57. ULUSAL DİYABET Metabolizma ve Beslenme Hastalıkları KONGRESİ

Dual GIP ve GLP1RA

Doç. Dr. Dilek Tüzün

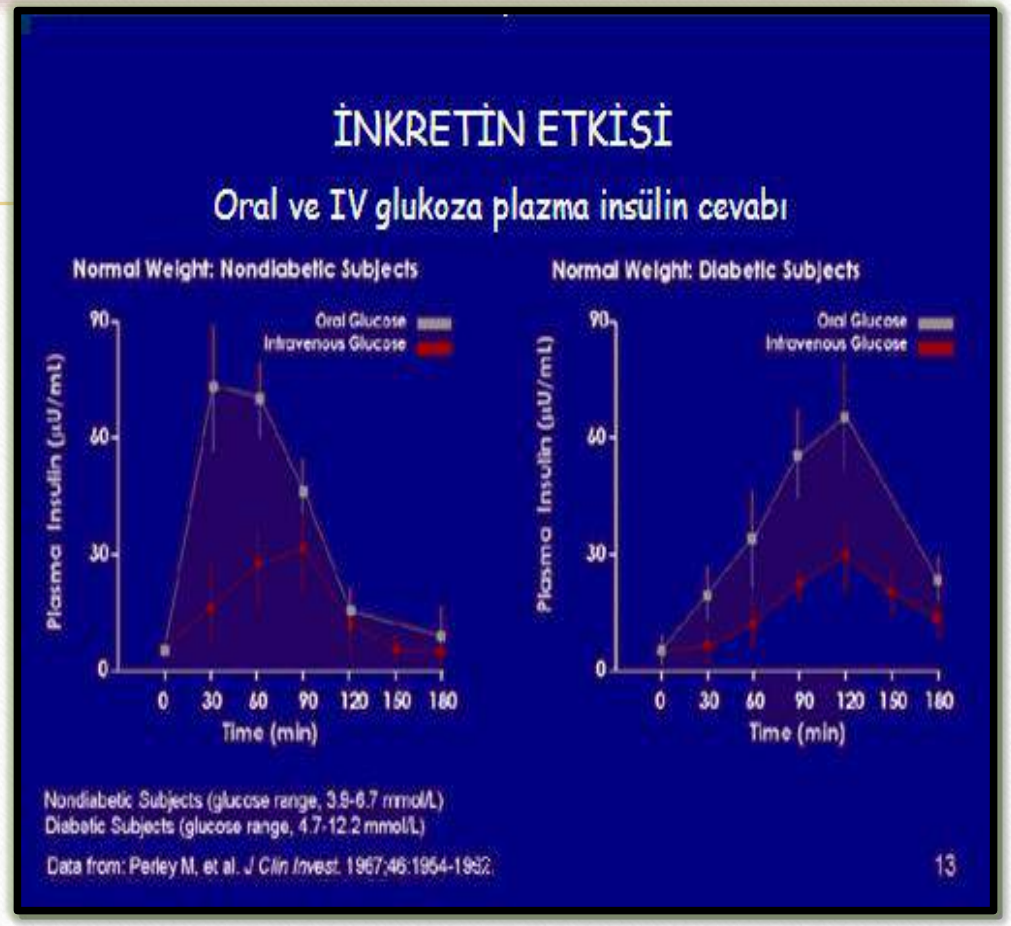
KSÜ Tıp Fakültesi Endokrinoloji BD

03.06.2021

KAHRAMANMARAŞ SÜTÇÜİMAM ÜNİVERSİTESİ TIP FAKÜLTESİ

INtestinal seCRETion of Insulin

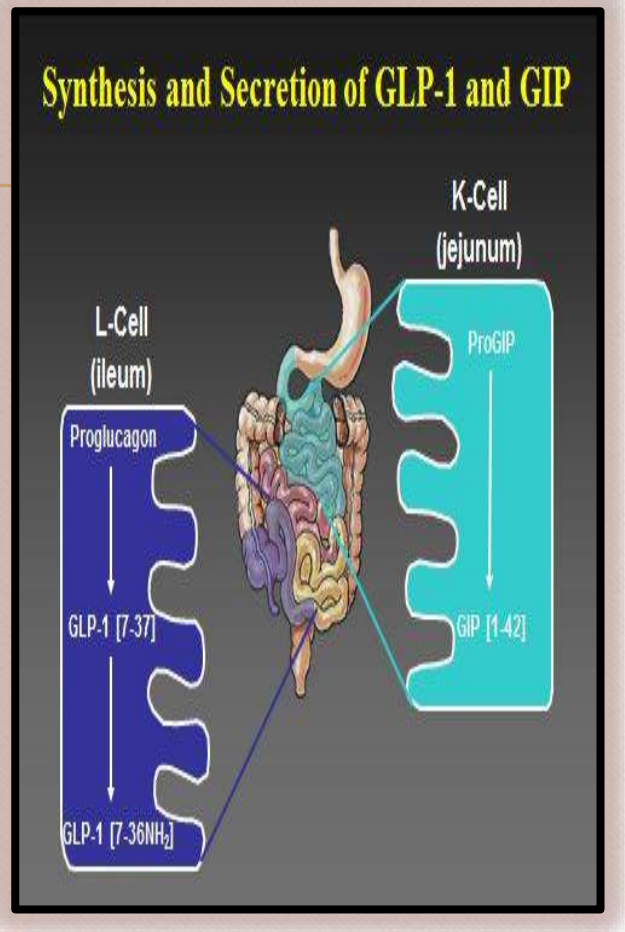
- Enteral beslenmenin, IV beslenmeye göre daha fazla insülin sekresyonuna yol açtığının gözlenmesinden sonra inkretin konsepti ortaya çıkmıştır
- **İlk defa 1932 de inkretin terimi tanımlanmıştır**
- Gastrointestinal sistemden emilen glukozun insülinotropik etkisinin daha fazla olması, barsaklardan salınan hormonlara bağlanmıştır. Bu hormonlar **İNKRETİNLER** olarak adlandırılır
- IV glukoza oranla, oral glukoz ile insülin sekresyonunda daha fazla artış olması **İNKRETİN ETKİSİ** adını alır



Diabetes Ther (2021) 12:143–157

İNKRETİNLER

- **Glukagon benzeri peptid-1 (GLP-1)**
  - İntestinal bölgeden salgılanan en potent inkretin
  - GİS'in **jejenum** ve **distal ileumunda** bulunan **L-hücreleri** tarafından sentez edilmekte
  - Gen paylaşımı ve moleküler homoloji(%50) nedeniyle : **GLP** ismini almış
  - GLP-1 evrimsel olarak tarih öncesinden gelen bir hormon, analogları veya paralogları omurgalılarda ve balıklarda mevcut



Diabetes Ther (2021) 12:143–157
Regul Pept 2001: 98:1–12
Curr Pharm Des 2006: 12:1731–1750

GIP=glukoza bağımlı insülinotropik peptid; GLP-1=glukagon benzeri peptid-1
Drucker DJ. *Diabetes Care.* 2003; 26: 2929–2940'dan uyarlanmıştır.

GLP-1 reseptörleri

Mide

Duedonum

Ekzokrin pankreas

Beyin sapı

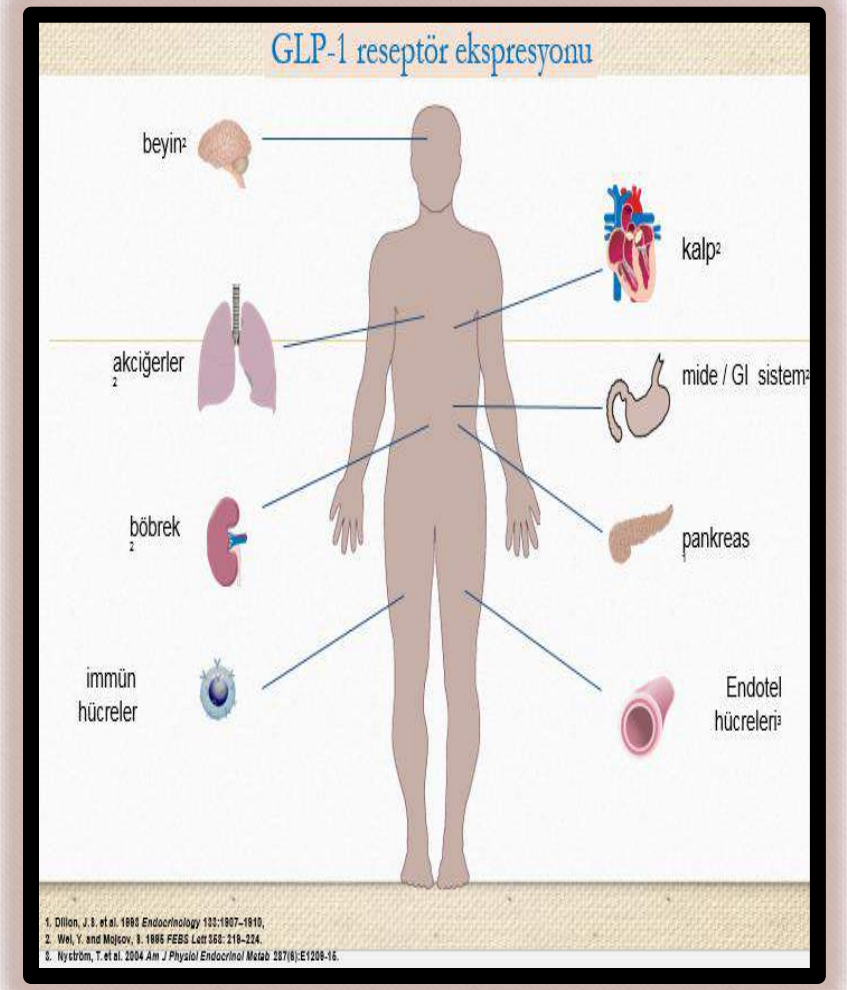
Talamus

Hipotalamus

Hippokampus

Akciğer

Böbrek



Kas hücreleri

Adipositler

Karaciğer

Kalp

Kardiyomyositler

Koroner endoteli

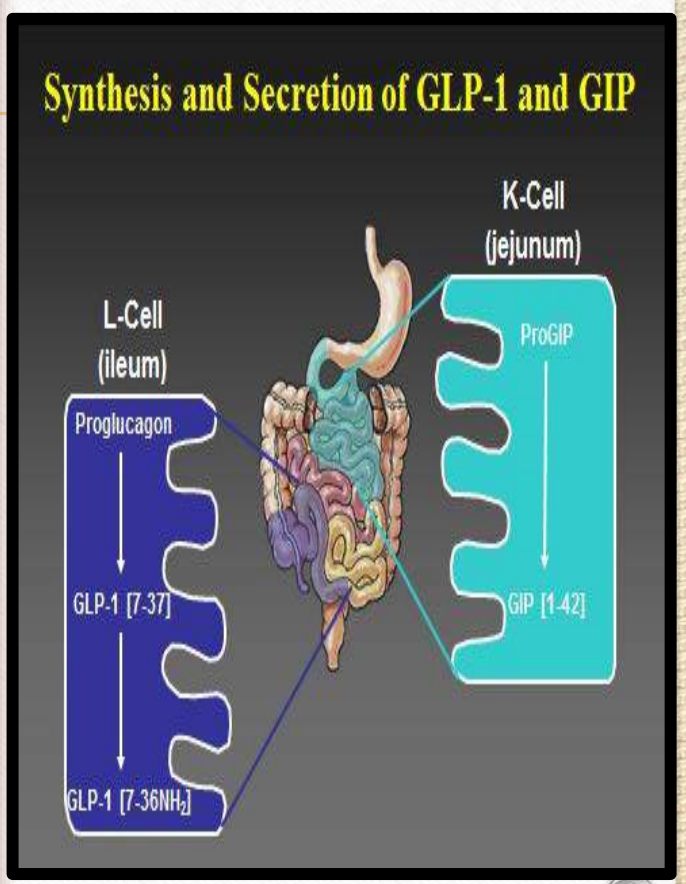
Vasküler endotel

Pankreas adacık hücrelerinde

İNKRETİNLER

GLUKOZ BAĞIMLI İNSÜLİNOTROPİK POLİPEPTİD(GIP)

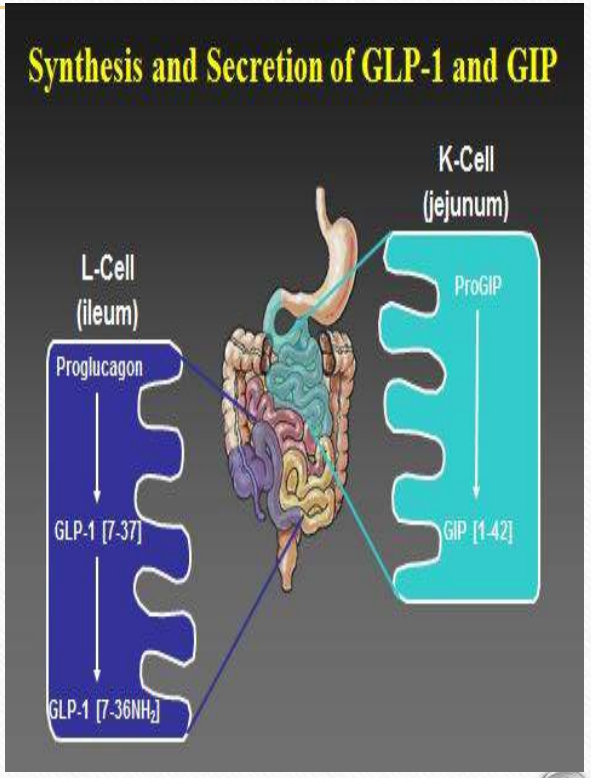
- 42 aa'li bir polipeptid
- **K hücreleri** olarak adlandırılan (**en fazla duodenumda ve jejenumda**) özel endokrin hücreler tarafından oral besinlere, özellikle karbonhidratlara ve lipitlere yanıt olarak salınır
- İlk izole edilen inkretin mide asidini inhibe ettiği için gastrik-inhibitör polipeptid (GIP) olarak adlandırılmıştır
- Daha sonra ise aslında GIP molekülünün insülotropik ve kan şekeri regüle edici etkisinin daha potent ve gastrik inhibitör etkisinin daha zayıf olduğu anlaşılmıştır ve molekülün ismi **Glukoz-bağımlı insülinotropik polipeptid** olarak değiştirilmiştir



Diabetes. 2011;60(12):3103–9
Lancet Diabetes Endocrinol. 2016;4(6):525–36.

GIP

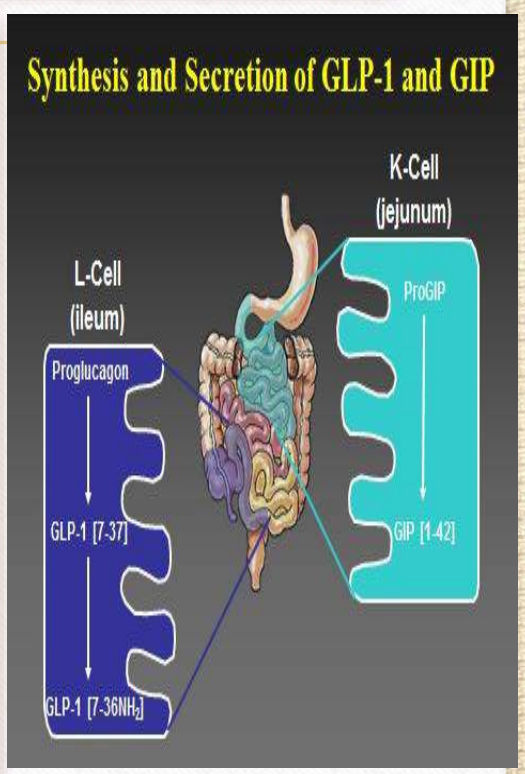
- **GIP reseptörleri,** pankreas, yağ dokusu, mide mukozası, kalp, adrenal korteks, kemik ve beyin gibi çeşitli dokularda mevcuttur
- Endojen GIP, ayrıca glikoza bağlı insülin salgılanmasını uyarır ve GLP-1'den daha büyük oranda inkretin etkisinden sorumludur
- GIP ve GLP-1 arasındaki bir fark, glukagon sekresyonu üzerindeki etkidir. GLP-1'den farklı olarak, **GIP'nin ikili işlevleri vardır:**
  - **normoglisemik ve hipoglisemik durumda bir glukagonotropik özellik**
  - **hiperglisemik durumda glukagonostatik**



Diabetes. 2011;60(12):3103–9
Lancet Diabetes Endocrinol. 2016;4(6):525–36.

GIP

- **GIP'nin** yağ dokusu ve vücut ağırlığı düzenlemesi üzerindeki etkisi henüz belirlenmemiştir
  - Bazı çalışmalar, GIP reseptörü devre dışı bırakılan farelerin diyetle indüklenen obeziteye dirençli olduğunu adipojenik etkiyi
  - Diğer çalışmalar, transgenik bir farede GIP konsantrasyonlarının kronik yükselmesinin diyetle indüklenen obeziteyi azalttığını ve insülin duyarlılığı, glukoz toleransı ve beta hücre işlevini artırdığını
- GIP'nin glukagonotropik özelliklere sahip olduğu bulunduğundan, GIP ile indüklenen kilo kaybının diğer varsayımsal mekanizması, glukagonun **anoreksik ve anti-lipojenik etkisidir**



Nat Med. 2002;8(7):738–42
PLoS One. 2012;7(7):e40156.
Diabetes. 2011;60(12):3103–9..

İNKRETİNLER

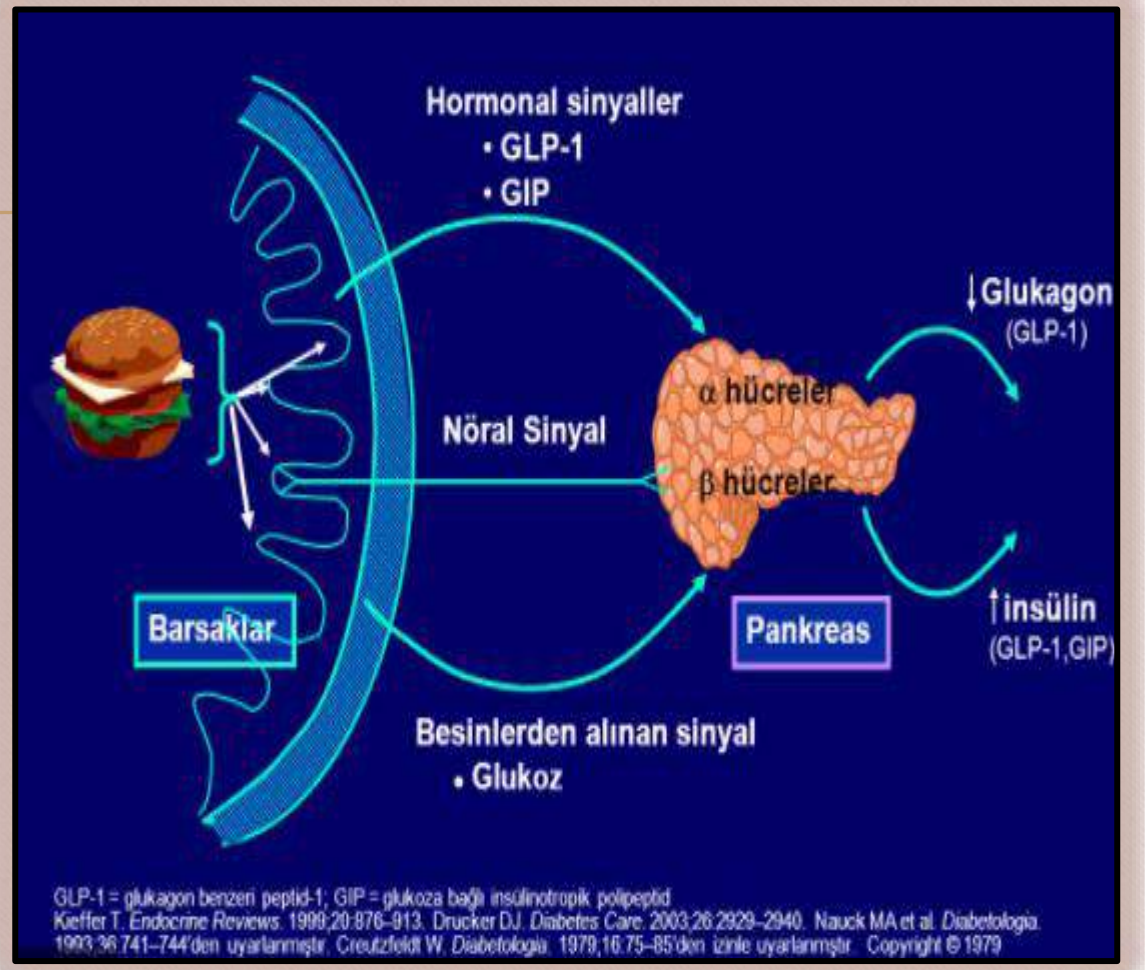
- **GIP ve GLP-1,** villuslardaki kapiller endotelden salınan Dipeptidil peptidaz-IV **(DPP-IV)** enzimi ile dakikalar içerisinde yıkılmaktadırlar

→ **GIP : 7 dk.**

→ **GLP- 1 : 4 dk**

- GIP ve GLP-1 glikoza bağımlı akut insülinotropik etkilerini pankreas β-hücre yüzey reseptörlerine bağlanıp cAMP artışı ile göstermektedirler

- **Kronik etkileri** ile ise β-hücrelerinin gen ekspresyonlarını artırıp insülin sentezinde artış ve hücre kitlesinde artışla birlikte **daha uzun β-hücre ömrü** sağlamaktadırlar

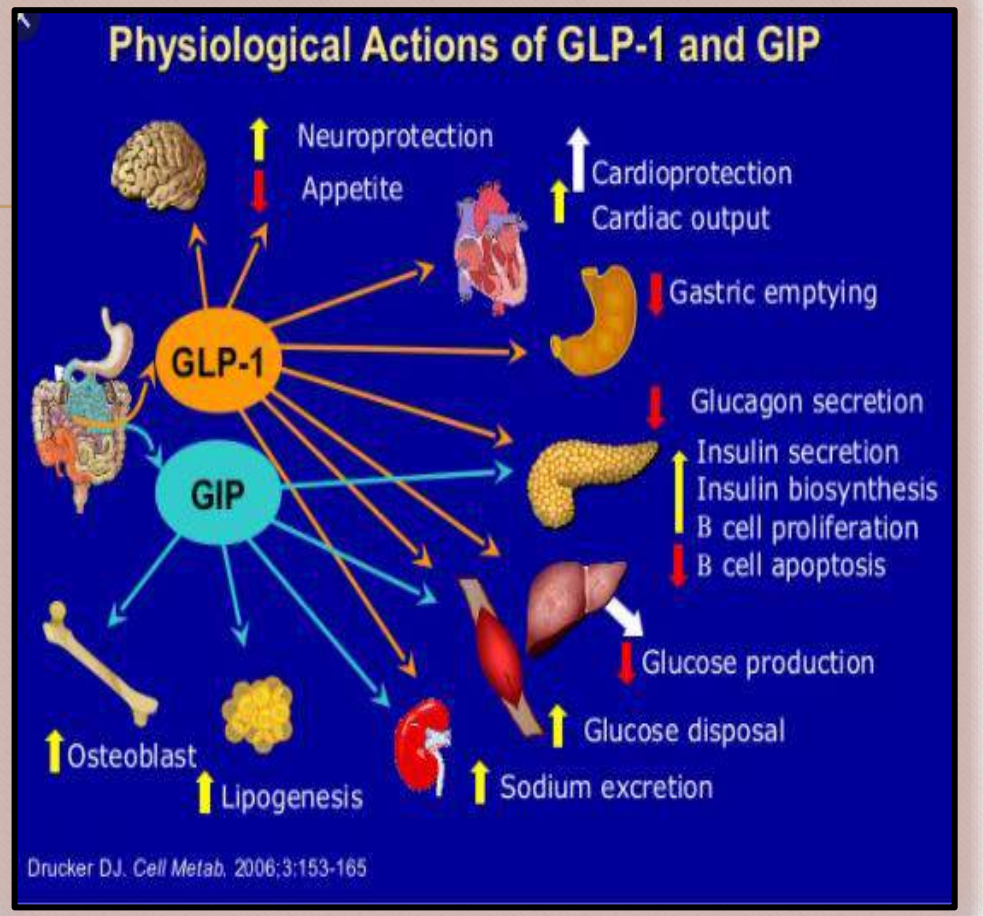


İNKRETİNLER

Tablo 1. İnkretin hormonlarının antidiyabetik etkilerinin karşılaştırılması [24].

Fizyolojik etki	GLP-1	GIP
Plazma glikozunun azaltılması	+	+
Glikoza bağımlı insülin sekresyonu	+	+
β-hücresinin glikoza cevabını artırma	+	+
β-hücresinin gen ekspresyonunu ve diferansiasyonunu artırma	+	+
Glukagon süpresyonu	+	-
Somatostatin süpresyonu	+	-
β-hücresinin artışı	+	+
β-hücresinin yaşam süresinin uzatılması	+	+
Pankreas dışı glikoz azaltıcı etki	+	+
Gastrik boşalmayı yavaşlatması	+	-
Doygunluğu artırıcı etkisi	+	-
Vücut ağırlığında azalma	+	-

GLP-1: "Glukagon like peptide-1"
GIP: "Glikoz-dependent insulotropic polypeptide".



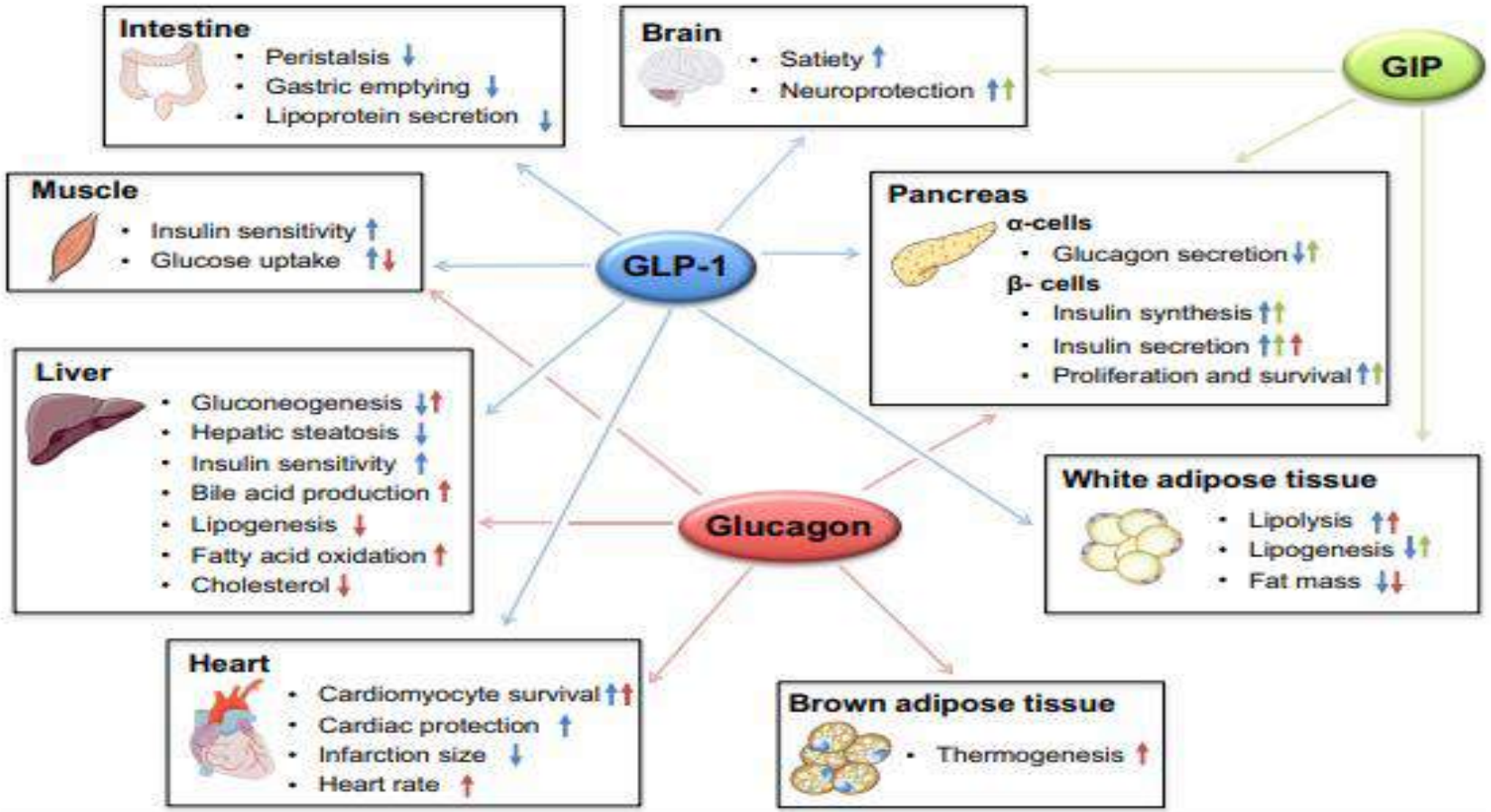
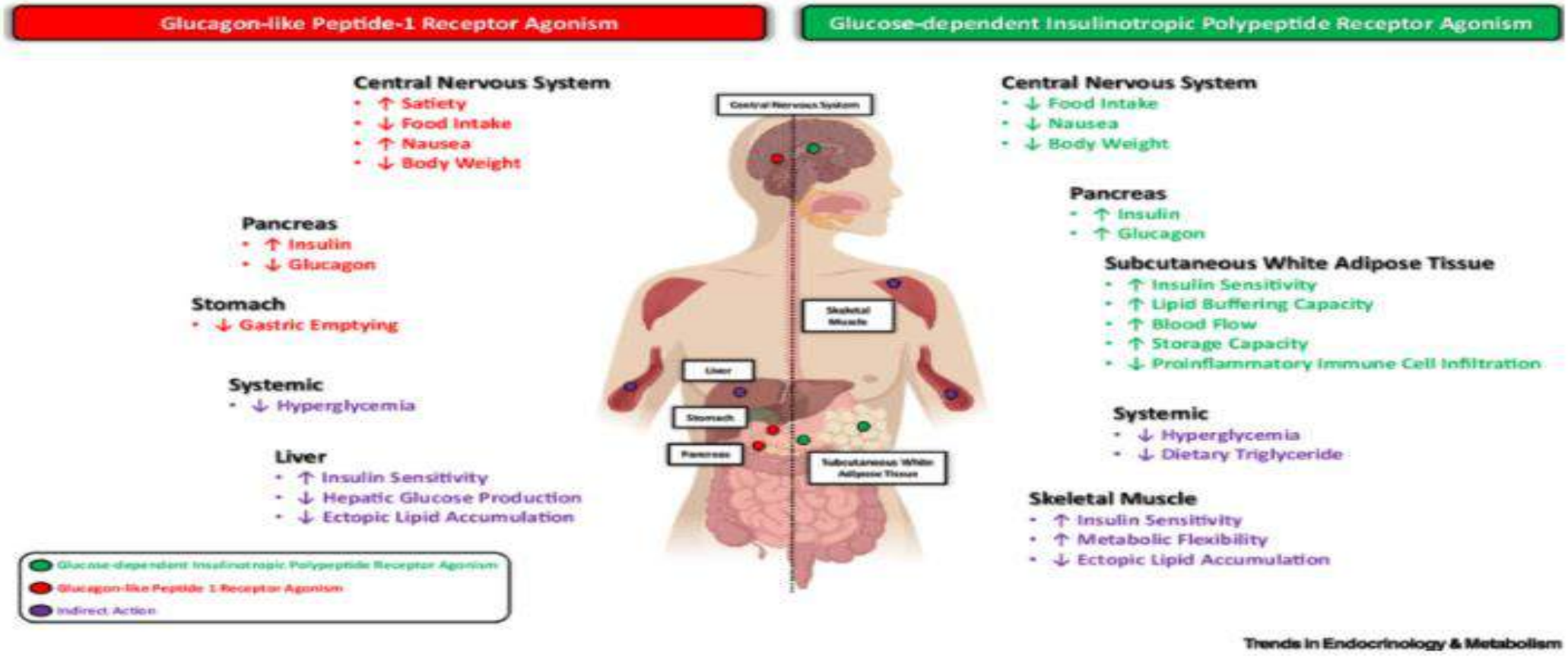


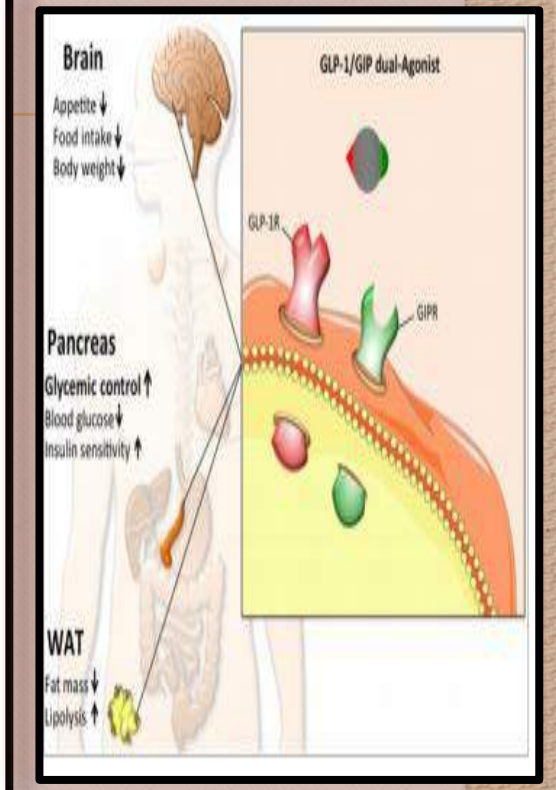
Fig. 2 *Effects of GLP-1 (blue arrows), glucagon (red arrows) and GIP (green arrows) on energy metabolism in key metabolic tissues. Small arrows in boxes pointing upwards indicate an increase or improvement of the respective metabolic function, whilst arrows pointing downwards indicate a decrease.*



Schematic Depiction of the Pleiotropic Benefits of Dual Glucose-Dependent Insulinotropic Polypeptide (GIP)/Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist Therapy in Type 2 Diabetes Mellitus. Activating both the GIP and GLP-1 receptors is attractive because the combination of these

DUAL GIP AND GLP-1 AGONİSTLERİ

- **GIP ve GLP-1 reseptör agonizminin** uzun vadeli etkisi ilk olarak Finan ve ark. tarafından gösterilmiştir
- '**Twincretin**' olarak adlandırılan GIP ve GLP-1 reseptörlerinin **tek moleküllü bir ikili agonisti** geliştirmişlerdir
- **Twincretin;**
  - İhmal edilebilir glukagon reseptör aktivitesi
  - GLP-1 ve GIP reseptörlerine yüksek afiniteye sahip olduğu gösterilmiştir
- **Hayvan çalışmalarında,** 1-3 haftada GIP ve GLP-1 reseptör ko-agonist tedavisi, plasebo, ekimolar eksendin-4 veya liraglutid dozuna kıyasla kan glikozunda, vücut ağırlığında, gıda alımında ve yağ kütlesinde doza bağlı bir azalma sağlamıştır
- Ko-agonist, yarı ömrü uzatmak için (haftalık dozlamaya izin vererek) bir polietilen glikol (PEG) veya bir 16-karbon asil zinciri eklenmiş
- Ko-agonist, hafif ila orta dereceli GI yan etkilerle iyi tolere edilmiş ve hiçbir hipoglisemik olay izlenmemiş



Diabetes Ther (2021) 12:143–157
Finan B, Ma T, Ottaway N, et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Sci Transl Med. 2013;5(209):209ra151

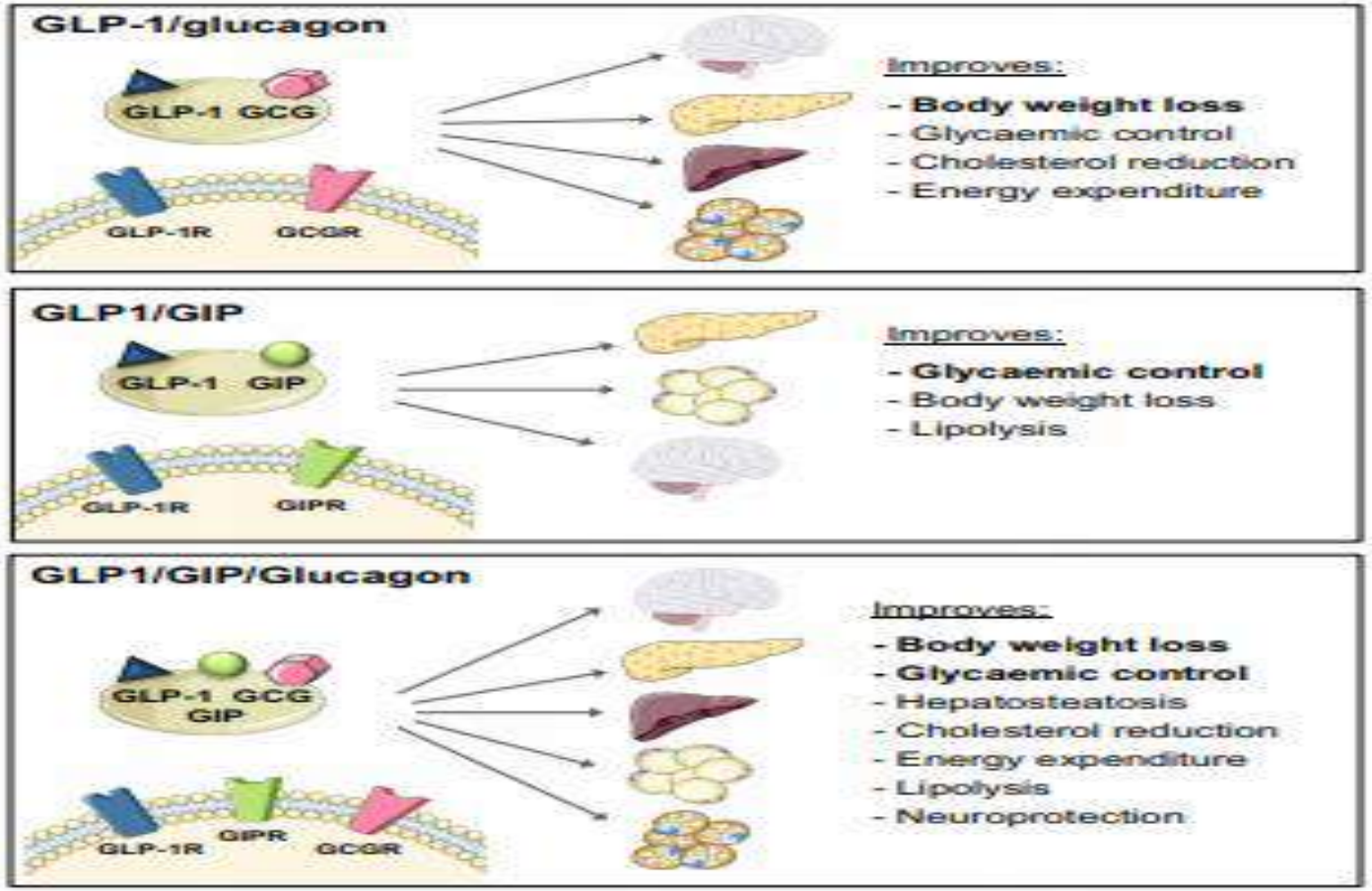


Fig. 3 *Effects, working principles and target tissues of dual agonists GLP-1/glucagon (upper panel) and GLP-1/GIP (middle panel), and triple agonist GLP-1/GIP/glucagon (lower panel). The most predominant metabolic effects are indicated in bold letters.*

International Journal of *Molecular Sciences*

MDPI

Review

The Effects of Dual GLP-1/GIP Receptor Agonism on Glucagon Secretion—A Review

David S. Mathiesen [1], Jonatan I. Bagger [1,2], Natasha C. Bergmann [1], Asger Lund [1], Mikkel B. Christensen [1,3,4], Tina Vilsbøll [1,2,4] and Filip K. Knop [1,2,4,5,*]

GLP-1 and GIP Dual Agonism

- Kemirgen beta hücrelerinin bir GLP-1 ve GIP kombinasyonu ile uyarılması, **glukoz veya GLP-1 ile indüklenen insülin sekresyonunun**, tek başına peptidlerden herhangi biri ile stimülasyona göre daha fazla güçlenmesine yol açmıştır

- Diyabetik olmayan ve tip 2 diyabetli donörlerden gelen insan adacıklarında, GIP'ye akut maruziyetin, insülin salınımı açısından eşmolar miktarlarda GLP-1 ile akut maruziyetten daha üstün olduğu bildirilmiştir

- **Uzun süreli maruziyetten sonra, her iki inkretin kombinasyonu, iki peptidden sadece biriyle inkübasyona kıyasla,**
  - **insülin sentezi**
  - **insülin sekresyonu**
  - **beta hücre farklılaşması ve hayatta kalma ile ilişkili genlerin ekspresyonu üzerinde sinerjik etkilere sahiptir**

Regul. Pept. 2010, 165, 129–132
Int. J. Mol. Sci. 2019, 20, 4092.

International Journal of *Molecular Sciences*

MDPI

Review

The Effects of Dual GLP-1/GIP Receptor Agonism on Glucagon Secretion—A Review

David S. Mathiesen [1], Jonatan I. Bagger [1,2], Natasha C. Bergmann [1], Asger Lund [1], Mikkel B. Christensen [1,3,4], Tina Vilsbøll [1,2,4] and Filip K. Knop [1,2,4,5,*]

GLP-1 ve GIP Co-infüzyonları ile Hayvan Çalışmaları

- **GLP-1 ve GIP'in** potansiyel ilave glukoz düzenleyici etkisine ilişkin hayvan çalışmalarından elde edilen sonuçlar tutarlı değildir
- Bazı çalışmalarda farelerde glukoz toleransı, insülin sekresyonu, vücut ağırlığı ve besin alımı üzerinde ikili GLP-1R ve GIPR agonizminin sinerjik etkileri gözlemlenmiştir
- Bazı çalışmalarda bir inkretin hormonu ile tedaviye kıyasla bu parametreler üzerinde ikili agonizmin hiçbir ek faydasını bulamamışlardır

Regul. Pept. 2009, 153, 70–76
Diabetes Metab. Res. Rev. 2007, 23, 572–579.
Clin. Sci. Lond. Engl. 1979 2011, 121, 107–117.

DUAL GIP-GLP-1 RESEPTÖR AGONİSTLERİ

Table 1 | List of antidiabetic drugs targeting glucagon-like peptide-1 receptor, glucose-dependent insulinotropic polypeptide receptor and glucagon receptor

	Drug	Company	Stage
GLP-1R/GIPR	LY3298176	Eli Lilly	Phase 2
	NN9709/MAR709/RG7697	Novo Nordisk/Marcadia	Phase 2
	SAR438335	Sanofi	Phase 1
	CPD86	Eli Lilly	Pre-clinical
	ZP-I-98	Zealand	Pre-clinical
	ZP-DI-70	Zealand	Pre-clinical
GLP-1R/GR	HM12525A	Hanmi Pharmaceuticals	Phase 2
	MEDI0382	Medimmune	Phase 2
	MK-8521	Merck	Phase 2
	SAR425899	Sanofi	Phase 2
	TT-401	Transition Therapeutics	Phase 2
	JNJ-54728518	Janssen Pharmaceuticals	Phase 1
	NN9277	Novo Nordisk	Phase 1
	MOD-6030/1	Prolor/OPKO Biologics	Phase 1
	ZP2929	Zealand	Phase 1
	VPD-107	Spitfire Pharma	Pre-clinical
GLP-1R/GIPR/GR	HM15211	Hanmi Pharmaceuticals	Phase 1
	MAR423	Novo Nordisk/Marcadia	Phase 1

GLP-1, glucagon-like polypeptide-1; GR, glucagon receptor; GIP, glucose-dependent insulinotropic polypeptide.

J Diabetes Investig Vol. 10 No. 4 July 2019

ORIGINAL ARTICLE

Pharmacodynamics, pharmacokinetics and safety of multiple ascending doses of the novel dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist RG7697 in people with type 2 diabetes mellitus

Christophe Schmitt PharmD, Agnès Portron PharmD, Shirin Jadidi MD, Neena Sarkar PhD, Richard DiMarchi PhD

First published: 20 July 2017 | https://doi.org/10.1111/dom.13024 | Citations: 33

Aims

To investigate the pharmacodynamics, pharmacokinetics and safety of multiple ascending doses of RG7697, a dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist, in patients with type 2 diabetes mellitus (T2D).

Methods

A total of 56 patients with T2D received once-daily subcutaneous (s.c.) injection of RG7697 (0.25-2.5 mg) or placebo for 14 days in a randomized, double-blind, dose-escalation study. Adverse events (AEs), vital signs, ECGs and routine laboratory variables were intensively monitored. Drug concentrations, fasting glycaemic variables, 24-hour glucose profiles, glycated haemoglobin (HbA1c) and antibody formation were measured. Several meal tolerance and gastric emptying tests were performed during the study.

Results

Daily s.c. injections of RG7697 were well tolerated by the majority of participants with T2D. The most frequently reported AEs with RG7697 were diarrhoea, nausea and decreased appetite. Asymptomatic events of hypoglycaemia were relatively uniformly distributed across dose groups including placebo. Pharmacokinetic steady-state was achieved within 1 week. Meaningful reductions in fasting, postprandial and 24-hour plasma glucose profile were observed at doses ≥0.75 mg, and were associated with numerical decreases in HbA1c (−0.67% [2.5-mg dose] vs −0.21% [placebo]). Decrease in postprandial insulin at doses ≥1.1 mg suggested improvement in insulin sensitivity. Minimum delay in gastric emptying and body weight reductions numerically greater than placebo (− 3.0 kg vs −0.9 kg) were seen at the highest dose of 2.5 mg.

Conclusions

Daily doses of RG7697 for 2 weeks were well tolerated by the majority of patients with T2D. Pharmacokinetic data supported once-daily dosing and pharmacodynamic effect displayed dose-dependent reductions in fasting and postprandial plasma glucose, without increasing the risk of hypoglycaemia.

RG7697/NNC0090-2746

- **Randomize, çift kör çalışma**
- **Günde bir kez 0.25, 0.75, 1.1, 1.5, 2 veya 2.5 mg dozu 2 hafta boyunca**
- **Plaseboya göre, 0.75 mg RG7697 / NNC0090-2746 dozu ile;**
  - **Açlık ve tokluk glikoz seviyelerinde doza bağlı düşüşler ve mide boşalması üzerinde hiçbir etki yok**
  - **Ama artmış insülin duyarlılığı saptanmış**
- **En yüksek 2,5 mg dozda, ko-agonist tedavisi ile**
  - **HbA1c seviyelerinde (plasebo için% 0,67'ye karşı% 0,21)**
  - **Vücut ağırlığında (3,0 kg ve plasebo için 0,9 kg) önemli düşüşler gözlenmiştir**
- **T2DM hastalarında ile ilişkili en sık görülen yan etkiler ;**
  - **Hafif yoğunlukta mide bulantısı, ishal ve iştah azalması**

Pharmacodynamics, pharmacokinetics, safety and tolerability of the novel dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist RG7697 after single subcutaneous administration in healthy subjects

Agnès Portron PharmD, Shirin Jadidi MD, Neena Sarkar PhD, Richard DiMarchi PhD, Christophe Schmitt PharmD

First published: 25 July 2017 | https://doi.org/10.1111/dom.13025 | Citations: 17

Aims

To evaluate the pharmacodynamics, pharmacokinetics and safety of single subcutaneous (s.c.) injection of ascending doses of RG7697, a dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist, in healthy subjects.

Methods

A total of 51 healthy volunteers were enrolled in this double-blind, placebo-controlled study investigating RG7697 doses ranging from 0.03 to 5 mg. Adverse events (AEs) were monitored and drug concentrations, fasting glycaemic variables, vital signs, ECG, antibody formation and routine laboratory variables were assessed. A meal tolerance test (MTT) was performed at the same time on day −1 (baseline) and day 1.

Results

RG7697 was generally well tolerated in healthy participants after s.c. injections up to 3.6 mg. Tolerability was limited by gastrointestinal AEs (nausea and vomiting) at the highest dose. There was a small dose-dependent increase in heart rate. No episodes of hypoglycaemia occurred. RG7697 concentrations peaked at 2 to 4 hours post-dose with a half-life of 19 to 25 hours. During MTT, RG7697 at doses ≥1.8 mg, reduced glucose maximum plasma concentration (C_{max}; −46%) without affecting overall glucose area under the curve (AUC). Its effect on insulin was more pronounced, with reductions in both C_{max} (−64%) and AUC (−51%). Pharmacodynamic variables were well correlated to RG7697 average plasma concentration during MTT, with IC_{50} (average concentration required for 50% reduction) values of 49 and 24.5 ng/mL for glucose and insulin, respectively.

Conclusion

Single s.c. injections of RG7697 up to 3.6 mg were generally well tolerated. Evidence of glycaemic effect and pharmacokinetic profiles consistent with once-daily dosing render this drug candidate suitable to be further tested in multiple-dose clinical trials in patients with type 2 diabetes.

RG7697/NNC0090-2746

- 51 sağlıklı gönüllü
- Çift kör, plasebo kontrollü bir çalışma
- 0.03 ila 5 mg arasında değişen dozlarda tek s.c
- İlacın 19-25 saat yarı ömrü günde bir kez dozlama için uygunluğunu doğruladı
- 1.8 mg dozlarda, yemek tolerans testi sırasında hem glikoz hem de insülin seviyelerini düşürdü
- İlaç 3,6 mg'lık dozlara kadar iyi tolere edildi ve mide bulantısı ve kusma gibi hafif advers gastrointestinal olaylar bildirildi
- Kalp atış hızında artışlar 1.8 mg dozlarda gözlendi ve test edilen en yüksek dozlar (3.6 ve 5 mg), nabız hızını plaseboya kıyasla dakikada yaklaşık 6-20 atış (bpm) artırdı
- Katılımcıların hiçbirinde tedaviyle ortaya çıkan anti-RG7697 / NNC0090-2746 antikorları saptanamadı

Randomized Controlled Trial > Cell Metab. 2017 Aug 1;26(2):343-352.e2.
doi: 10.1016/j.cmet.2017.07.011.

The Sustained Effects of a Dual GIP/GLP-1 Receptor Agonist, NNC0090-2746, in Patients with Type 2 Diabetes

Juan Pablo Frias [1], Edward J Bastyr 3rd [2], Louis Vignati [3], Matthias H Tschöp [4], Christophe Schmitt [5], Kiara Owen [6], Rune Haubo Christensen [6], Richard D DiMarchi [7]

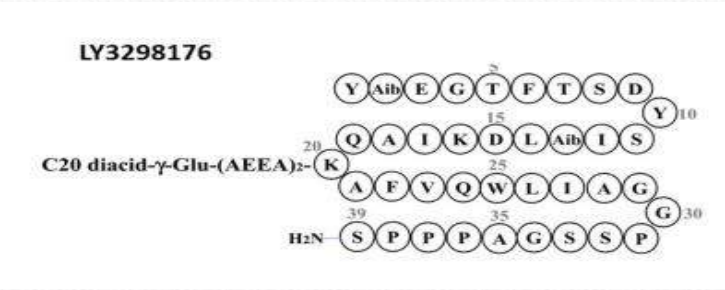
RG7697/NNC0090-2746

Abstract

Unimolecular dual incretins derived from hybridized glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) sequences have demonstrated synergistic reduction of adiposity in animal models and reductions of hyperglycemia in short-duration human trials. Here, we extend the characterization of NNC0090-2746 (also known as RG7697), a fatty-acylated dual agonist possessing in vitro balanced GIPR and GLP-1R agonism. In this 12-week, randomized, placebo-controlled, double-blind phase 2a trial, patients with type 2 diabetes inadequately controlled with metformin received 1.8 mg of NNC0090-2746 or placebo subcutaneously once daily. Liraglutide 1.8 mg (Victoza), starting with 2-week dose escalation, was administered subcutaneously once daily as an open-label reference arm. Measurements were collected at regular intervals after randomization. NNC0090-2746 significantly improved glycemic control and reduced body weight compared with placebo. Total cholesterol, alone among a range of lipid parameters, and leptin were both significantly reduced compared with placebo. Treatment with NNC0090-2746 was generally safe and well tolerated.

- 12 haftalık, randomize, plasebo kontrollü, çift kör faz 2a
- Metformin ile yetersiz kontrollü Tip 2 diyabetli hastalara, 1.8 mg NNC0090-2746 veya plasebo, günde bir kez sc
- NNC0090-2746, glisemik kontrolü önemli ölçüde iyileştirdi ve plaseboya kıyasla vücut ağırlığını azalttı
- Total kolesterol ve leptin, plaseboya kıyasla önemli ölçüde azaldı
- NNC0090-2746 ile tedavi genellikle güvenliydi ve iyi tolere edildi

TIRZEPATIDE



- Tirzepatide (LY3298176, doğal GIP sekansına dayalı olarak 39 amino asit içeren sentetik bir peptit olarak formüle edilmiş yeni bir ikili GIP / GLP-1 reseptör agonistidir
- Yarı ömrünü 5 güne uzatan ve böylece haftada bir dozlama sağlayan 20 karbonlu yağlı bir diasit kısmı albümine bağlanır
- Tirzepatid, doğal GIP'ye benzer bir GIP reseptör bağlanma afinitesine ve doğal GLP-1'inkinden beş kat daha düşük GLP1 reseptör afinitesine sahiptir

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REVIEW

The Role of Tirzepatide, Dual GIP and GLP-1 Receptor Agonist, in the Management of Type 2 Diabetes: The SURPASS Clinical Trials

Thinzar Min · Stephen C. Bain

- **Tirzepatide** 5 günlük yarılanma ömrü olduğundan **haftada bir kez** subkutan uygulanır
- **Faz 1 ve faz 2 çalışmalarında**, T2DM hastalarında tirzepatid doza bağımlı olarak ;
  - **HbA1c'd**e (% 2,4'e kadar)
  - **Vücut ağırlığında** (11,3 kg'a kadar) azalma yapmıştır
- **Tirzepatidin klinik etkinliği** ; GLP-1 RA dulaglutide'den daha üstün
- **En yaygın yan etkiler ;** gastrointestinal sistem ile ilişkilidir ve GLP-1 RA dulaglutide ile benzer
- Çeşitli glikoz düşürücü tedaviler alan T2DM'li bireylerde tirzepatid etkinlik ve güvenliğini araştıran SURPASS klinik çalışmaları mevcuttur
- SURPASS-CVOT randomize, çift kör, kardiyovaskuler sonuç içeren büyük bir faz 3 çalışmasıdır (tirzepatid ve dulaglutide (1.5 mg/ hafta)

Table 2 Summary of phase 1 and phase 2 trials of tirzepatide for the treatment of T2DM

Trial	Baseline characteristics	Treatment arms	Duration of treatment (weeks)	Efficacy		Safety		
				Change in mean HbA1c from baseline (%)	Change in mean body weight from baseline (kg)	Treatment discontinuation [*n* (%)]	GI adverse events [*n* (%)]	Hypoglycaemia (BG ≤ 70 mg/dL) [*n* (%)]
Phase 1 POC trial [30] (*n* = 53)	Age 56.8 years BMI 31.2 kg/m^2 HbA1c 8.4%	Tirzepatide 0.5 mg	4	− 0.30	− 0.70			
		Tirzepatide 1.5 mg		− 0.46	− 1.54			
		Tirzepatide 10 mg		− 1.00	− 2.39			
		Tirzepatide 15 mg		− 0.74	− 2.95			
		Placebo		− 0.16	− 0.32			
Phase 1 Japanese trial [31] (*n* = 48)	Age 57.4 years BMI 25.4 kg/m^2 HbA1c 8.0%	Tirzepatide 5 mg	8	− 1.62	− 1.90			
		Tirzepatide 10 mg		− 1.78	− 3.60			
		Tirzepatide 15 mg		− 2.05	− 5.10			
		Placebo		− 0.48	+ 1.50			

Table 2 continued

Trial	Baseline characteristics	Treatment arms	Duration of treatment (weeks)	Efficacy		Safety		
				Change in mean HbA1c from baseline (%)	Change in mean body weight from baseline (kg)	Treatment discontinuation [*n* (%)]	GI adverse events [*n* (%)]	Hypoglycaemia (BG ≤ 70 mg/dL) [*n* (%)]
Phase 2 trial [32] (n = 318)	Age 56–58 BMI 32.0 kg/m^2 HbA1c 8.2%	Tirzepatide 1 mg	26	− 0.70	− 0.90	2 (3.8)	18 (23.1)	1 (1.9)
		Tirzepatide 5 mg		− 1.60	− 4.80	5 (9.1)	18 (32.7)	4 (7.3)
		Tirzepatide 10 mg		− 2.00	− 8.70	3 (5.9)	26 (51.0)	5 (9.8)
		Tirzepatide 15 mg		− 2.40	− 11.3	13 (24.5)	35 (66)	4 (7.5)
		Dulaglutide 1.5 mg		− 1.10	− 2.70	6 (11.1)	23 (42.6)	2 (3.7)
		Placebo		+ 0.10	− 0.40	2 (3.9)	5 (9.8)	2 (3.9)
Phase 2 [Dose escalation] trial [33] (n = 111)	Age 57.4 years BMI 32.0 kg/m^2 HbA1c 8.4%	Tirzepatide 12 mg[a]	12	− 1.70	− 5.30	1 (3.4)	14 (48.3)	2 (6.9)
		Tirzepatide 15 mg[b]		− 2.00	− 5.50	1 (3.6)	16 (57.1)	5 (17.9)
		Tirzepatide 15 mg[c]		− 1.80	− 5.70	0	13 (46.4)	5 (17.9)
		Placebo		+ 0.20	− 0.50	1 (3.8)	3 (11.5)	0

BMI body mass index, *HbA1c* haemoglobin A1c, *BG* blood glucose

[a] Tirzepatide 4 mg for 4 weeks, 8 mg for 4 weeks and 12 mg for 4 weeks

[b] Tirzepatide 2.5 mg for 2 weeks, 5 mg for 2 weeks, 10 mg for 4 weeks and 15 mg for 4 weeks

[c] Tirzepatide 2.5 mg for 4 weeks, 7.5 mg for 4 weeks and 15 mg for 4 weeks

Table 3 Overview of the SURPASS phase 3 clinical trials of tirzepatide for the treatment of T2DM

Trial/ Identifier	Estimated enrolment	Concomitant therapy	TZP groups	Comparator group	Primary outcome	Treatment duration (weeks)	Primary outcome completion date
SURPASS-1 NCT03954834	472	None	5 mg 10 mg 15 mg	Placebo	Change from baseline in HbA1c	40	Oct 2020
SURPASS-2 NCT03987919	1881	Metformin	5 mg 10 mg 15 mg	Semaglutide	Change from baseline in HbA1c	40	Feb 2021
SURPASS-3 NCT03882970	1420	Metformin or metformin plus SGLT2i	5 mg 10 mg 15 mg	Insulin degludec	Change from baseline in HbA1c	52	Jan 2021
SURPASS-4 NCT03730662	1878	1–3 OAMs of metformin, SGLT2i or SU	5 mg 10 mg 15 mg	Insulin glargine	Change from baseline in HbA1c	52	June 2021
SURPASS-5 NCT04039503	472	Insulin glargine once daily with or without metformin	5 mg 10 mg 15 mg	Placebo	Change from baseline in HbA1c	40	Feb 2021
SURPASS-6 NCT04537923	1182	Insulin glargine once daily with or without metformin	5 mg 10 mg 15 mg	Insulin lispro	Change from baseline in HbA1c	52	Aug 2022
SURPASS-J mono NCT03861052	636	OAM-naïve or OAM monotherapy	5 mg 10 mg 15 mg	Dulaglutide 0.75 mg	Change from baseline in HbA1c	52	April 2021
SURPASS-J combo NCT03861039	441	OAM monotherapy	5 mg 10 mg 15 mg	N/A	Number of participants with ≥ 1 SAE	52	Mar 2021
SURPASS-AP combo NCT04093752	956	Metformin with or without SU	5 mg 10 mg 15 mg	Insulin glargine	Change from baseline in HbA1c	40	Feb 2022
SURPASS-CVOT NCT04255433	12,500	Oral or injectable anti-hyperglycaemic medications	Maximum tolerated dose up to 15 mg	Dulaglutide 1.5 mg	Time to first occurrence of a component of event of MACE-3	Event driven	Oct 2024

HbA1c glycated haemoglobin, *MACE* major adverse cardiac event, *OAM* oral anti-hyperglycaemic medication, *SAE* serious adverse event, *SGLT2i* sodium–glucose co-transporter 2, *SU* sulfonylurea

Table 1. Trials in the tirzepatide Phase 3 clinical development program for type 2 diabetes.

NCT Number	Title	Estimated enrollment (n)	Baseline Diabetes Therapy	Interventions	Primary outcome	Treatment duration for primary outcome	Primary outcome completion date
NCT03954834 SURPASS-1 NCT03954834	A randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of three tirzepatide doses versus placebo in patients with type 2 diabetes, inadequately controlled with diet and exercise alone (SURPASS-1)	472	Diet and exercise alone	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Placebo	Change from baseline in HbA1c	40 weeks	Oct 2020
NCT03882970 SURPASS-3 NCT03882970	A randomized, phase 3, open-label trial comparing the effect of LY3298176 versus titrated insulin degludec on glycemic control in patients with type 2 diabetes (SURPASS-3)	1420	MET ± SGLT-2 inh.	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Insulin degludec	Change from baseline in HbA1c (10 mg and 15 mg tirzepatide doses)	52 weeks	Dec 2020
NCT04039503 SURPASS-5 NCT04039503	A randomized, phase 3, double-blind trial comparing the effect of the addition of tirzepatide versus placebo in patients with type 2 diabetes inadequately controlled on insulin glargine with or without metformin (SURPASS-5)	472	Insulin glargine (U100) ± MET	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Placebo	Change from baseline in HbA1c (10 mg and 15 mg tirzepatide doses)	40 weeks	Dec 2020
NCT03861039 SURPASS-J combo NCT03861039	A phase 3, long-term safety study of tirzepatide in combination with monotherapy of oral antihyperglycemic medications in patients with type 2 diabetes mellitus (SURPASS J-combo)	441	Oral agent monotherapy with SFU, MET, TZD, AGI, glinide, or SGLT-2 inh.	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: None	Incidence of SAEs considered by the investigator to be related to study drug administration	52 weeks	Feb 2021
NCT03987919 SURPASS-2 NCT03987919	A phase 3, randomized, open-label trial comparing efficacy and safety of tirzepatide versus semaglutide once weekly as add-on therapy to metformin in patients with type 2 diabetes (SURPASS-2)	1872	MET monotherapy	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Semaglutide	Change from baseline in HbA1c (10 mg and 15 mg tirzepatide doses)	40 weeks	Jan 2021

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Table 1. Trials in the tirzepatide Phase 3 clinical development program for type 2 diabetes.

NCT Number	Title	Estimated enrollment (n)	Baseline Diabetes Therapy	Interventions	Primary outcome	Treatment duration for primary outcome	Primary outcome completion date
NCT03861052 (SURPASS J-mono)	A phase 3 study of tirzepatide monotherapy compared to dulaglutide 0.75 mg in patients with type 2 diabetes mellitus (SURPASS J-mono)	636	Oral agent naïve or oral agent monotherapy	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Dulaglutide 0.75 mg	Change from baseline in HbA1c	52 weeks	Mar 2021
NCT03730662 SURPASS-4 NCT03730662	Efficacy and safety of LY3298176 once weekly versus insulin glargine in patients with type 2 diabetes and increased cardiovascular risk (SURPASS-4)	1878	At least 1 and no more than 3 oral agents, which may include MET, SGLT-2 inh., and or SFU	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Insulin glargine	Change from baseline in HbA1c (10 mg and 15 mg tirzepatide doses)	52 weeks	May 2021
NCT04093752 (SURPASS-AP-Combo)	A randomized, phase 3, open-label trial comparing the effect of tirzepatide once weekly versus titrated insulin glargine on glycemic control in patients with type 2 diabetes on metformin with or without a sulfonylurea (SURPASS-AP-Combo)	956	MET ± SFU	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Insulin glargine	Change from baseline in HbA1c (10 mg and 15 mg tirzepatide doses)	40 weeks	Feb 2022
NCT04255433 SURPASS-CVOT NCT04255433	The effect of tirzepatide versus dulaglutide on major adverse cardiovascular events in patients with type 2 diabetes (SURPASS-COVT)	12,500	Type 2 diabetes, specific baseline therapy not mentioned in ClinTrials.gov	• TZP doses: 5 mg, 10 mg, and 15 mg • Comparator: Dulaglutide	Time to first occurrence of death from CV causes, MI, or stroke (MACE-3)	Approximate maximum 54 months	Oct 2024

Abbreviations: AGI, alpha-glucosidase inhibitor; CV, cardiovascular; MACE, major adverse cardiac events; MET, metformin; MI, myocardial infarction; SAE, serious adverse event; SFU, sulfonylurea; SGLT-2 inh., sodium-glucose co-transporter-2 inhibitor; TZD, thiazolidinedione; TZP, tirzepatide

Source: ClinicalTrials.gov. Bethesda, MD. National Library of Medicine, USA.

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Clinical Trial > Lancet. 2018 Nov 17;392(10160):2180-2193. doi: 10.1016/S0140-6736(18)32260-8. Epub 2018 Oct 4.

Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

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Background: LY3298176 is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for the treatment of type 2 diabetes. We aimed to examine the efficacy and safety of co-stimulation of the GLP-1 and GIP receptors with LY3298176 compared with placebo or selective stimulation of GLP-1 receptors with dulaglutide in patients with poorly controlled type 2 diabetes.

Methods: In this double-blind, randomised, phase 2 study, patients with type 2 diabetes were randomly assigned (1:1:1:1:1:1) to receive either once-weekly subcutaneous LY3298176 (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1·5 mg), or placebo for 26 weeks. Assignment was stratified by baseli glycated haemoglobin A_{1c} (HbA_{1c}), metformin use, and body-mass index (BMI). Eligible participants (aged 18-75) had type 2 diabetes for at least 6 months (HbA_{1c} 7·0-10·5%, inclusive), that was inadequately controlled with diet and exercise alone or with stable metformin therapy, and a BMI of 23-50 kg/m^2. The primary efficacy outcome was change in HbA_{1c} from baseline to 26 weeks in the modified intention-to-treat (mITT) population (all patients who received at least one dose of study

Findings: Between May 24, 2017, and March 28, 2018, 555 participants were assessed for eligibility, of whom 318 were randomly assigned to one of the six treatment groups. Because two participants did not receive treatment, the modified intention-to-treat and safety populations included 316 participants. 258 (81·7%) participants completed 26 weeks of treatment, and 283 (89·6%) completed the study. At baseline, mean age was 57 years (SD 9), BMI was 32·6 kg/m^2 (5·9), duration from diagnosis of diabetes was 9 years (6), HbA_{1c} was 8·1% (1·0), 53% of patients were men, and 47% were women. At 26 weeks, the effect of LY3298176 on change in HbA_{1c} was dose-dependent and did not plateau. Mean changes from baseline in HbA_{1c} with LY3298176 were -1·06% for 1 mg, -1·73% for 5 mg, -1·89% for 10 mg, and -1·94% for 15 mg, compared with -0·06% for placebo (posterior mean differences [80% credible set] vs placebo: -1·00% [-1·22 to -0·79] for 1 mg, -1·67% [-1·88 to -1·46] for 5 mg, -1·83% [-2·04 to -1·61] for 10 mg, and -1·89% [-2·11 to -1·67] for 15 mg). Compared with dulaglutide (-1·21%) the posterior mean differences (80% credible set) for change in HbA_{1c} from baseline to 26 weeks with the LY3298176 doses were 0·15% (-0·08 to 0·38) for 1 mg, -0·52% (-0·72 to -0·31) for 5 mg, -0·67% (-0·89 to -0·46) for 10 mg, and -0·73% (-0·95 to -0·52) for 15 mg. At 26 weeks, 33·90% of patients treated with LY3298176 achieved the HbA_{1c} target of less than 7·0% (vs 52% with dulaglutide, 12% with placebo) and 15·82% achieved the HbA_{1c} target of at least 6·5% (vs 39% with dulaglutide, 2% with placebo). Changes in fasting plasma glucose ranged from -0·4 mmol/L to -3·4 mmol/L for LY3298176 (vs 0·9 mmol/L for placebo, -1·2 mmol/L for dulaglutide). Changes in mean bodyweight ranged from -0·9 kg to -11·3 kg for LY3298176 (vs -0·4 kg for placebo, -2·7 kg for dulaglutide). At 26 weeks, 14·71% of those treated with LY3298176 achieved the weight loss target of at least 5% (vs 22% with dulaglutide, 0% with placebo) and 6·39% achieved the weight loss target of at least 10% (vs 9% with dulaglutide, 0% with placebo). Changes in waist circumference ranged from -2·1 cm to -10·2 cm for LY3298176 (vs -1·3 cm for placebo, -2·5 cm for dulaglutide). Changes in total cholesterol ranged from 0·2 mmol/L to -0·3 mmol/L for LY3298176 (vs 0·3 mmol/L for placebo, -0·2 mmol/L for dulaglutide). Changes in HDL or LDL cholesterol did not differ between the LY3298176 and placebo groups. Changes in triglyceride concentration ranged from 0 mmol/L to -0·8 mmol/L for LY3298176 (vs 0·3 mmol/L for placebo, -0·3 mmol/L for dulaglutide). The 12-week outcomes were similar to those at 26 weeks for all secondary outcomes. 13 (4%) of 316 participants across the six

- Faz 2 çalışması
- Ort 9 yıllık DM olan 258 katılımcı 26 haftalık tedaviyi tamamladı
- 1mg, 5mg,10mg veya 15 mg tirzepatid, 1.5 mg dulaglutide veya plasebo
- LY3298176 ile HbA1c'de başlangıca göre
  - 1 mg için %1,06
  - 5 mg için %1,73
  - 10 mg için % 1,89
  - 15 mg için %1,94
  - Dulaglutide % 1,21
- Ortalama vücut ağırlığındaki değişiklikler
  - LY3298176 için −0, 9 kg ila 11, 3 kg arasında değişti
  - plasebo için −0,4 kg
  - Dulaglutide için 2,7 kg
- Yan etki ;
  - Gastrointestinal olaylar (bulantı, ishal ve kusma) tedaviyle ortaya çıkan en yaygın yan etkilerdi
  - Gastrointestinal olayların insidansı doza bağlıdır

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LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept

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Abstract

Objective: A novel dual GIP and GLP-1 receptor agonist, LY3298176, was developed to determine whether the metabolic action of GIP adds to the established clinical benefits of selective GLP-1 receptor agonists in type 2 diabetes mellitus (T2DM).

Methods: LY3298176 is a fatty acid modified peptide with dual GIP and GLP-1 receptor agonist activity designed for once-weekly subcutaneous administration. LY3298176 was characterised in vitro, using signaling and functional assays in cell lines expressing recombinant or endogenous incretin receptors, and in vivo using body weight, food intake, insulin secretion and glycemic profiles in mice. A Phase 1, randomised, placebo-controlled, double-blind study was comprised of three parts: a single-ascending dose (SAD; doses 0.25-8 mg) and 4-week multiple-ascending dose (MAD; doses 0.5-10 mg) studies in healthy subjects (HS), followed by a 4-week multiple-dose Phase 1 b proof-of-concept (POC; doses 0.5-15 mg) in patients with T2DM (ClinicalTrials.gov no. NCT02759107). Doses higher than 5 mg were attained by titration, dulaglutide (DU) was used as a positive control. The primary objective was to investigate safety and tolerability of LY3298176.

Results: LY3298176 activated both GIP and GLP-1 receptor signaling in vitro and showed glucose-dependent insulin secretion and improved glucose tolerance by acting on both GIP and GLP-1 receptors in mice. With chronic administration to mice, LY3298176 potently decreased body weight and food intake; these effects were significantly greater than the effects of a GLP-1 receptor agonist. A total of 142 human subjects received at least 1 dose of LY3298176, dulaglutide, or placebo. The PK profile of LY3298176 was investigated over a wide dose range (0.25-15 mg) and supports once-weekly administration. In the Phase 1 b trial of diabetic subjects, LY3298176 doses of 10 mg and 15 mg significantly reduced fasting serum glucose compared to placebo (least square mean [LSM] difference [95% CI]: -49.12 mg/dL [-78.14, -20.12] and -43.15 mg/dL [-73.06, -13.21], respectively). Reductions in body weight were significantly greater with the LY3298176 1.5 mg, 4.5 mg and 10 mg doses versus placebo in MAD HS (LSM difference [95% CI]: -1.75 kg [-3.38, -0.12], -5.09 kg [-6.72, -3.46] and -4.61 kg [-6.21, -3.01], respectively) and doses of 10 mg and 15 mg had a relevant effect in T2DM patients (LSM difference [95% CI]: -2.62 kg [-3.79, -1.45] and -2.07 kg [-3.25, -0.88], respectively. The most frequent side effects reported with LY3298176 were gastrointestinal (vomiting, nausea, decreased appetite, diarrhoea, and abdominal distension) in both HS and patients with T2DM; all were dose-dependent and considered mild to moderate in severity.

Conclusions: Based on these results, the pharmacology of LY3298176 translates from preclinical to clinical studies. LY3298176 has the potential to deliver clinically meaningful improvement in glycaemic control and body weight. The data warrant further clinical evaluation of LY3298176 for the treatment of T2DM and potentially obesity.

- Sağlıklı deneklerde 4 haftalık çoklu artan doz çalışması
- **0.5 ve 15 mg arasında tirzepatid dozları, 1.5 mg dulaglutide veya plasebo**
- 1.5 mg dulaglutide (1.3 kg) kıyasla 4.5 mg (4.52 kg) veya 10 mg dozlarda (4.05 kg) tirzepatid alan bireylerde vücut ağırlığı başlangıç seviyesine göre azalmıştır.
- Plasebo ile karşılaştırıldığında titre edilmiş **tirzepatid** dozu alan iki grupta HbA1c, açlık glikozu ve insülin düzeylerinde belirgin düşüşler gözlenmiştir
- Glikoz toleransı, en yüksek üç tirzepatid dozu ile de iyileşmiştir ve bir oral glukoz tolerans testi sırasında plazma insülin seviyeleri, plaseboya kıyasla 15 mg tirzepatid ile tedavi edilen deneklerde artmıştır
- Plaseboya göre tüm tirzepatid dozlarında vücut ağırlığında doza ve zamana bağlı azalmalar görülmüştür, ancak istatistiksel anlamlılığa yalnızca en yüksek iki dozda ulaşılmıştır (10 mg için 2.39 kg ve 15 mg için 2.95 kg ve plasebo için 0.32 kg)
- T2D'li deneklerde vücut ağırlığındaki azalmalar, ikinci çalışmada sağlıklı bireylerde tirzepatid ile gözlenen kilo kaybı miktarına kıyasla daha az güçlü olmuştur
- **En sık bildirilen advers olaylar** ;
  - Gastrointestinal olaylardır
  - Doza bağlı olan ve hafif ila orta şiddette olduğu düşünülen mide bulantısı, kusma, ishal, iştah azalması ve abdominal distansiyonu içerir

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The dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist, tirzepatide, improves lipoprotein biomarkers associated with insulin resistance and cardiovascular risk in patients with type 2 diabetes

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Abstract

Aim: To better understand the marked decrease in serum triglycerides observed with tirzepatide in patients with type 2 diabetes, additional lipoprotein-related biomarkers were measured post hoc in available samples from the same study.

Materials and methods: Patients were randomized to receive once-weekly subcutaneous tirzepatide (1, 5, 10 or 15 mg), dulaglutide (1.5 mg) or placebo. Serum lipoprotein profile, apolipoprotein (apo) A-I, B and C-III and preheparin lipoprotein lipase (LPL) were measured at baseline and at 4, 12 and 26 weeks. Lipoprotein particle profile by nuclear magnetic resonance was assessed at baseline and 26 weeks. The lipoprotein insulin resistance (LPIR) score was calculated.

Results: At 26 weeks, tirzepatide dose-dependently decreased apoB and apoC-III levels, and increased serum preheparin LPL compared with placebo. Tirzepatide 10 and 15 mg decreased large triglyceride-rich lipoprotein particles (TRLP), small low-density lipoprotein particles (LDLP) and LPIR score compared with both placebo and dulaglutide. Treatment with dulaglutide also reduced apoB and apoC-III levels but had no effect on either serum LPL or large TRLP, small LDLP and LPIR score. The number of total LDLP was also decreased with tirzepatide 10 and 15 mg compared with placebo. A greater reduction in apoC-III with tirzepatide was observed in patients with high compared with normal baseline triglycerides. At 26 weeks, change in apoC-III, but not body weight, was the best predictor of changes in triglycerides with tirzepatide, explaining up to 22.9% of their variability.

Conclusions: Tirzepatide treatment dose-dependently decreased levels of apoC-III and apoB and the number of large TRLP and small LDLP, suggesting a net improvement in atherogenic lipoprotein profile.

- Hastalar **haftada bir kez subkutan tirzepatid (1, 5, 10 veya 15 mg)**, **dulaglutide (1.5 mg)** veya plasebo almak üzere randomize edildi.
- Serum lipoprotein profili, apolipoprotein (apo) A-I, B ve C-III ve preheparin lipoprotein lipaz (LPL) başlangıçta ve 4, 12 ve 26. haftalarda ölçüldü. Nükleer manyetik rezonans ile lipoprotein partikül profili, başlangıçta ve 26. haftada değerlendirildi. Lipoprotein insülin direnci (LPIR) skoru hesaplandı.
- 26. haftada **tirzepatid** doza bağlı olarak apoB ve apoC-III seviyelerini düşürdü ve plaseboya kıyasla serum preheparin LPL'yi artırdı.
- **Tirzepatid** 10 ve 15 mg, hem plasebo hem de dulaglutide kıyasla büyük trigliseritten zengin lipoprotein partiküllerini (TRLP), küçük düşük yoğunluklu lipoprotein partiküllerini (LDLP) ve LPIR skorunu düşürmüştür.
- **Dulaglutid** ile tedavi ayrıca apoB ve apoC-III seviyelerini düşürdü, ancak serum LPL veya büyük TRLP, küçük LDLP ve LPIR skoru üzerinde hiçbir etkisi olmadı.
- Toplam LDLP sayısı da tirzepatid 10 ve 15 mg ile plaseboya kıyasla azalmıştır.
- Normal başlangıç trigliseridleri ile karşılaştırıldığında yüksek olan hastalarda tirzepatid ile apoC-III'de daha büyük bir azalma gözlenmiştir.
- 26. haftada, vücut ağırlığında değil, apoC-III'teki değişiklik, tirzepatid ile trigliseridlerdeki değişikliklerin en iyi öngörücüydü ve değişkenliklerinin% 22.9'unu açıklıyordu.

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Clinical Research Article

Clinical Research Article

Dual GIP and GLP-1 Receptor Agonist Tirzepatide Improves Beta-cell Function and Insulin Sensitivity in Type 2 Diabetes

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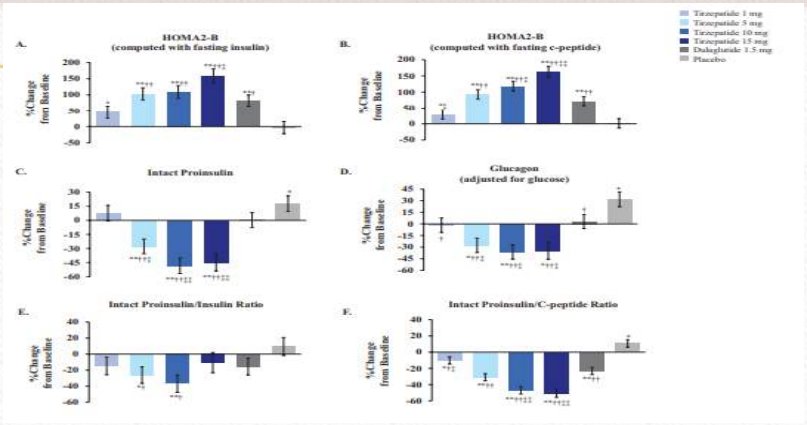
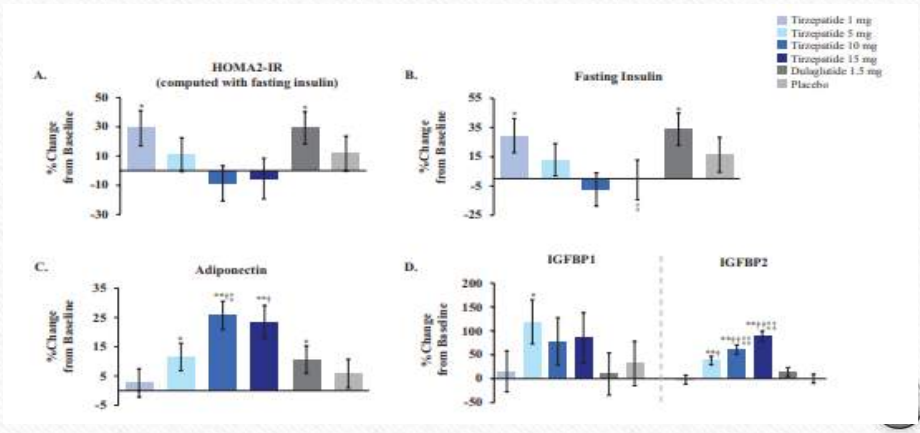
- 316 Tip 2 DM li hasta
- **Tirzepatide (1, 5, 10, 15 mg), dulaglutide (1.5 mg),** placebo
- 4 ülkede kırk yedi bölge
- (HOMA) 2-B, plaseboya kıyasla dulaglutide ve tirzepatide 5, 10 ve 15 mg ile anlamlı şekilde artmıştır (P ≤ 02)
- Proinsülin / insülin ve proinsülin / C-peptid oranları, plasebo ve dulaglutide kıyasla tirzepatid 10 ve 15 mg ile önemli ölçüde azalmıştır (P ≤ 007)
- Tirzepatid 10 ve 15 mg, plasebo ve dulaglutide kıyasla açlık insülini (P ≤ .033) ve tirzepatid 10 mg, HOMA2-IR'yi (P = .004) önemli ölçüde azaltmıştır
- Artmış insülin duyarlılığı (IS) adiponektin, IGFBP-1 ve IGFBP-2 belirteçleri, 1 veya daha fazla tirzepatid dozu ile önemli ölçüde artmıştır (P <.05)





TİRZEPATİDİN DİĞER KLİNİK ÇALIŞMALARI

- Tirzepatid ayrıca T2DM olmayan bireylerde obezitenin yönetimi için araştırılmıştır
- **SURMOUNT-1**
  - Faz 3, randomize, çift kör, plasebo kontrollü bir çalışma olarak devam etmektedir
  - T2DM si olmayan ,obezitesi olan (BMI ≥30 kg / m2 veya ≥27 kg / m2 olanlar ve komorbiditelerden en az 1 komorbiditesi (hipertansiyon, dislipidemi, obstrüktif uyku apnesi, kardiyovasküler hastalık) olan 2400 katılımcıyı planlanmaktadır
  - Birincil son noktalar, vücut ağırlığındaki başlangıca göre değişiklik ve 72 hafta sonra en az% 5 kilo kaybına ulaşan katılımcı yüzdesidir
- **SYNERGY-NASH**
  - NASH hastalarında tirzepatidin etkililiğini ve güvenliğini karşılaştıran randomize, çift kör, plasebo kontrollü bir faz 2 çalışmasıdır

ClincalTrial.gov. A study of tirzepatide (LY3298176) in participants with nonalcoholic steatohepatitis (NASH) (SYNERGY-NASH). https://clinicaltrials. gov/ct2/show/NCT04166773. 2019. Accessed 20 Nov 20.
ClinicalTrial.gov. A study of tirzepatide (LY3298176) in participants with obesity or overweight (SURMOUNT-1). https://clinicaltrials.gov/ ct2/show/NCT04184622. 2019. Accessed 20 Nov 20

Diabetes Care Volume 43, June 2020

Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes

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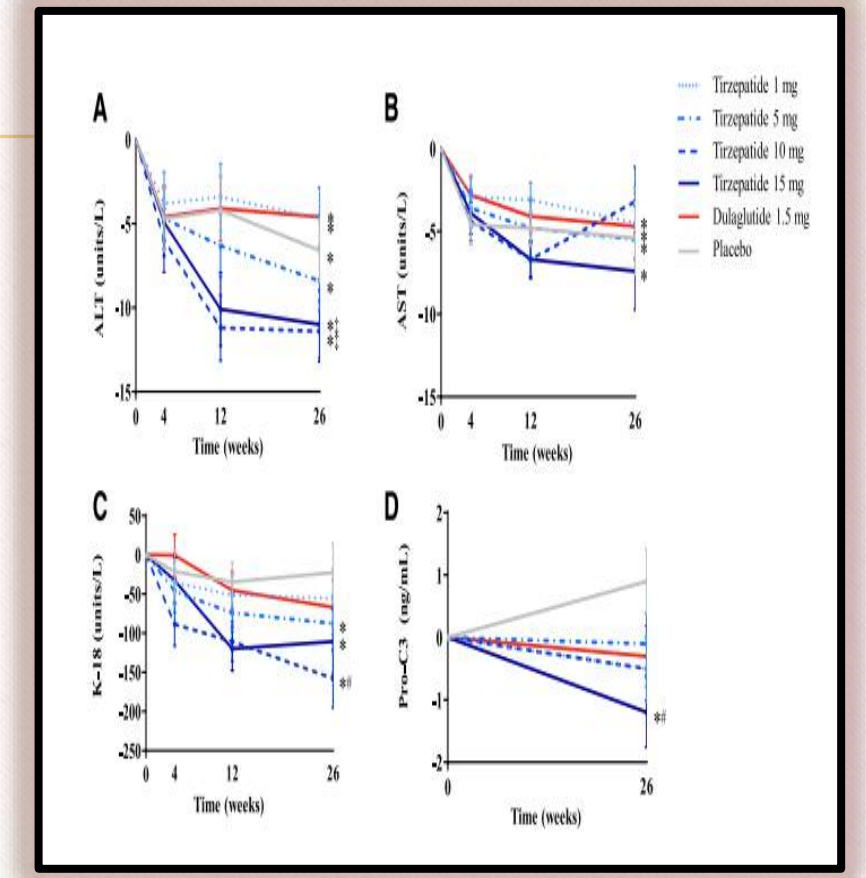
- T2DM ve NASH ve fibrosisi olan hastalara haftada bir kez tirzepatid (1, 5, 10 veya 15 mg) veya **Dulaglutide (1.5 mg)** veya 26 hafta boyunca plasebo verilmiş
- Başlangıca göre değişiklikler (ALT), (AST), keratin-18 (K-18),prokolajen III (Pro-C3) ve adiponektin, modifiye edilmiş tedavi amaçlı bir popülasyonda analiz edilmiş
- ALT (tüm gruplar), AST (tirzepatid 10 mg hariç tüm gruplar), K-18 (tirzepatid 5, 10, 15 mg) ve Pro-C3'te (tirzepatid 15 mg) başlangıca göre önemli (P <0.05) düşüşler gözlenmiş
- Dulaglutide ile karşılaştırıldığında 26. haftada. Tirzepatid ile K-18 (10 mg) ve Pro-C3 (15 mg) ve ALT (10, 15 mg) ile azalmalar izlenmiş
- Adiponektin, plaseboya kıyasla tirzepatid (10, 15 mg) ile başlangıca göre anlamlı şekilde artmış



Tirzepatide Effect on NASH Biomarkers in T2DM Diabetes Care Volume 43, June 2020

Table 1 All GLP1R/GIPR Coagonists Developed To The End Of 2018

Table 1 All GLP1R/GIPR Coagonists Developed To The End Of 2018

Drug	Originator	Developer	Status	Administration	Benefits	Unmet Needs
LYS3298176 (tirzepatide)	Eli Lilly	Eli Lilly	Phase III	Once-weekly SC administration	15 mg LYS3298176/week compared to placebo or to dulaglutide 1.5 mg/week for 26 weeks[45] Significant reduction in body weight, waist circumference, daily glucose excursion, HOMA2IR, and total cholesterol Significant increase n HOMA2B No change in mean systolic, diastolic blood pressure, mean pulse rate, PR interval, or total/severe hypoglycemia	No reduction n gastrointestinal adverse effects when compared to dulaglutide 1.5 mg/week
NN9709/ MAR709/ RG7697/ NNCOO90-2746/ RO6811135	Marcadia Biotech	Novo Nordisk	Phase II	Daily SC administration	1.8 mg NNCOO90-2746/day vs placebo or 1.8 mg liraglutide/day for 12 weeks[44] Significant reduction in body weight at 8 weeks, HbA_{1c}, fasting blood glucose, total cholesterol, postprandial glucose, postprandial insulin, Significant increase in fasting C-peptide	No significant change vs placebo: body weight at 12 weeks, fasting insulin, postprandial C-peptide, HDL-cholesterol,LDL-cholesterol, or triglycerides No reduction in gastrointestinal adverse effects when compared to liraglutide 1.8 mg/day Because AUC_{0-2h} of insulin is reduced while AUC_{0-2h} of C-peptide is unchanged after a meal test, further studies needed to better understand the effect of NNCOO90-2746 on insulin secretion, clearance, and sensitivity Rate of hypoglycemia, not reported[44] but increased vs placebo Significant increase vs placebo in heart rate[43]
SAR438335	Sanofi	Sanofi	Discontinued			
CPD86	Eli Lilly	Eli Lilly	Preclinical			
ZP-I-98	Zealand Pharma	Zealand Pharma	Preclinical (no recent development reported)			
ZP-DI-70	Zealand Pharma	Zealand Pharma	Preclinical (no recent development reported)			

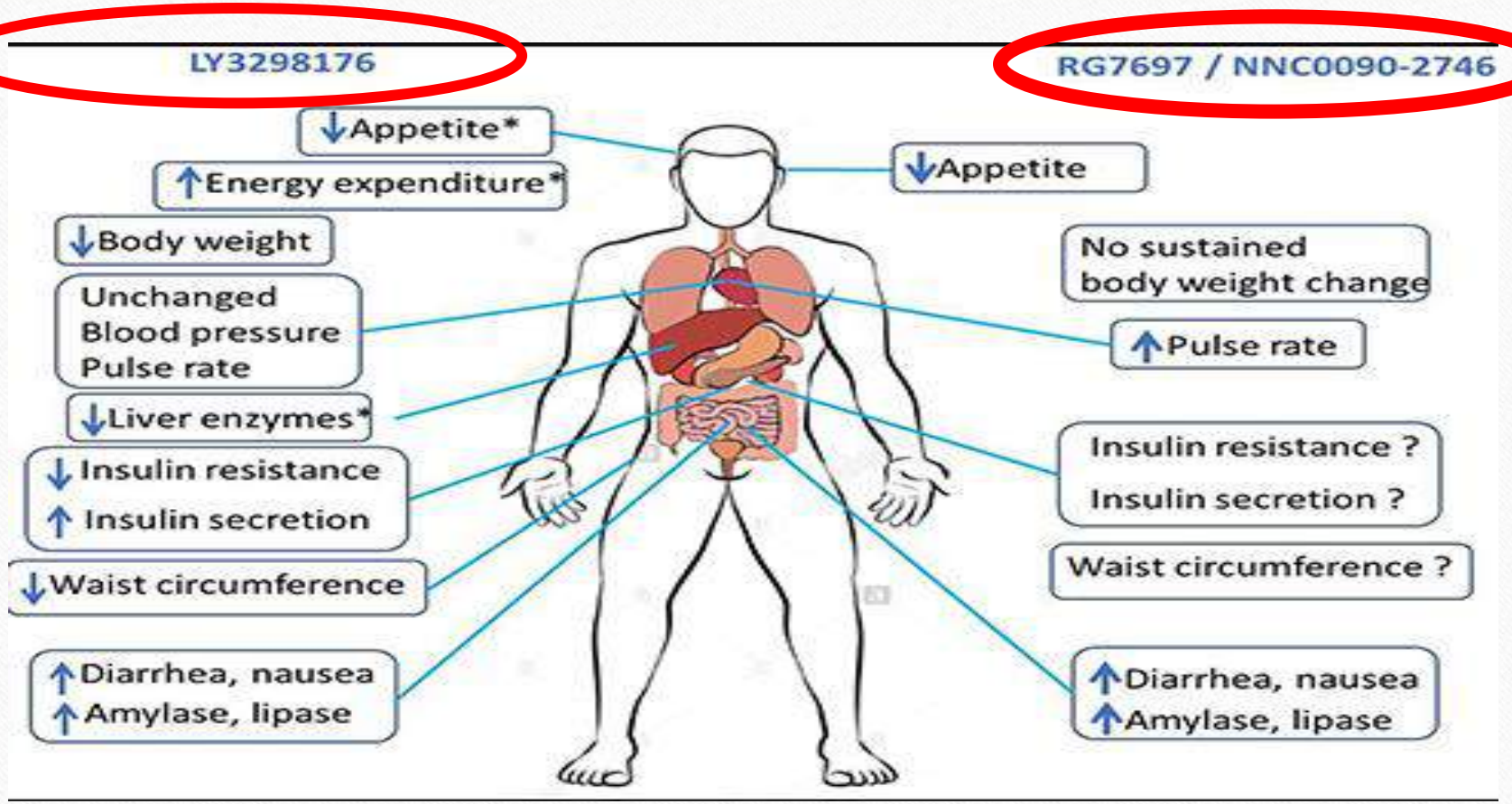
2019;12:1973-1985
https://doi.org/10.2147/DMSO.S191438

Table 2 Main results of NNCOO90-2746 and LY3298176 clinical trials[39,42–44] in patients with T2D

Drug	LYS3298176 (tirzepatide)	NN9709/MAR709/RG7697/NNCOO90-2746/RO6811135
Administration	Once-weekly	Daily SC injections
%Δ in HbA_{1c} from baseline	Placebo 0.1% (0.16) from −0.7% (0.16) [1 mg] to −1.1% (0.15) [5 mg]	Placebo −0.41% (0.25), from −0.54% (0.52) [0.25 mg] to −0.77% (0.37) [2.5 mg]
%/kgΔ in body weight from baseline	Placebo −0.40 kg (0.81), from −0.90 kg (0.80) [1 mg] to −11.3 kg (0.88) [15 mg]	Placebo −0.89 kg (1.37), from 0.9 kg (1.00) [0.25 mg] to −3.0 kg (2.33) [2.5 mg]
Fasting plasma glucose (mg/dL)	Placebo 15.5 (6.66), from −6.8 (6.43) [1 mg] to −57.5 (7.10) [15 mg]	Placebo 135.8 (22.6), from 139.6 (38.8) [0.25 mg] to 115.3 (21.3) [2.5 mg]
%Δ in postprandial glucose levels (OGTT or MTT)	Compared to placebo, from −7.05% [0.5 mg] to −39.9% [15 mg]	Placebo 10%, from 5% [2.5 mg] to −37.0% [2.5 mg]
%Δ in postprandial insulin levels (OGTT or MTT)	Compared to placebo, from 83.3% [0.5 mg] to +155.5% [15 mg]	−9.5% (placebo) vs −20% [2.5 mg]
%Δ in postprandial C peptide levels (OGTT or MTT)	NA	5% (placebo) vs −5% [2.5 mg]
Δ (mg/dL) in total cholesterol from baseline*	Placebo 11.6 (5.02) from 7.73 (5.02) [1 mg] to −11.60 (5.03) [5 mg]	Placebo −17.4mg, from −13.9 (0.25 mg) to −48.0 (2.5 mg)
Δ (mg/dL) in LDL cholesterol from baseline*	Placebo 7.73 (4.64) from 7.73 (5.02) [1 mg] to −3.86 (4.64) [5 mg]	Placebo −11.5 mg, from −14.3 (0.25 mg) to −35.0 (2.5 mg)
Δ (mmol/L) in triglycerides from baseline	Placebo 0.30 (0.16) from 0 (0.16) [1 mg] to −0.80 (0.16) [5 mg]	
Mean amylase value (normal range 31–124 U/L)	Placebo 1.8 U/L (23.2), from 8.2 U/L (25.6) [1 mg] to 18.0 U/L (37.0) [5 mg]	Placebo 59.9 U/L, from 47.5 U/L (0.25 mg) to 61.0 U/L (2.5 mg)
Mean lipase value (normal range 0–59 U/L U/L)	Placebo 4 U/L (40.2), from 63.2 U/L (33.9) [1 mg] to 59.3 U/L (27.7) [5 mg]	Placebo 36.0 U/L, from 33.6 U/L (0.25 mg) to 57.7 U/L (2.5 mg)

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2019:12

DUAL GIP-GLP-1 RESEPTÖR AGONİSTLERİ



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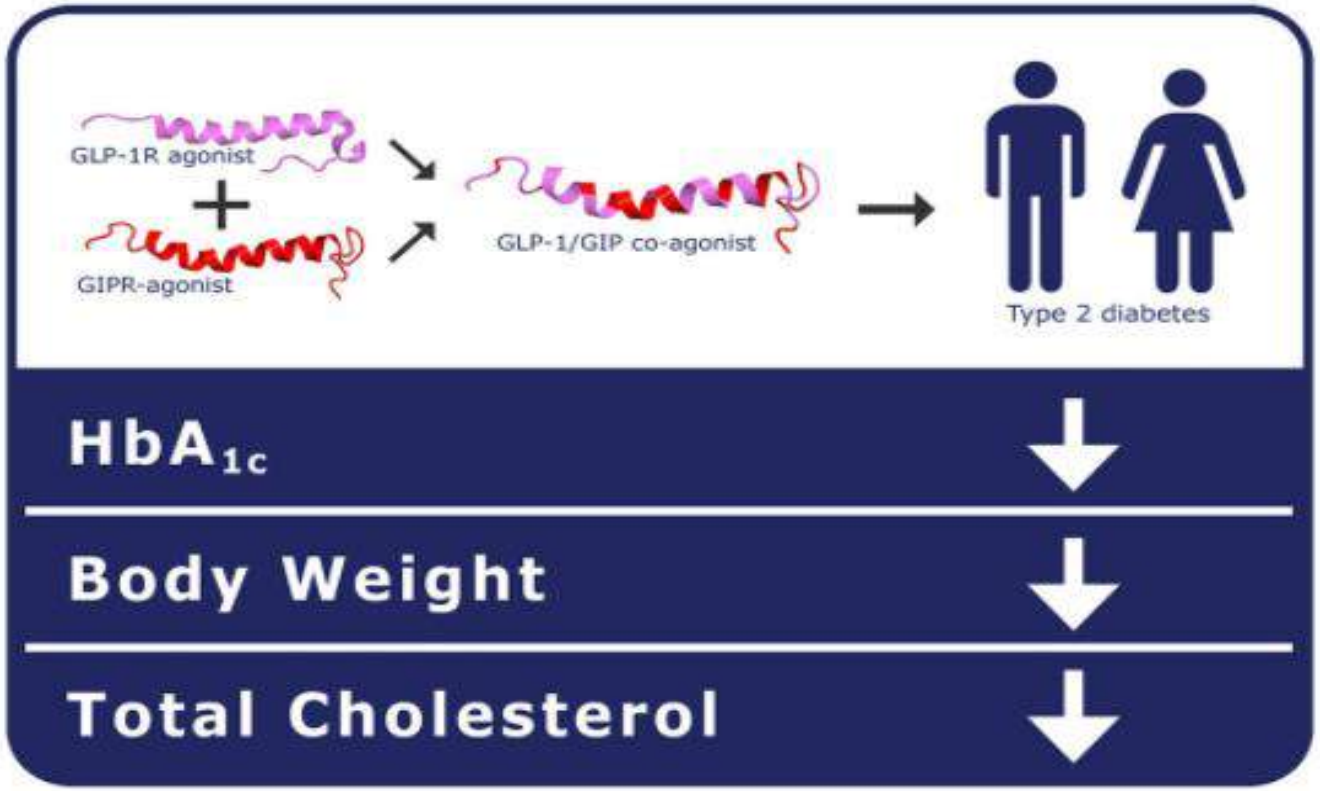
https://doi.org/10.2147/DMSO.S191438

DUAL GIP-GLP-1 RESEPTÖR AGONİSTLERİ



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