Drugs and Therapies: Expanding Coverage and Future Options

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Disclosures

- None

Outline

1. Non-insulin agents to improve glycemic control and prevent diabetes complications

- SGLT2 inhibitors
- GLP-1 receptor agonists

2. Immune approach to prevent or delay loss of beta cell mass

- Teplizumab

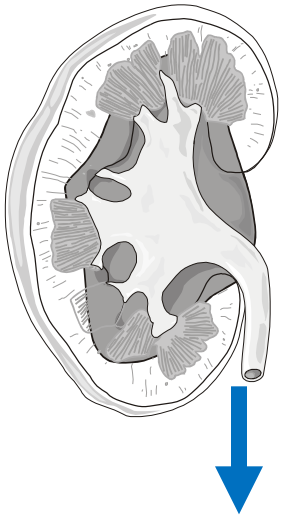
3. Update on glucagon

- Nasal, pre-filled liquid, and generic versions

Sodium Glucose Transporter 2 (SGLT2) Inhibitors

Kidneys Filter + Reabsorb Glucose: 180 g/day
SGLT2 (proximal tubules): 90%

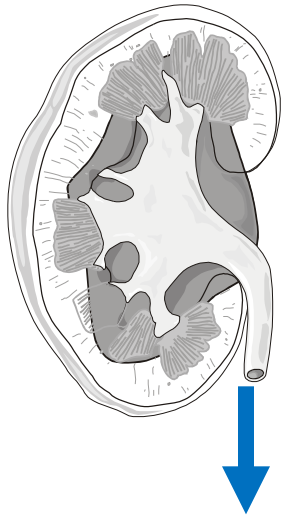
Normal



Glycosuria

BG > 180 mg/dl

SGLT2 Inhibitor



Glycosuria

BG > 80 mg/dl

Glucose Loss
80-100 g/day
320-400 kcal/day

Blood Glucose ↓
Weight Loss

No Renal Damage

GU Infections / UTI

Sodium/Glucose Co-Transporter 2 Inhibitors

FDA Approved for Adults with T2DM

Generic	Trade Name	Doses
Canagliflozin	Invokana	100, 300 mg
Dapagliflozin	Farxiga	5, 10 mg
Empagliflozin	Jardiance	10, 25 mg
Ertugliflozin	Steglatro	5, 15 mg

Proven Benefits in T2DM:

- Delayed kidney disease progression
- Decreased heart failure hospitalizations
- Decreased heart attacks

Diabetes ketoacidosis (DKA) with BG 150-250 mg/dl Occasionally with These Agents

Most Common Precipitants: Low Carb Diets and Fasting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

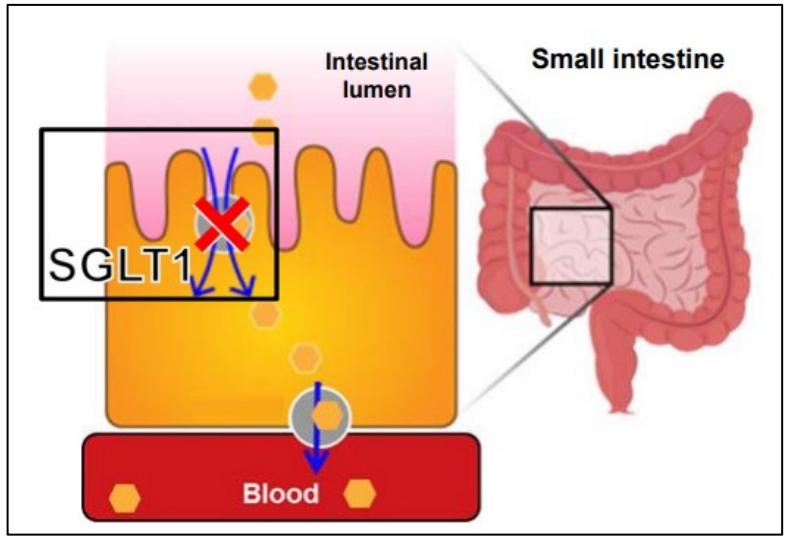
Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes

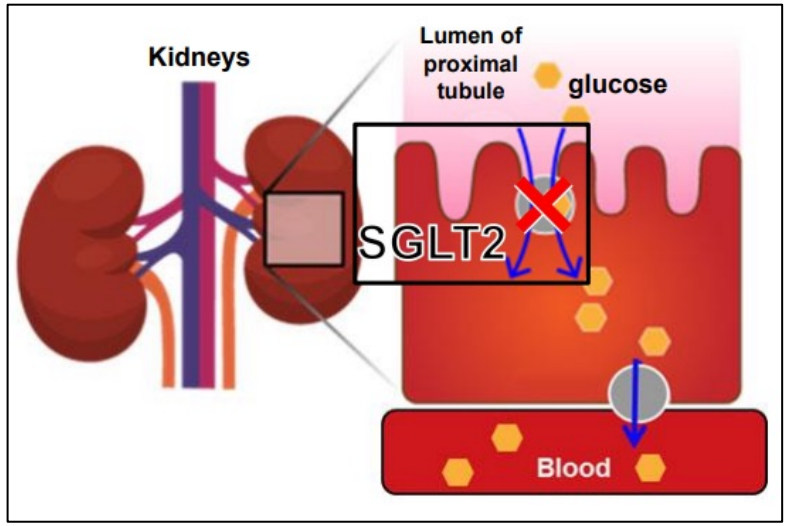
2017 Study

Phase 3 trial, blinded trial in 1402 patients with type 1 diabetes (on pump or injections) who added **sotagliflozin** (oral SGLT1 and SGLT2 inhibitor) vs placebo.

***Primary end point*:** A1c <7.0% at week 24 with no episodes of severe hypoglycemia or ketoacidosis

***Patient population*:** age ~43 yrs, ~50% women, 89% white, diabetes duration ~20 years, initial A1c 8.3% on average





The NEW ENGLAND JOURNAL of MEDICINE

FDA Turns Down Sotagliflozin for Type 1 Diabetes

Miriam E. Tucker

March 22, 2019

Add to Email Alerts

The US Food and Drug Administration (FDA) has rejected sotagliflozin (Sanofi/Lexicon) as an adjunct to insulin for the treatment of type 1 diabetes.

The decision follows a split vote in January 2019 by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee, during which panel members expressed concerns about an increased risk for diabetic ketoacidosis (DKA) with the drug in type 1 diabetes. Even panel members who voted to recommend approval said they would endorse strict rules for a Risk Evaluation and Mitigation Strategies (REMS) program for the drug's use in the event of it being approved.

The FDA decision contrasts with the positive opinion of the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) earlier this month. This will allow marketing of sotagliflozin (to be known there as *Zynquista*) as an adjunct to insulin to improve blood glucose in adults with type 1 diabetes with a body mass index ≥ 27 kg/m ^{2} who haven't achieved adequate glycemic control with optimal insulin therapy and are under the care of specialist physicians.

SGLT2 Inhibitors

Other Developments in Type 1 Diabetes

March 20, 2020 | 3 min read SAVE

FDA rejects lower-dose empagliflozin 2.5 mg for type 1 diabetes

ADD TOPIC TO EMAIL ALERTS

The FDA on Friday issued a complete response letter for a supplemental new drug application for a 2.5 mg dose of the SGLT2 inhibitor empagliflozin as an adjunct to insulin for adults with type 1 diabetes, according to a press release from Boehringer Ingelheim and Eli Lilly.

News > Medscape Medical News

Outrage Over Dapagliflozin Withdrawal for Type 1 Diabetes in EU

Liam Davenport
December 15, 2021

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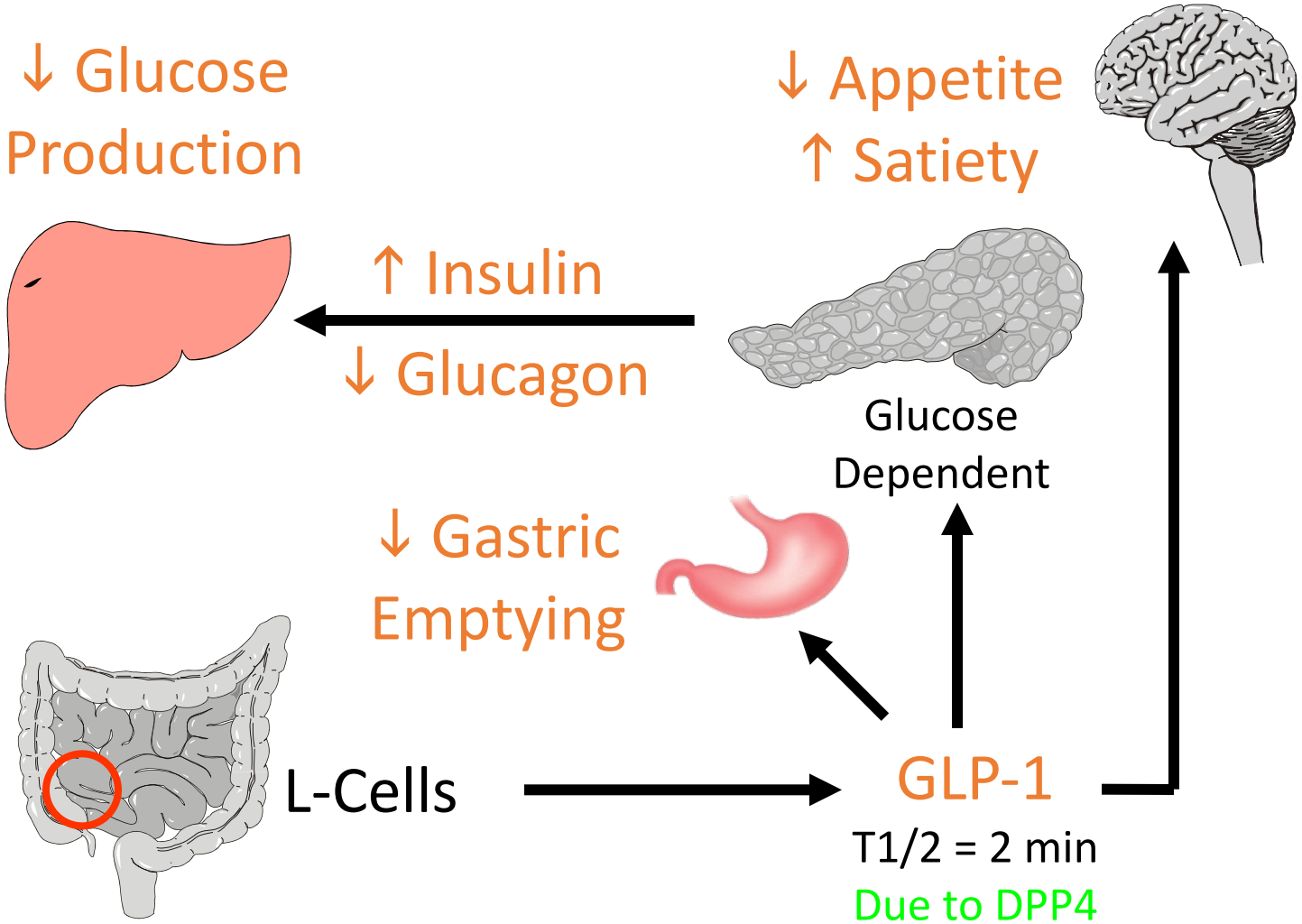
In a shocking, yet low-key, announcement, the sodium-glucose transporter 2 (SGLT2) inhibitor dapagliflozin (Forxiga, AstraZeneca) has been withdrawn from the market in all EU countries for the indication of type 1 diabetes.

Incretin Physiology: GLP-1 Receptor Agonists



GLP-1 = Glucagon Like Peptide-1

DPP4 = Dipeptidyl Peptidase 4

FDA-Approved GLP-1 Receptor Agonists

Exenatide (Byetta) – twice daily

Liraglutide (Victoza) – daily

Lixisenatide (Adlyxin) – daily

Exenatide QW (Bydureon) – weekly

Dulaglutide (Trulicity) – weekly

Semaglutide (Ozempic) – weekly

Blood Glucose ↓↓

Weight Loss

FDA-Approved GLP-1 Receptor Agonists

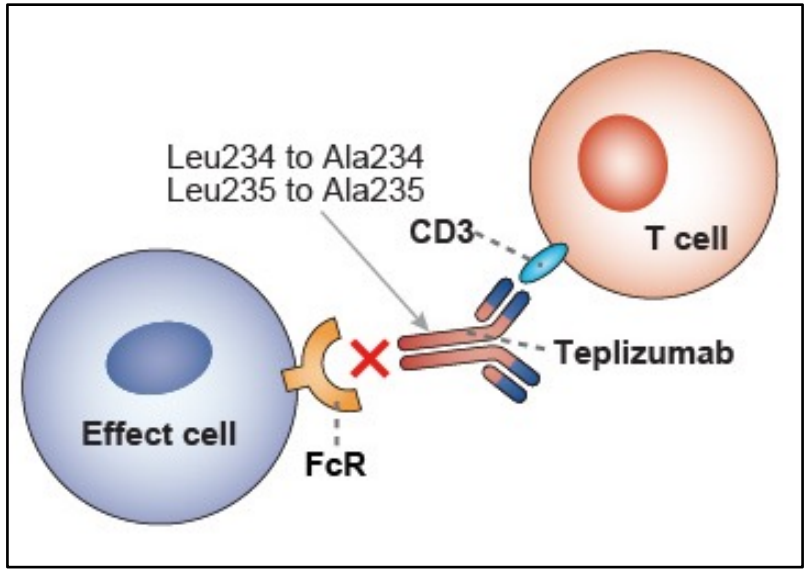
Use in Type 1 Diabetes?

GLP-1 receptor agonists	Type 1 diabetes	Type 2 diabetes
HbA_{1c}	(↓) (up to 0·5 %), often not significant	↓↓ (up to 1·5 %)
Fasting plasma glucose	≈ (depending on basal insulin)	↓↓ (more pronounced with long-acting GLP-1 RAs)
Post-meal plasma glucose	(↓) (even with short-acting GLP-1 RAs)	↓↓ (more pronounced with short-acting GLP-1 RAs)
Insulin dose	↓↓ (predominantly concerning meal-related rapid-acting insulin)	↓ (variable, protocol-dependent)
Bodyweight	↓↓↓ (more pronounced than in type 2 diabetes?)	↓↓
Hypoglycaemia	≈ or ↑ (depending on appropriate adaptation of insulin dose/ timing)	≈ or ↓ or ↑ (depending on insulin dose adaptations)
Ketosis/ ketoacidosis	Potentially ↑ (related to insulin dose reduction)	≈ (generally a minor problem in type 2 diabetes)
Gastrointestinal adverse events	Nausea, vomiting, diarrhoea	Nausea, vomiting,diarrhoea
Cardio-renal endpoints	Not yet studied	MACE ↓ albumin excretion ↓

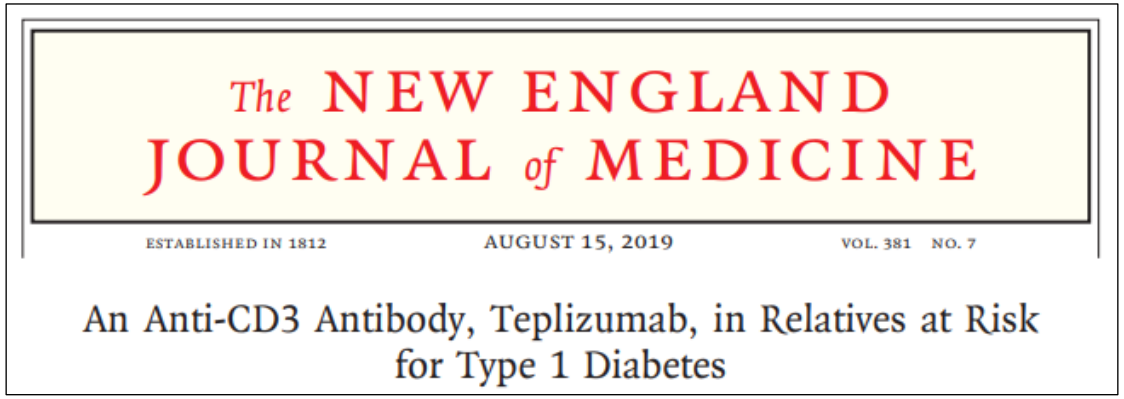
Nauck and Meier. Lancet Diabetes Endocrinol. 2020 Apr;8(4).

Teplizumab

- Teplizumab is a humanized anti-CD3 monoclonal antibody
- Goal of the antibody is to protect remaining β-cells in newly diagnosed type 1 diabetes

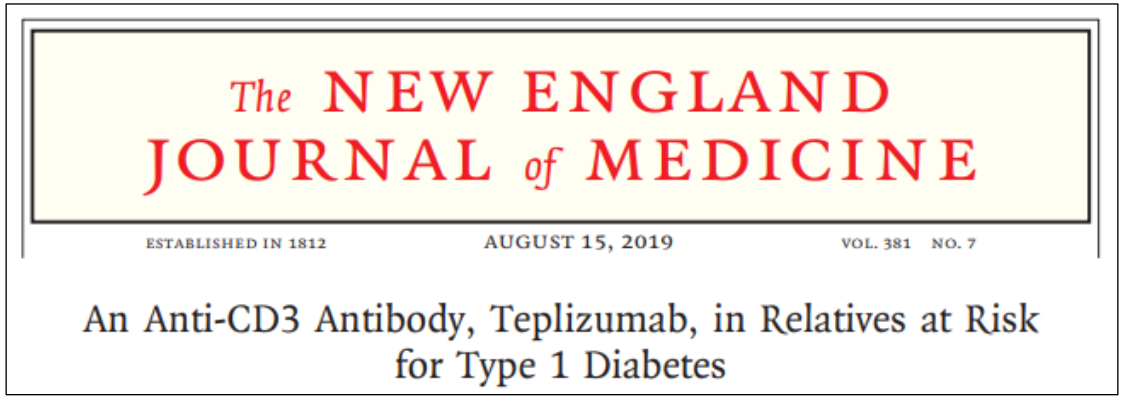


https://www.creativebiolabs.net/teplizumab-overview.htm



- Phase 2, blinded trial of teplizumab in relatives of patients with T1DM at high risk of developing diabetes
- *Intervention*: 14-day course of teplizumab vs placebo, then follow-up every 6 months
- *Participants*: 76 total people; average age 14 yrs (range 8-49), most had a sibling with type 1 diabetes; ~90% GAD Ab positive; A1c 5.2%

Harold KC. NEJM 2020;382(6):586



Results

	Teplizumab (N=44)	Placebo (N=32)
Time to diagnosis	48.4 months	24.4 months
T1DM diagnosed	19 (43%)	23 (72%)
Annual rate of T1DM diagnosis	14.9%	35.9%

Delays onset of T1DM by 2 years

Harold KC. NEJM 2020;382(6):586

Teplizumab

FDA Decisions & Developments

May 27, 2021 | 5 min read SAVE

FDA advisory committee recommends approval of immunotherapy to delay type 1 diabetes

ADD TOPIC TO EMAIL ALERTS

An FDA advisory panel voted 10-7 in favor of recommending approval of teplizumab to delay development of type 1 diabetes in high-risk children and adults, with most committee members expressing some concerns about trial size and safety.

News > Medscape Medical News

FDA Rejects Teplizumab for Type 1 Diabetes Delay

Miriam E. Tucker
July 07, 2021

Add to Email Alerts

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The US Food and Drug Administration (FDA) has declined to approve the anti-CD3 monoclonal antibody teplizumab (Tzield, Provention Bio) for the delay of type 1 diabetes in at-risk individuals, despite narrow endorsement in a 10-7 vote in favor of approval by one of its advisory panels in May.

FDA Accepts Resubmitted BLA for Teplizumab For Delay of Type 1 Diabetes

March 21, 2022

Update on Glucagon

- Newer versions available on the market
- More stable glucagons will eventually allow for bihormonal pump system

Nasal Glucagon (Baqsimi)

Pre-filled liquid glucagon (Gvoke)

FDA NEWS RELEASE

FDA Approves First Generic of Drug Used to Treat Severe Hypoglycemia

Agency Supports Development of Complex Generic Drugs to Improve Competition and Access to More Affordable Medicines

Share Tweet Linkedin Email Print

For Immediate Release: December 28, 2020

Today, the U.S. Food and Drug Administration approved the first generic of glucagon for injection USP, 1 mg/vial packaged in an emergency kit, for the treatment of severe hypoglycemia (very low blood sugar), which may occur in patients with diabetes mellitus. The drug is also indicated as a diagnostic aid in the radiologic examination of the stomach, duodenum (the first part of the small intestine beyond the stomach), small bowel and colon when diminished intestinal motility (reduced ability to move) would be advantageous.


Thank You!