

Supplementary Material 1.

Search strategy

ghrelin AND (diabetic OR diabetes) AND (gastroparesis OR gastropathy)

PubMed

User query: ghrelin AND (diabetic OR diabetes) AND (gastroparesis OR gastropathy)

Query translation: ("ghrelin"[MeSH Terms] OR "ghrelin"[All Fields]) AND (diabetic[All Fields] OR ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields])) AND (("gastroparesis"[MeSH Terms] OR "gastroparesis"[All Fields]) OR ("stomach diseases"[MeSH Terms] OR ("stomach"[All Fields] AND "diseases"[All Fields]) OR "stomach diseases"[All Fields] OR "gastropathy"[All Fields]))

EMBASE

The following combination of terms was used in the Quick search menu ghrelin and (diabetic or diabetes) and (gastroparesis or gastropathy)

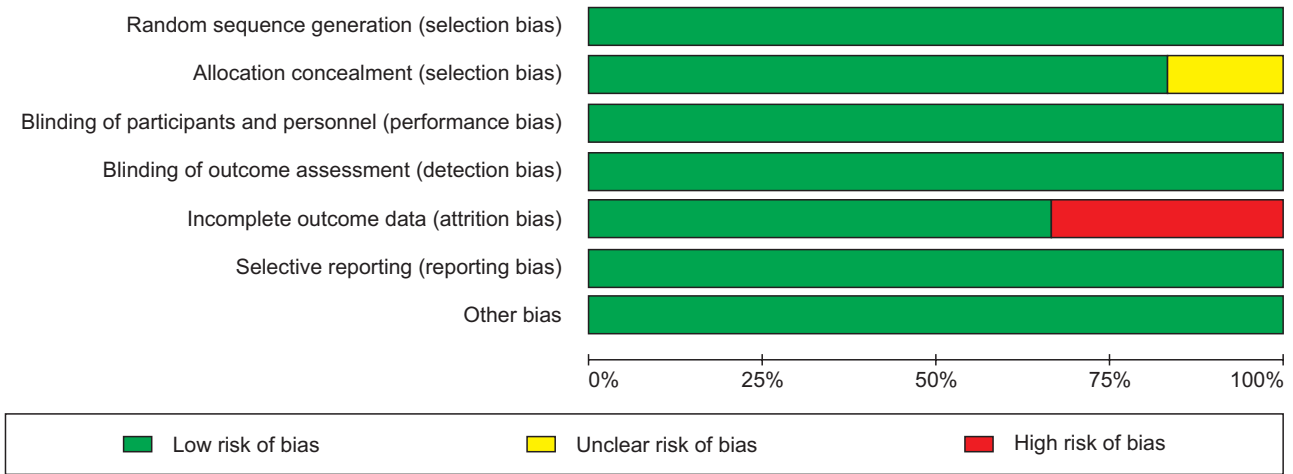
Cochrane library

Ghrelin AND (diabetic OR diabetes) AND (gastroparesis OR gastropathy) in Title Abstract Keyword

Supplementary Table 1. Number of Patients and Study Outcomes for Each Regimen in the Dose-Dependent Trials

Dosage regimen	No. of patients	Available study outcomes	Regimen of the largest population	Regimen of the greatest efficacy based on overall symptom score
Ejskjaer <i>et al.</i> (2010) ¹				
TZP-101				
20 µg/kg	8	NA		
40 µg/kg	17	NA	+	
80 µg/kg	13	OSS, SSS		+
160 µg/kg	6	NA		
320 µg/kg	6	NA		
600 µg/kg	7	NA		
Ejskjaer <i>et al.</i> (2013) ²				
TZP-102				
10 mg qd	22	OSS, SSS, GET		
20 mg qd	21	OSS, SSS, GET		+
40 mg qd	23	OSS, SSS, GET	+	
McCallum <i>et al.</i> (2013) ³				
TZP-102				
10 mg qd	69	OSS, SSS, GET	+	+
20 mg qd	66	OSS, SSS, GET		
10 mg tid	44	OSS, SSS, GET		
Lembo <i>et al.</i> (2016) ⁴				
RM-131				
10 µg qd	67	OSS, SSS, GET		
10 µg bid	68	OSS, SSS, GET	+	+
Camilleri <i>et al.</i> (2017) ⁵				
RM-131				
10 µg bid	86	OSS, SSS, GET		
30 µg bid	91	OSS, SSS, GET	+	
100 µg bid	63	OSS, SSS, GET		+

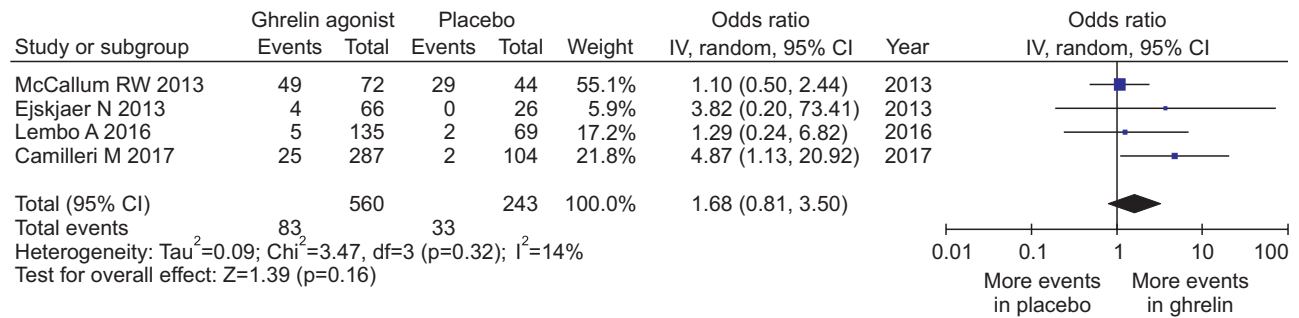
NA, not available; OSS, overall symptoms score; SSS, specific symptoms score; GET, gastric emptying time; qd, once daily; bid, twice daily.



Supplementary Fig. 1. Risk of bias included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Camilleri M 2017	●	●	●	●	●	●	●
Lembo A 2016	●	●	●	●	●	●	●
Ejskjaer N 2010	●	●	●	●	●	●	●
Ejskjaer N 2013	●	●	●	●	●	●	●
McCallum RW 2013	●	●	●	●	●	●	●
Shin A 2013	●	●	●	●	●	●	●

Supplementary Fig. 2. Summary of risk of bias. Green, low risk of bias; yellow, unclear risk of bias; red, high risk of bias.



Supplementary Fig. 3. Forest plot of adverse events linked to hyperglycemia (ghrelin agonist vs placebo). IV, inverse variance; CI, confidence interval.

REFERENCES

1. Ejskjaer N, Dimcevski G, Wo J, et al. Safety and efficacy of ghrelin agonist TZP-101 in relieving symptoms in patients with diabetic gastroparesis: a randomized, placebo-controlled study. *Neurogastroenterol Motil* 2010;22:e1069-e1281.
2. Ejskjaer N, Wo JM, Esfandyari T, et al. A phase 2a, randomized, double-blind 28-day study of TZP-102 a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol Motil* 2013;25:e140-e150.
3. McCallum RW, Lembo A, Esfandyari T, et al. Phase 2b, randomized, double-blind 12-week studies of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol Motil* 2013;25:e705-e717.
4. Lembo A, Camilleri M, McCallum R, et al. Relamorelin reduces vomiting frequency and severity and accelerates gastric emptying in adults with diabetic gastroparesis. *Gastroenterology* 2016;151:87-96.
5. Camilleri M, McCallum RW, Tack J, Spence SC, Gottesdiener K, Fiedorek FT. Efficacy and safety of relamorelin in diabetics with symptoms of gastroparesis: a randomized, placebo-controlled study. *Gastroenterology* 2017;153:1240-1250.
6. Shin A, Camilleri M, Busciglio I, et al. Randomized controlled phase Ib study of ghrelin agonist, RM-131, in type 2 diabetic women with delayed gastric emptying: pharmacokinetics and pharmacodynamics. *Diabetes Care* 2013;36:41-48.