor**
  - Baselines: **64.5 years**, **90% with prior CV disease**, 32% with eGFR < 60 mL/min/1.73m², **BMI = 32.7 kg/m²**, A1c = 8.9%, eGFR = 72 mL/min/1.73m², 63% are using insulin, 15% SGLT-2s
  - Main results:
    - Summary of the different glycemic, CV and renal outcomes ->
    - Similar use of different diabetes therapies between the 2 arms at the end of the trial

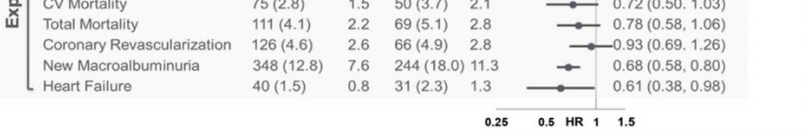
Effect of Efpeglenatide on Clinical Measures

Summary

	Efpeglenatide LSM ± SE	Placebo LSM ± SE	Adjusted LSM Difference 95% CI	P
HbA1c (%)	-1.42 ± 0.02	-0.17 ± 0.03	-1.24 (-1.32, -1.17)	<0.001
Systolic BP (mm Hg)	-2.56 ± 0.23	-1.08 ± 0.32	-1.48 (-2.19, -0.76)	<0.001
Diastolic BP (mm Hg)	0.47 ± 0.14	-0.11 ± 0.19	0.58 (0.15, 1.01)	0.008
Pulse Pressure (mm Hg)	-3.01 ± 0.20	-0.96 ± 0.27	-2.05 (-2.65, -1.44)	<0.001
Heart Rate (bpm)	4.62 ± 0.15	0.72 ± 0.21	3.89 (3.43, 4.36)	<0.001
Body Mass Index (kg/m²)	-1.15 ± 0.03	-0.23 ± 0.05	-0.92 (-1.03, -0.81)	<0.001
Body Weight (kg)	-3.21 ± 0.10	-0.62 ± 0.13	-2.59 (-2.90, -2.29)	<0.001
LDL Cholesterol (mmol/L)	-0.05 ± 0.02	0.02 ± 0.02	-0.07, (-0.12, -0.03)	0.003

Summary of CV/Kidney Effects of Efpeglenatide

	Outcome	N (%)	%/y	N (%)	%/y	HR (95%CI)	
Significant	MACE	189 (7.0)	3.9	125 (9.2)	5.3	0.73 (0.58, 0.92)	Primary
	MACE/Cor Revasc/UA	257 (9.5)	5.4	158 (11.6)	6.8	0.79 (0.65, 0.96)	Secondary
	Renal Composite	353 (13.0)	7.7	250 (18.4)	11.6	0.68 (0.57, 0.79)	
	MACE or Death	216 (7.9)	4.5	143 (10.5)	6.0	0.73 (0.59, 0.91)	
	Renal (no MA) or Death	121 (4.5)	2.5	76 (5.6)	3.1	0.77 (0.57, 1.02)	
	MACE, Death, HF, Renal	243 (8.9)	5.1	164 (12.1)	7.0	0.71 (0.59, 0.87)	
Exploratory	Fatal or Nonfatal MI	91 (3.3)	1.9	58 (4.3)	2.4	0.75 (0.54, 1.05)	
	Nonfatal MI	85 (3.1)	1.7	53 (3.9)	2.2	0.78 (0.55, 1.10)	
	Fatal or Nonfatal Stroke	47 (1.7)	1.0	31 (2.3)	1.3	0.74 (0.47, 1.17)	
	Nonfatal Stroke	41 (1.5)	0.8	25 (1.8)	1.0	0.80 (0.48, 1.31)	
	CV Mortality	75 (2.8)	1.5	50 (3.7)	2.1	0.72 (0.50. 1.03)	
	Total Mortality	111 (4.1)	2.2	69 (5.1)	2.8	0.78 (0.58, 1.06)	
	Coronary Revascularization	126 (4.6)	2.6	66 (4.9)	2.8	0.93 (0.69. 1.26)	
	New Macroalbuminuria	348 (12.8)	7.6	244 (18.0)	11.3	0.68 (0.58, 0.80)	
	Heart Failure	40 (1.5)	0.8	31 (2.3)	1.3	0.61 (0.38, 0.98)	

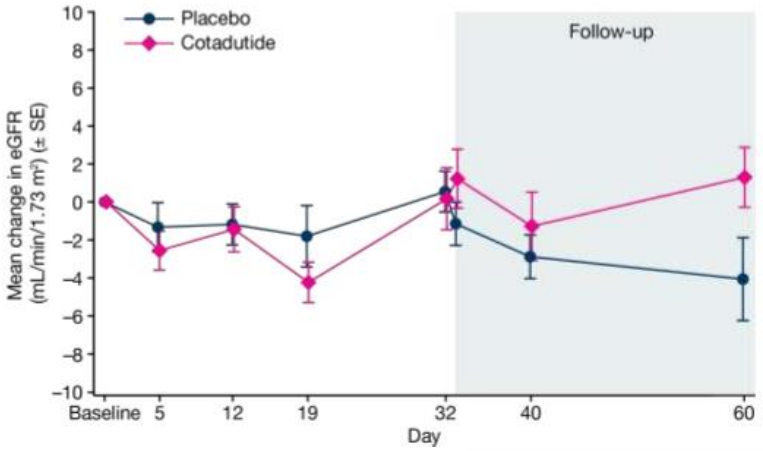


Good CV results. Efpe is an exendin based GLP-1. Some previously exposed theories were that exendin based GLP-1s have a lower CV/renal benefits. This is not the case with Efpe.

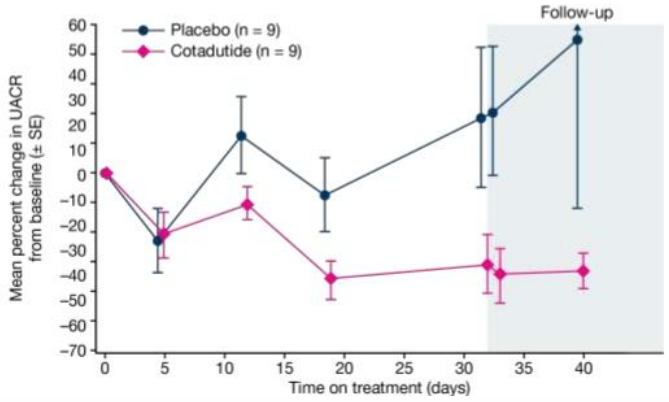
Astrazeneca – Cotadutide – Phase 2a

- AstraZeneca presented the results of the Phase 2a testing their daily **GLP-1/glucagon** co-agonist named **cotadutide in adults with T2D and kidney problems**
- Double-blind, placebo-controlled trial, testing **300µg/day** of cotadutide during **32 days in n=41 T2D**
- Inclusion criteria: 18-85 years, BMI between 25 & 45kg/m², A1c between 6.5 & 10.5%, T2D with or without oral treatments (as DPP-4 & SGLT-2) and/or insulin
- Baselines: **70.9-71.1 years, A1c = 7.85-7.88%, BMI = 32.4-32.9kg/m²**, eGFR = 44.73-47.63 mL/min/1.73m², 76% using insulin
- Main results:
  - Better post prandial glucose control during a meal test (Glucose AUC 0-4h -26.71% vs +3.68% at day 32, p<0.001)
  - **Time in range (70-180mg/dL) improved by 14.8% vs -21.2% (p<0.001)**
  - **-3.69% of body weight vs -0.21% (p<0.001)**
  - No differences in eGFR, **better decrease of UACR in patients with baseline micro or macroalbuminuria** (51% vs placebo, p=0.0504), reduction of NT-proBNP (-79.73 vs -9.42 ng/dL, p=0.040)
- No severe hypoglycemia, one death in the cotadutide group due to ketoacidosis
- Results also available on ct.gov
- AstraZeneca also presented results of another Phase 2a in obese and overweight T2Ds with strong weight reduction (~-4kg vs ~-1.4kg) after 42 days

Mean change in eGFR over time

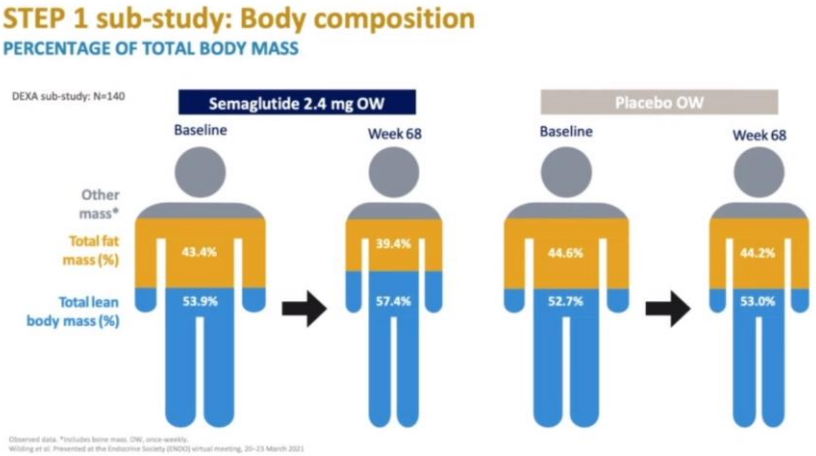


Mean percent change in UACR over time (subgroup analysis)



Novo Nordisk - Semaglutide in obesity – STEP trials

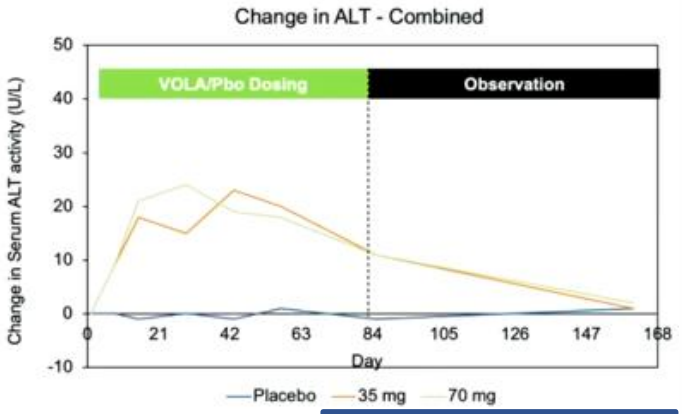
- Novo Nordisk did a symposium presenting results from the STEP program testing semaglutide in obesity. Synthesis of STEP 1, STEP 2 (in T2D), STEP 3 (with intense behavior therapy), & STEP 4 (sustained weight management) results already published (STEP 1, STEP 2, STEP 3 & STEP 4).
- They also presented cardiovascular markers results, such as blood pressure, lipid profiles, and body mass composition showing consistent improvements as observed in T2D trials.
- Semaglutide is currently tested in a long cardiovascular trial in obese patients (SELECT) with results to come in the next years.



OTHER TREATMENTS

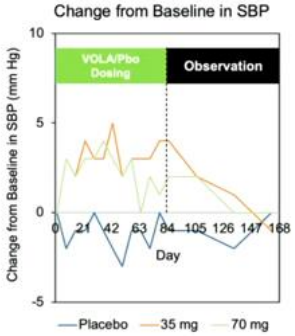
REMD – Volagidemab – Phase 2 in T1D

- Volagimdemab is a **human monocloncal antibody** that targets **receptors of glucagon**. REMD presented the results of their Phase 2, double-blind, placebo-controlled, 2 parts trial testing **2 doses (35mg and 70mg**) of **weekly volagidemab in n=75+78 adults T1D during 12 weeks.**
- Inclusion criteria: 18-65 years, BMI between 18.5-32 kg/m², A1c between > 10% in trial 1 and between 7-10% in trial 2, C-peptide < 0.7ng/mL, MDI or CSII, ALT and/or AST ≤ 1.5x upper limit of normal, no severe hypo in the past 6 months
- Differences between the 2 parts (called trials 1 & 2), unblinded CGM in trial 1 and blinded CGM in trial 2
- **Increase in ALT, weight (not significant) and blood pressure that will be monitored during Phase 3**



VOLA shows good glucose control in uncontrolled T1D, but AE needs to be monitored in Phase 3, especially on the liver and on CV diseases.

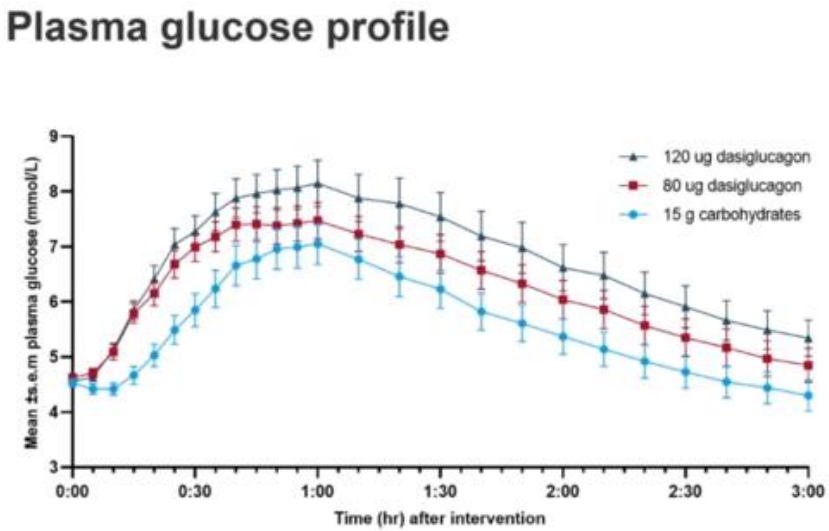
Item	Pl. Trial 1	35mg T1	70mg T1	Pl. Trial 2	35mg T2	70mg T2
Baselines (age, A1c, BMI)	45, 7.6, 27.2	41, 7.5, 25.8	43, 7.4, 27.2	42, 7.7, 26.0	42, 8.1, 25.9	38, 8.0, 26.8
A1c reduction	-0.43%	-0.67%	-0.66%	-0.11%	-0.64%*	-0.6%*
A1c reduction in patients with A1c≥7.5%	-0.68%	-1.02%*	-0.94%	-0.08%	-0.97%*	-0.59%*
Baseline time in range (70-180mg/dL)	60.6%	59.6%	57.0%	51.1%	54.2%	52.7%
Change time in range	**+1.5%**	**+1.1%**	**+7%**	**-3%**	**+4.5%**	**+6.2%**
Baseline time < 70mg/dL	5.0%	4.3%	3.4%	3.8%	5.8%	4.6%
Change time < 70mg/dL	-0.2%	-0.28%	-0.44%	-0.78%	-2.75%	+1.57%
Baseline total daily insulin	47.5 UI/day	46.0 UI/day	44.2 UI/day	50 UI/day	42.6 UI/day	47.1 UI/day
Change total daily insulin	-1.4 UI/day	-6.7 UI/day	-5.3 UI/day	-1.3 UI/day	-7.6 UI/day*	-6.6 UI/day
Body weight change	+0.4 kg	+1.3 kg	+1.1 kg	+0.4 kg	+1.0 kg	+0.8 kg



* p<0.05 vs placebo

Zealand – Low dose dasiglucagon – prevention of hypoglycemia

- Partially single-blinded, cross-over Phase 2 trial testing 2 doses of **dasiglucagon, 80µg and 120µg, versus 15g of oral carbohydrate** during a **single insulin-induced hypoglycemia event in n=20 adults T1D**
- Inclusion criteria: 18-64 years, A1c ≤ 8.0%, MDI or CSII, using insulin aspart
- Design Insulin-induced hypoglycemia with intervention when plasma glucose reach 4.5 mmol/L (t=0)
- Baselines: **45 years, A1c = 6.8%,** BMI = 25.8 kg/m²
- Main results, **significantly fewer cases of hypoglycemia** (< 3.9 mmol/L)
- Low number of nausea and headache



Zealand and Xeris are developing micro-doses of their glucagon technology to prevent hypoglycemia in different situations (here, insulin induced hypo). It could become a new therapeutic options in the next few years.

Analysis provided by Sam Collaudin

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