

**Cell Metabolism, Volume 26**

**Supplemental Information**

**The Sustained Effects of a Dual**

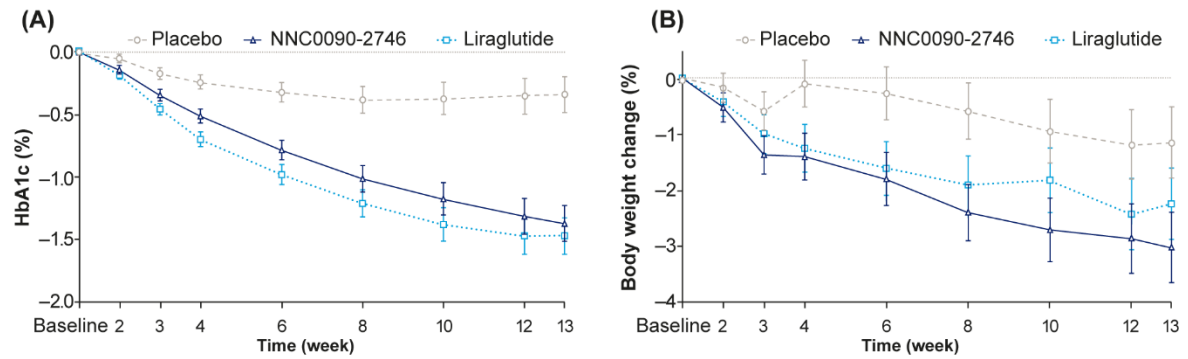
**GIP/GLP-1 Receptor Agonist, NNC0090-2746,**

**in Patients with Type 2 Diabetes**

**Juan Pablo Frias, Edward J. Bastyr, III, Louis Vignati, Matthias H. Tschöp, Christophe Schmitt, Klara Owen, Rune Haubo Christensen, and Richard D. DiMarchi**

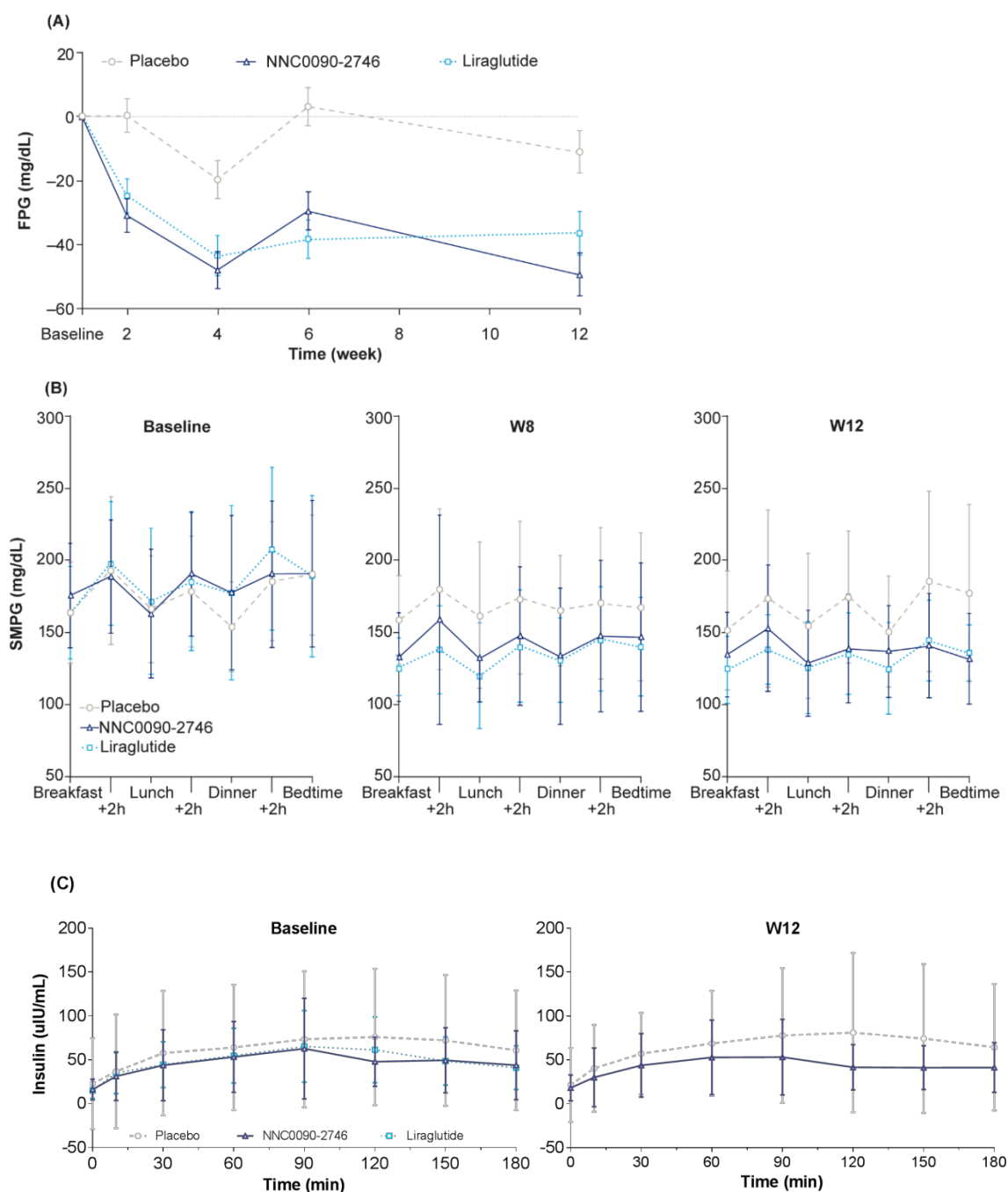
## Supplemental Information

**Figure S1, related to Figure 3: Effect of NNC0090-2746 and Liraglutide on HbA<sub>1c</sub> and Body Weight**  
Time course of estimated mean ( $\pm$ SEM) change from baseline in HbA<sub>1c</sub> (A) and body weight (B).

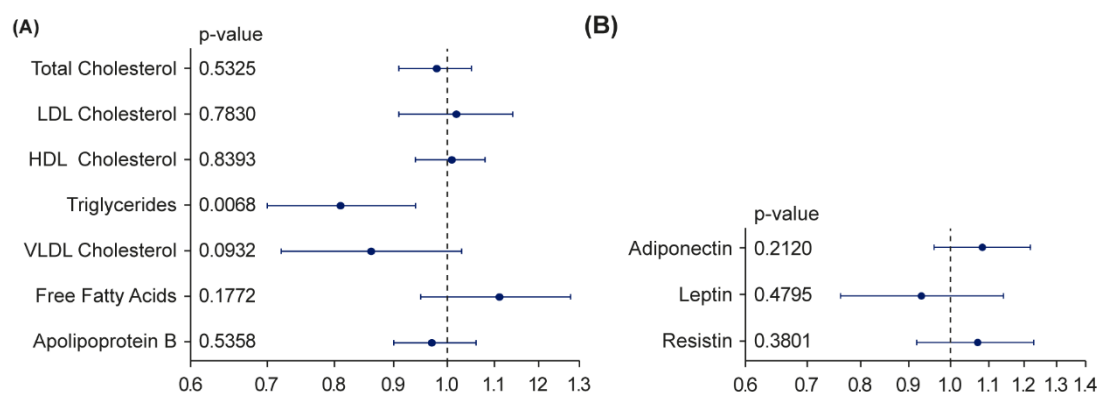


**Figure S2, related to Table 2: Effect of NNC0090-2746 and Liraglutide on FPG, SMPG and observed mean insulin**

Time course of estimated mean ( $\pm$ SEM) change from baseline in fasting plasma glucose (FPG) (A), summary of observed mean self-measured plasma glucose (SMPG) at baseline, W8, and W12 (B) and summary of observed mean insulin after a meal tolerance test (MTT) at baseline and W12 (C).



**Figure S3, related to Figure 4: Effect of Liraglutide on Adipose Biomarkers and Lipid Parameters**  
 Treatment ratios with 95% CI for fasting lipids from baseline to W13 (A), and for adipose biomarkers from baseline to W12 (B) with liraglutide compared with placebo HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.



**Table S1, related to STAR Methods, Serious Adverse Event Narrative**

A 57-year-old female was randomised to receive NNC0090-2746 from 08 May 2015 to 09 Jul 2015. The medical history and concomitant illness at screening included ectopic pregnancy, oophorectomy and scar (1978); cerebrovascular accident, hypoesthesia and muscular weakness (1995), hypertension and type 2 diabetes mellitus (1999), polyuria, left ventricular hypertrophy, retinopathy hypertensive and myocardial ischemia (2001), type 2 hyperlipidaemia, obesity and menopause (2002), left ventricular hypertrophy, oedema peripheral, urinary tract infection (2006, 2008 and 2009), dermatitis allergic, eye pruritus and nephropathy (2008), supraventricular extrasystoles (2010), onychomycosis (2012), fungal infection and ecchymosis (2013) and back pain (2014). The concomitant medications at the time of the event included aspirin, atorvastatin, digoxin and hydrochlorthiazide, metformin and metoprolol and warfarin.

The patient experienced an event of atrial fibrillation on 10 Jul 2015, on trial day 64, and this event subsequently led to withdrawal of the patient from the trial. The patient received her last dose of NNC0090-2746 on 09 Jul 2015. The event of atrial fibrillation was moderate in intensity and resolved 4 days after the onset. The event of atrial fibrillation was not considered to be related to the trial product according to the investigator's assessment.

**Table S2, related to Table 2: Post-hoc analyses**

	n		ETD [95% CI]	Treatment by subgroup interaction p-value
	NNC0090-2746	Placebo		
HbA <sub>1c</sub> (%)				
Baseline HbA <sub>1c</sub> < 8.5%	18	22	-1.34 [-1.86;-0.81]	0.0596
Baseline HbA <sub>1c</sub> ≥8.5%	18	14	-0.60 [-1.16;-0.05]	
Body weight (%)				
Baseline HbA <sub>1c</sub> < 8.5%	18	22	-3.38 [-5.76;-1.00]	0.0409
Baseline HbA <sub>1c</sub> ≥8.5%	18	14	0.27 [-2.29;2.83]	

Estimated treatment difference (ETD) with 95% confidence interval (CI) and interaction p-value for glycated hemoglobin (HbA<sub>1c</sub>) and body weight effect of different subgroups. n; number of patients included in the model.

**Table S3, related to Table 2: Summary of Change in HbA<sub>1c</sub>, Body Weight, and Glycemic Control Parameters for Liraglutide**

Parameter	Liraglutide	Liraglutide vs. placebo ETD [95% CI]	p-value
<b>HbA<sub>1c</sub> (%)</b>	<b>n = 35</b>		
Week 8	7.12	-0.83 [-1.14;-0.53]	<.0001
Week 12	6.87	-1.12 [-1.53;-0.71]	<.0001
<b>Mean of 7-point SMPG (mg/dL)</b>	<b>n = 30</b>		
Week 8	134.8	-38.3 [-55.6;-21.1]	<.0001
Week 12	135.2	-32.5 [-47.9;-17.1]	<.0001
<b>FPG (mg/dL)</b>	<b>n = 35</b>		
Week 12	129.3	-25.4 [-44.2;-6.5]	0.0089
<b>Body weight (%)</b>	<b>n = 35</b>		
Week 8	-1.90	-1.31 [-2.76;0.13]	0.0747
Week 12	-2.42	-1.23 [-3.00;0.54]	0.1710
		Liraglutide vs. placebo ETR [95% CI]	
<b>Fasting insulin (μIU/mL)</b>	<b>n = 35</b>		
Week 12	15.80	1.33 [1.04;1.71]	0.0252
<b>Fasting C-peptide (ng/mL)</b>	<b>n = 35</b>		
Week 12	3.694	1.26 [1.10;1.44]	0.0010

Estimated mean values for several metabolic parameters for liraglutide as well as the estimated treatment difference (ETD) or estimated treatment ratio (ETR) with 95% confidence interval (CI) and p-value for liraglutide versus placebo. FPG, fasting plasma glucose; HbA<sub>1c</sub>, glycated hemoglobin; n, number of patients included in the model; SMPG, self-measured plasma glucose.

**Table S4, related to Table 3: Adverse Events and Treatment-Emergent Adverse Events for the Liraglutide Arm**

Category	Liraglutide (N = 35)		
	n	%	E
AEs	24	68.6	71
TEAEs	22	62.9	60
AEs leading to death	0	0	0
AEs leading to discontinuation	0	0	0
TEAEs leading to discontinuation	0	0	0
AE related to trial drug	13	37.1	26
TEAE related to trial drug	12	34.3	24
SAE	0	0	0
TEAEs reported by ≥5% of patients in any treatment group by SOC			
Gastrointestinal disorders	11	31.4	23
Musculoskeletal and connective tissue disorders	7	20.0	9
Investigations	3	8.6	4
Infections and infestations	3	8.6	4
Metabolism and nutrition disorders	3	8.6	3
General disorders and administration site conditions	4	11.4	5
Nervous system disorders	5	14.3	5
Injury, poisoning, and procedural complications	0	0.0	0
Respiratory, thoracic, and mediastinal disorders	1	2.9	1

Adverse events (AEs), treatment-emergent AEs (TEAEs) and serious AEs (SAEs) for patients on liraglutide in the safety population. AEs are coded by MedDRA. N, number of patients, n; the number of patients in each category; E; number of events in each category.