SUPPLEMENTARY MATERIAL

Table S1. Intensity definitions of pre-specified GI AEs

	Mild	Moderate	Severe
Diarrhea	Increase of <4 stools per day over baseline	Increase of 4–6 stools per day over baseline	Increase of ≥7 stools per day over baseline
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Associated with significant weight loss or malnutrition. Inadequate oral caloric or fluid intake
Vomiting	1–2 episodes (separated by 5 min) in 24 h	Oral intake altered without significant weight loss or malnutrition	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake)
Decreased appetite	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake)
Abdominal pain	Mild pain	Moderate pain	Severe pain

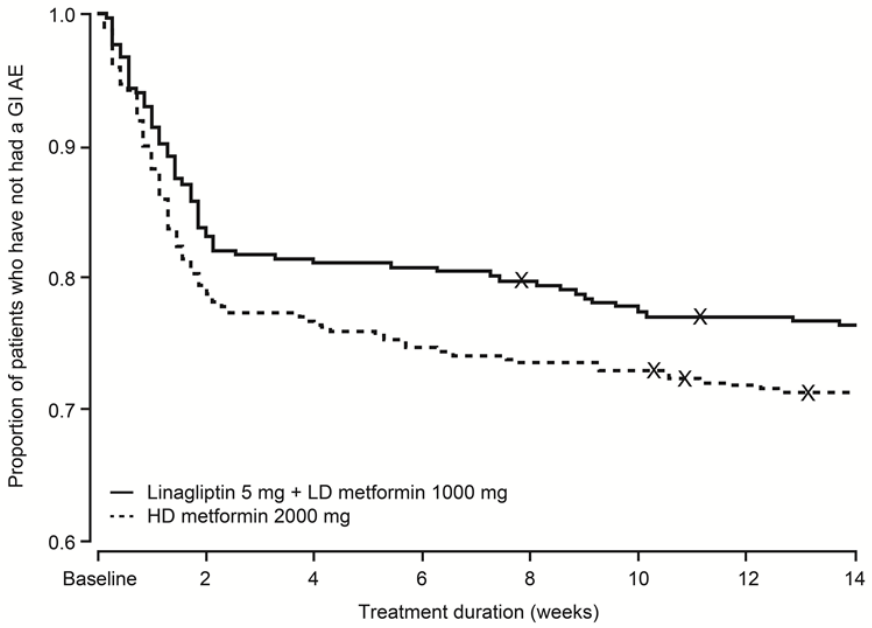
AE adverse event, *GI* gastrointestinal

Table S2. Proportion of patients achieving pre-specified HbA1c targets

	Linagliptin 5 mg + LD metformin 1000 mg	HD metformin 2000 mg
Patients (FAS_{1000mg}[a]), *n*	298	341
HbA1c <6.5% (48 mmol/mol), %	32.9	31.7
HbA1c reduction ≥0.8% (9 mmol/mol), %	54.4	54.8
HbA1c <6.5% (48 mmol/mol) without occurrence of pre-specified moderate or severe GI events, %	30.2	28.7
HbA1c reduction ≥0.8% (9 mmol/mol) without occurrence of pre-specified moderate or severe GI events, %	50.0	51.3

[a] Full analysis set (FAS_{1000mg}) – all patients who had a baseline and ≥1 on-treatment HbA1c measurement, who tolerated a daily metformin dose of at least 1000 mg at the end of the titration phase. *GI* gastrointestinal, *HbA1c* glycated hemoglobin, *HD* high dose, *LD* low dose

Fig. S1. Kaplan-Meier estimates of time to start of the first pre-specified GI AE of any intensity (mild, moderate, and severe) (FAS_{1000mg}; original results)



Patients at risk								
Linagliptin 5 mg + LD metformin 1000 mg	298	250	243	241	237	231	228	226
HD metformin 2000 mg	341	271	262	255	251	249	243	240

FAS_{1000mg} – all patients who had a baseline and ≥1 on-treatment HbA1c measurement, who tolerated a daily metformin dose of ≥1000 mg at the end of the titration phase.

AE adverse event, *FAS* full analysis set, *GI* gastrointestinal, *HbA1c* glycated hemoglobin, *HD* high dose, *LD* low dose