INSULINA E GLP-1 RAS: INSIEME O SEPARATI?

Terapia Iniettiva Combinata Iniziale?

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Boehringer Ingelheim , Astra Zeneca, Johnson&Johnson, Lilly Italia, Medtronic, MOVI, Novo Nordisk, Roche, Sanofi Aventis, Takeda (*consulenza scientifica*)

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Quando considerare una combinazione fissa basale – GLP-1 RA?

Necessità di intensificare una terapia iniettiva

Pazienti già in terapia con insulina basale + OAD

Pazienti già in terapia con GLP-1 RA + OAD

Necessità di iniziare una terapia iniettiva:

Pazienti già in terapia con OAD

→ *Iniziamo basale, GLP-1 RA o la combinazione?*

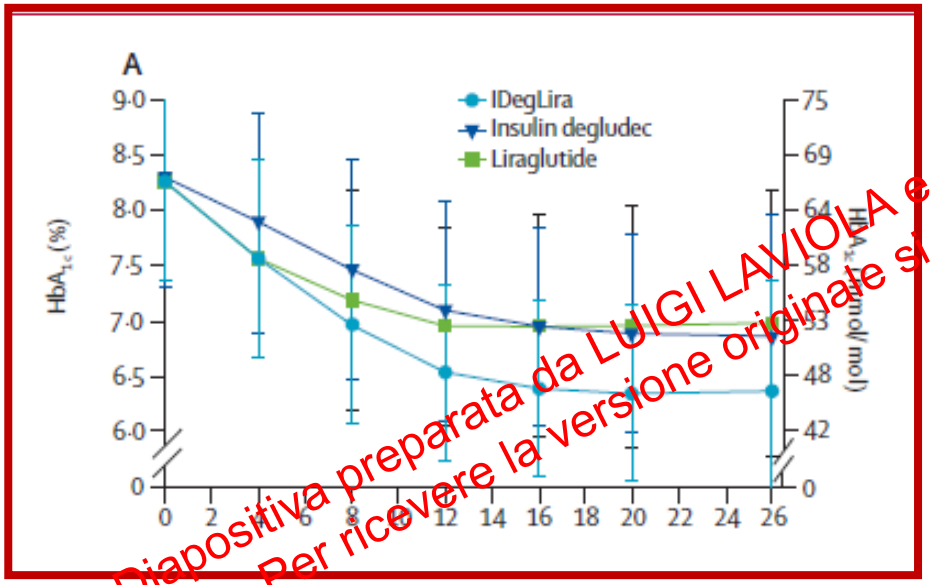
DUAL I: IDegLira vs Ideg vs Lira

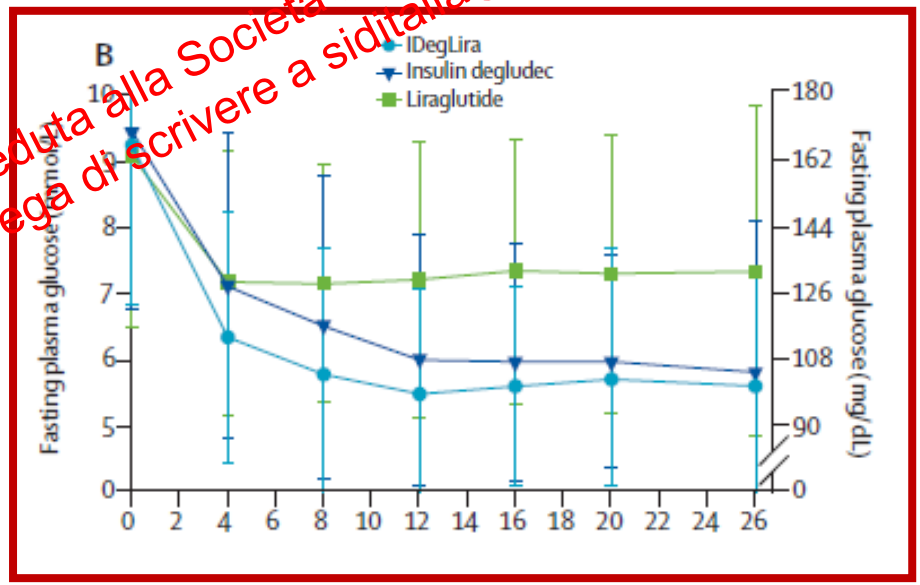
	IDegLira (n=833)	Insulin degludec (n=413)	Liraglutide (n=414)
Female	398 (48%)	213 (52%)	206 (50%)
Ethnic origin			
White	513 (62%)	257 (62%)	258 (62%)
Black	72 (9%)	23 (6%)	28 (7%)
Asian	228 (27%)	120 (29%)	116 (28%)
Other	18 (2%)	11 (3%)	11 (3%)
Age (years)	55·1 (9·9)	54·9 (9·7)	55·0 (10·2)
Bodyweight (kg)	87·2 (19·0)	87·4 (19·2)	87·4 (18·0)
BMI (kg/m^2)	31·1 (5·2)	31·2 (5·3)	31·3 (4·8)
Duration of diabetes (years)	6·6 (5·1)	7·0 (5·3)	7·2 (6·1)
HbA_{1c} (%)	8·3% (0·9)	8·3% (1·0)	8·3% (0·9)
HbA_{1c} (mmol/mol)*	67·0 (9·7)	67·3 (10·7)	66·8 (10·3)
Fasting plasma glucose (mmol/L)	9·2 (2·4)	9·4 (2·7)	9·0 (2·6)
Oral antidiabetic drug at screening			
Metformin	691 (83%)	343 (83%)	338 (82%)
Metformin plus pioglitazone†	142 (17%)	70 (17%)	75 (18%)

Data are n (%) or mean (SD). The median daily dose of metformin at screening was 2000 mg; the median daily dose of pioglitazone at screening was 30 mg (see appendix p 10 for more details). IDegLira=insulin degludec–liraglutide.
*Calculated by use of the formula: HbA_{1c} (mmol/mol)=(HbA_{1c} [%]−2·15)×10·929. †One patient in the liraglutide group was receiving metformin plus glimepiride at screening.

Gough et al. Lancet Diab Endocr 2014

DUAL I: HbA1c and FPG





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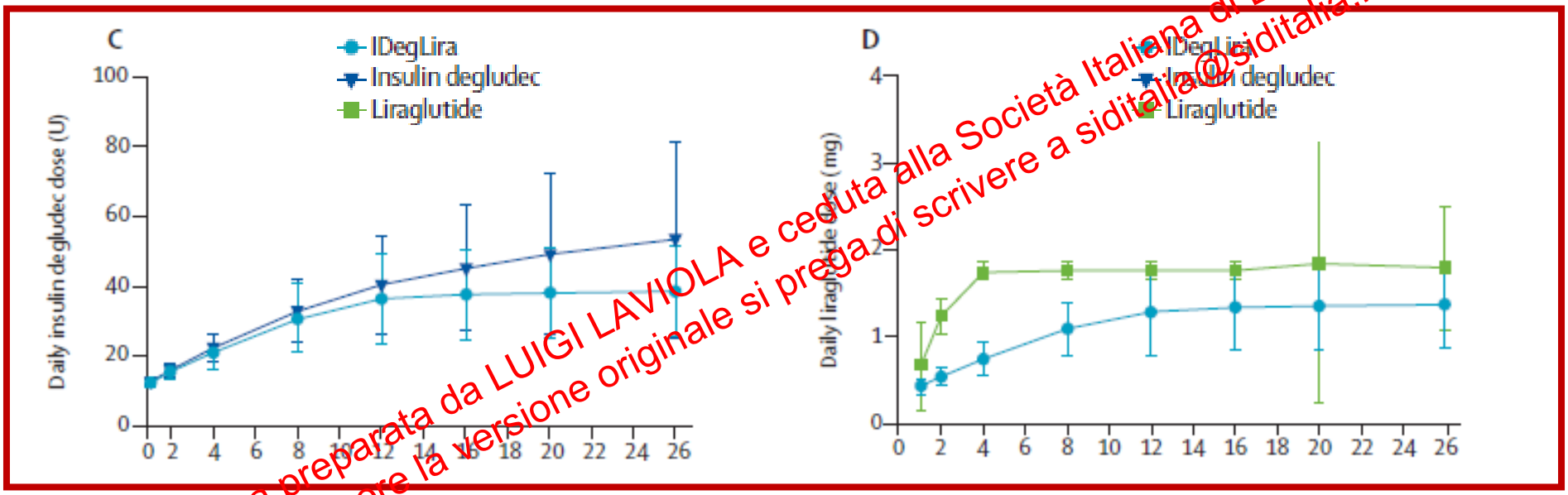
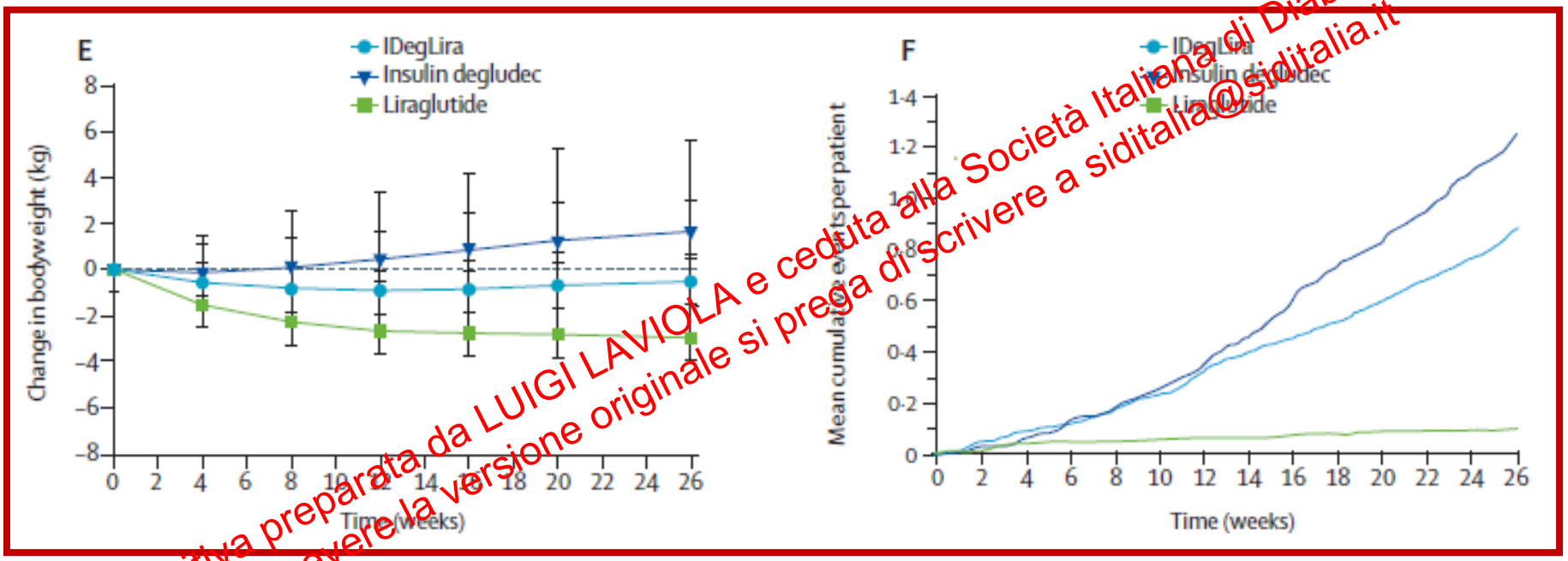
DUAL I: Ideg Dose and Lira Dose



Gough et al. Lancet Diab Endocr 2014

DUAL I: Body Weight and Hypoglycaemia



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DUAL I: Composite outcomes

	Proportion of subjects (%)			
	IDegLira	IDeg	Lira	*p*-value
HbA_{1c} <7%	81	65	60	<0.001
HbA_{1c} <7%, no weight gain	46	21	54	<0.001
HbA_{1c} <7%, no hypoglycaemic episodes	60	41	58	<0.001/NS
HbA_{1c} <7%, no weight gain and no hypoglycaemic episodes	36	14	52	<0.001

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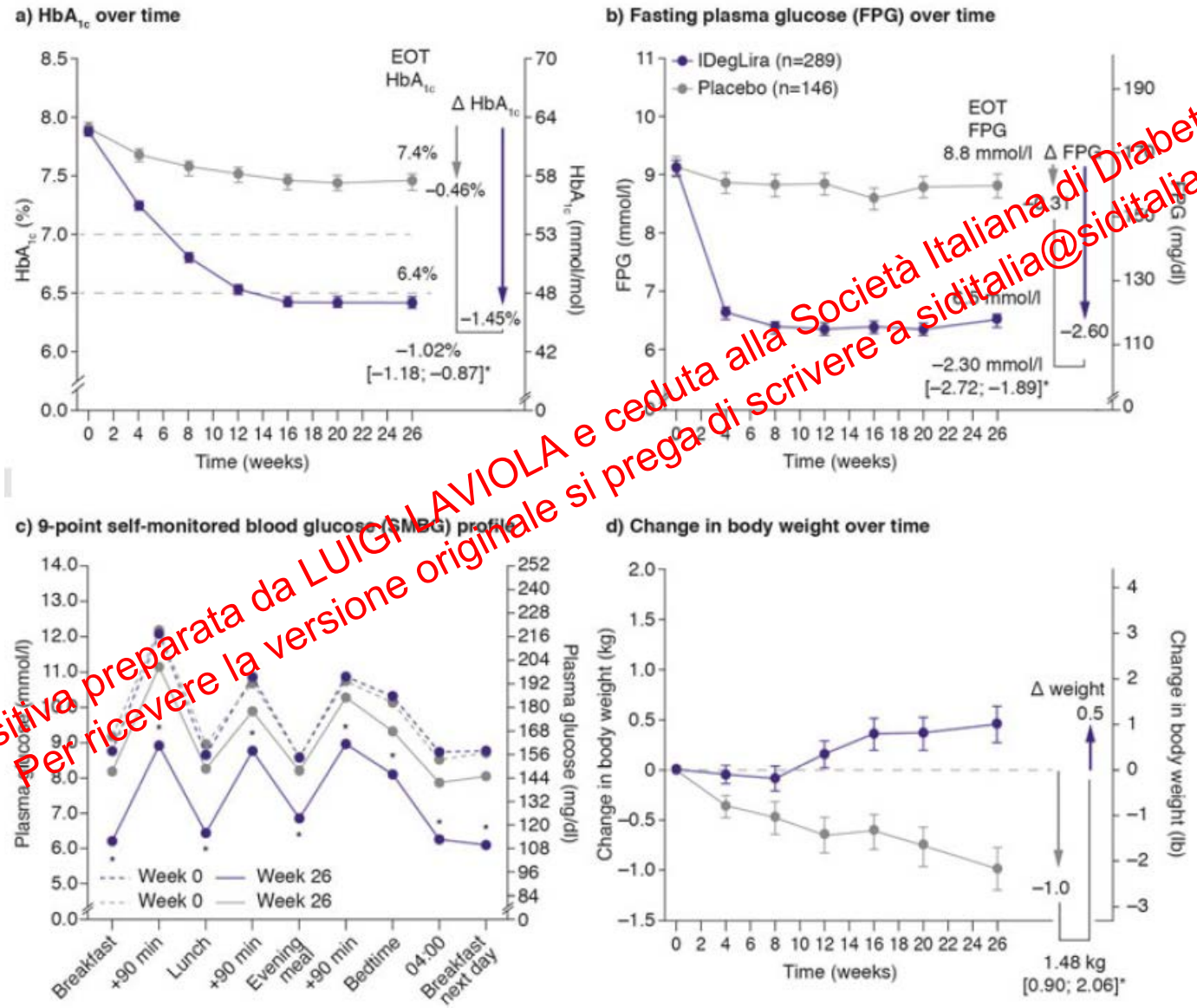
E con la Sulfonilurea che Succede? DUAL IV



Rodbard HV et al. 2017

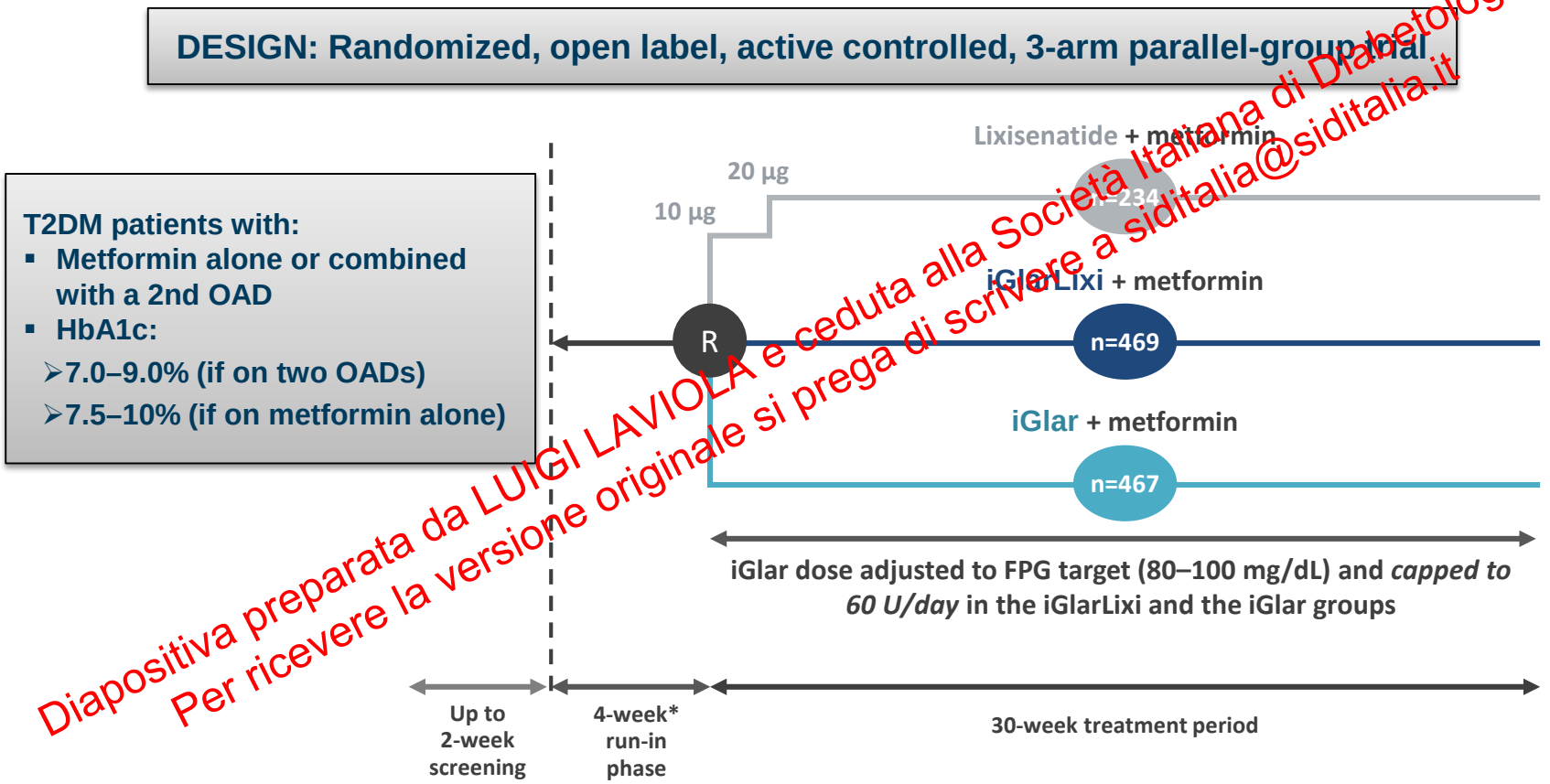
E con la Sulfonilurea che Succede? DUAL IV

		IDegLira				Placebo				P
		N	%	Number of events	Events per PYE	*N*	%	Number of events	Events per PYE	
Severe	Overall	2	0.7	2	0.015	–	–	–	–	–
Confirmed	Overall	120	41.7	467	3.517	25	17.1	84	1.352	<0.001
	Nocturnal	34	11.8	65	0.490	10	6.8	20	0.322	0.053

PYE, patient-years of exposure.

Rodbard HV et al. 2017

LixiLan-O: Patients with T2DM not controlled on OADs



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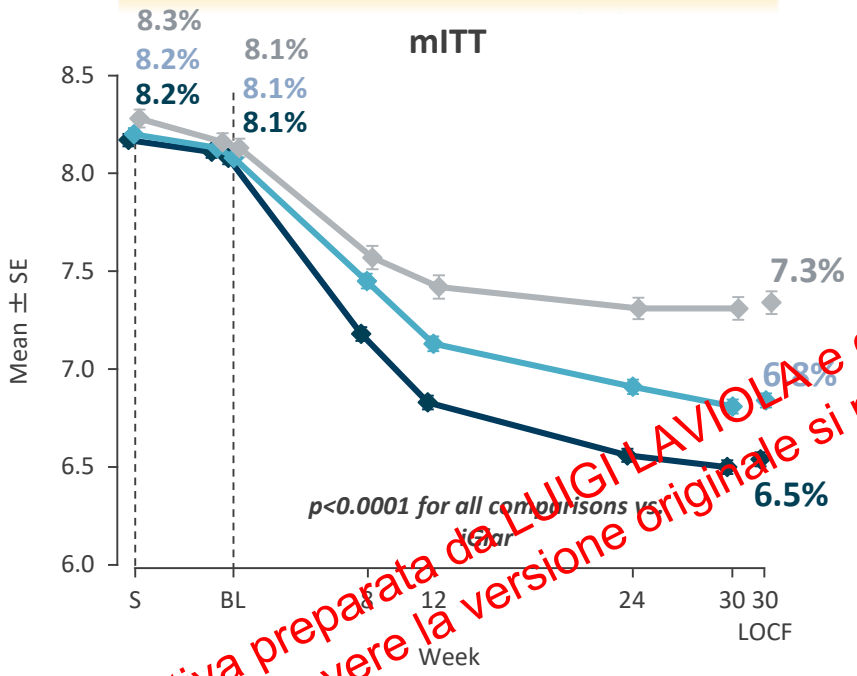
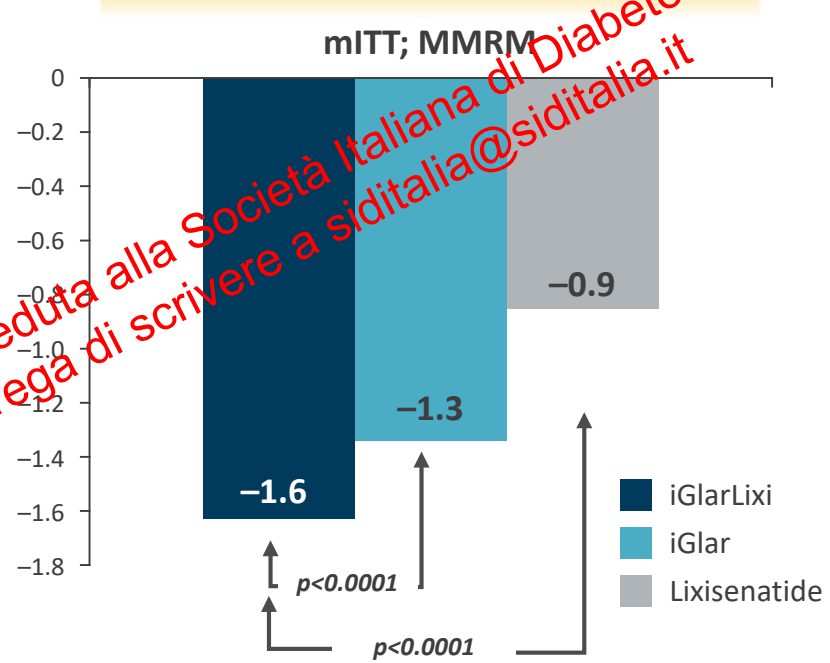
LixiLan-O: Primary objectives met

Superiority in HbA1c change from baseline shown vs. both comparators

HbA1c over time (%)



LS mean change in HbA1c (%)



LS mean difference vs. iGlar: –0.3 (95% CI –0.4 to –0.2)
LS mean difference vs. lixisenatide: –0.8 (95% CI –0.9 to –0.7)

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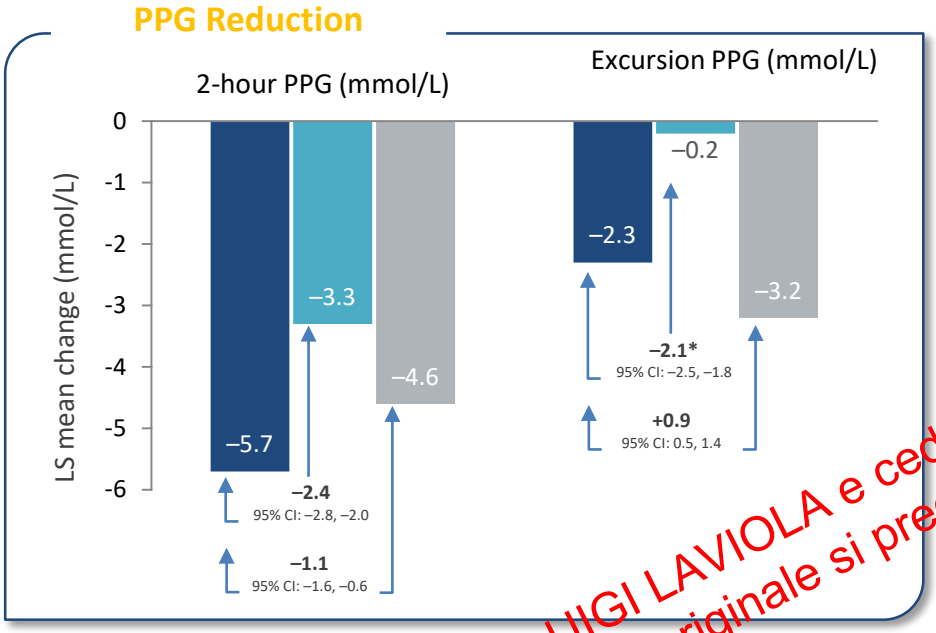
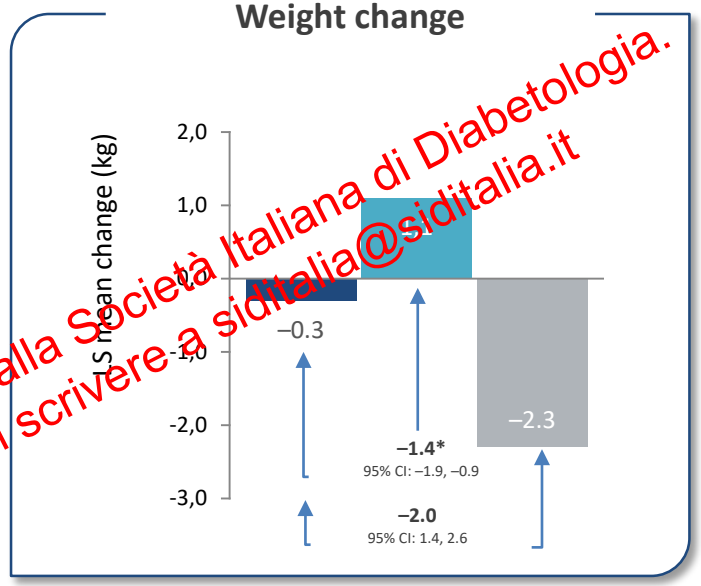
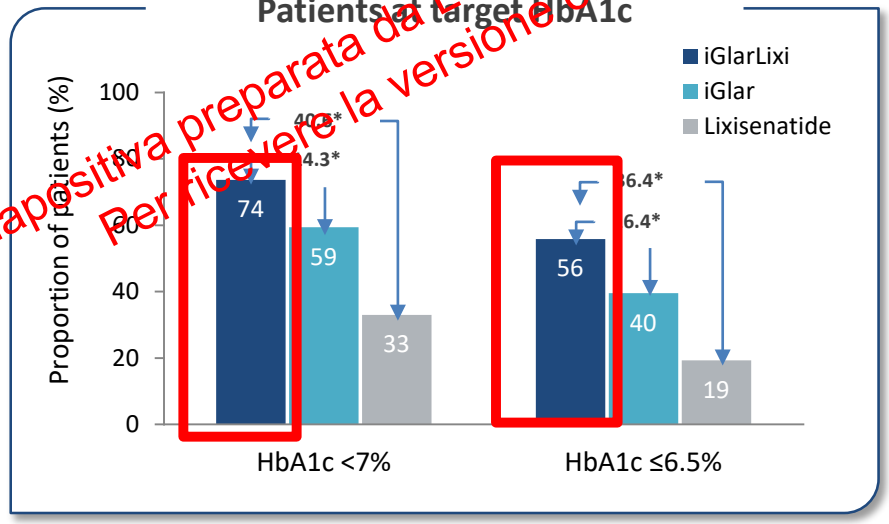
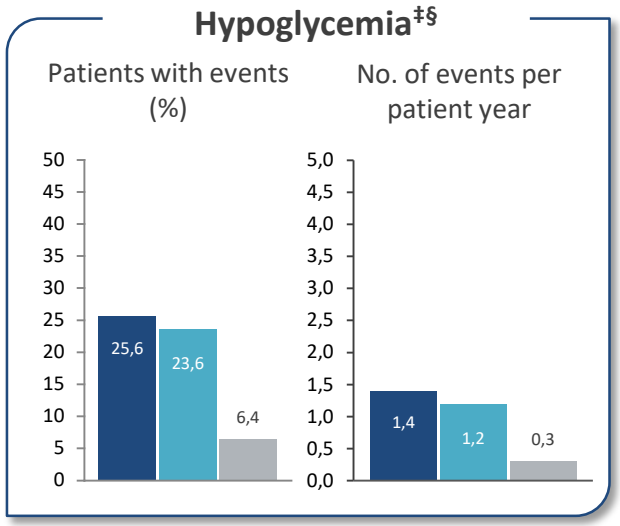
LixiLan-O: Key results









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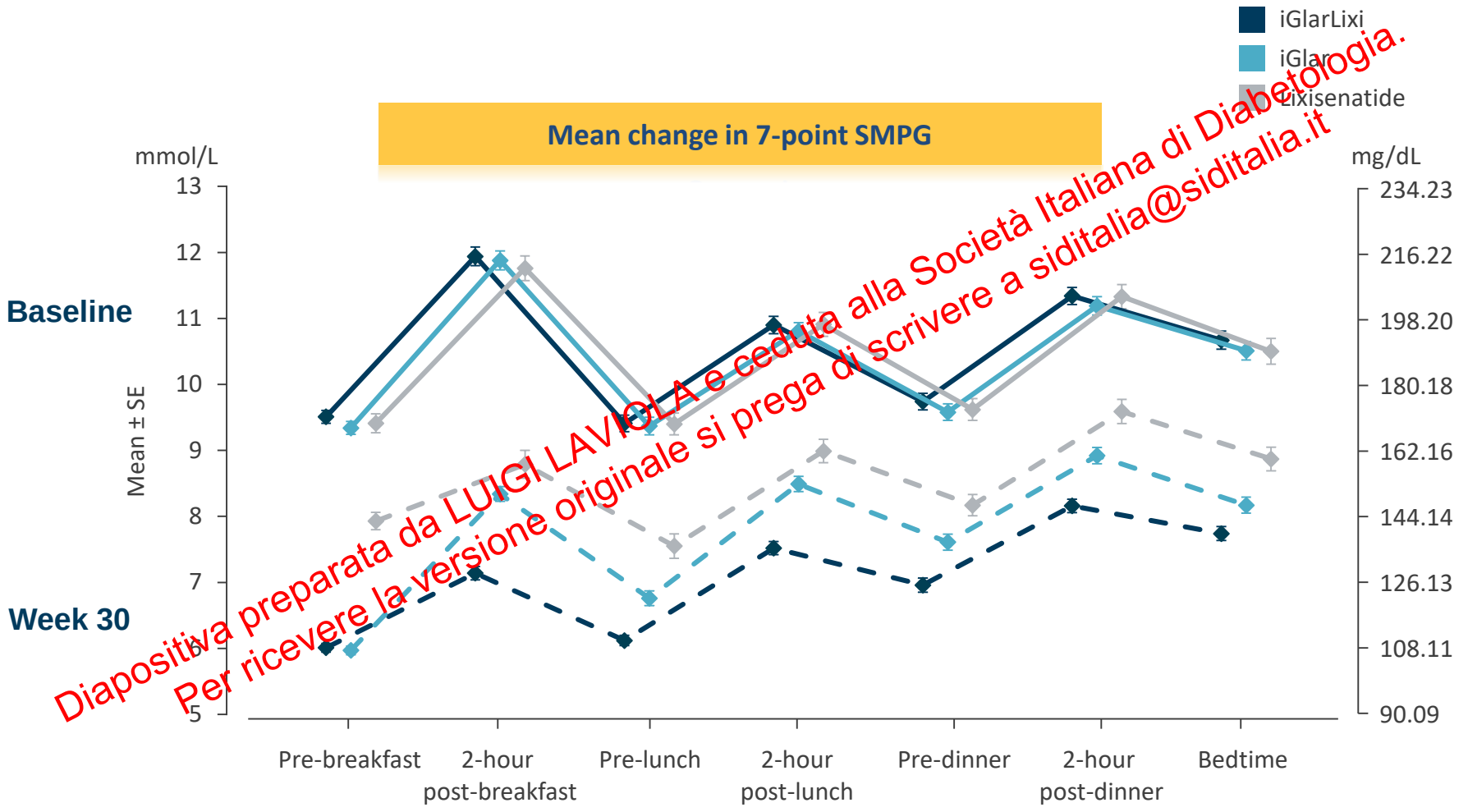
LixiLan-O: 7-point self-measured glucose profiles



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LixiLan-O: Overview of adverse events profile

Patients, n (%), with at least one:	iGlarLixi (n=469)	iGlar (n=467)	Lixisenatide (n=233)
TEAE			
Any	267 (56.9)	227 (48.6)	157 (67.4)
Serious	18 (3.8)	19 (4.1)	9 (3.9)
Leading to death	2 (0.4)	3 (0.6)	1 (0.4)
Leading to discontinuation	12 (2.6)	9 (1.9)	21 (9.0)
GI TEAEs			
Nausea	45 (9.6)	17 (3.6)	56 (24.0)
Leading to discontinuation	2 (0.4)	0	6 (2.6)
Vomiting	15 (3.2)	7 (1.5)	15 (6.4)
Leading to discontinuation	2 (0.4)	0	4 (1.7)
Diarrhea	42 (9.0)	20 (4.3)	21 (9.0)
Leading to discontinuation	1 (0.2)	0	2 (0.9)

- The incidence of documented symptomatic hypoglycemia (≤70 mg/dL) was similar in the iGlarLixi and iGlar treatment groups and lower in the lixisenatide group, as expected
- Overall, iGlarLixi was well tolerated with a safety profile reflecting those of iGlar and lixisenatide
  - Nausea and vomiting were reported considerably less frequently with iGlarLixi compared with lixisenatide

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LixiLan-O: Composite outcomes

	Proportion of subjects (%)			
	IGlarLixi	IGlar	Lixi	*p*-value
HbA_{1c} <7%	74	59	33	<0.001
HbA_{1c} <7%, no weight gain	43	25	28	<0.001
HbA_{1c} <7%, no hypoglycaemic episodes	54	44	31	NS
HbA_{1c} <7%, no weight gain and no hypoglycaemic episodes	32	19	26	<0.001/NS

Gough et al. Lancet Diab Endocr 2014

Combo Bas/GLP-1RA vs Basale vs GLP-1RA

- HbA1c: vince Combo
- Pazienti a target: vince Combo
- Glicemia a digiuno: pari merito Combo e Basale
- Calo ponderale: vince GLP-1 RA
- Rischio di ipoglicemia: vince GLP-1 RA
- Effetti collaterali gastrointestinali: vince Basale, poi Combo meglio di GLP-1 RA
- Dosi di farmaco: vice Combo (minore dose di Basale e di GLP-1 RA)

Cosa a chi? Punti da considerare…

- Compliance paziente + combattere inerzia (*meglio Combo: 1 iniezione, effetti GI lievi, outcome composito gratificante*)
- Necessità di perdere peso senza ipoglicemie (*meglio GLP-1 RA*)
- Ridurre glicemia a digiuno (*meglio Combo o Basale*)
- Agire globalmente sul profilo glicemico – FPG e PPG (*meglio Combo → IDegLira*)
- Problemi GI *(meglio basale)*
- Paziente fragile *(meglio Combo)*

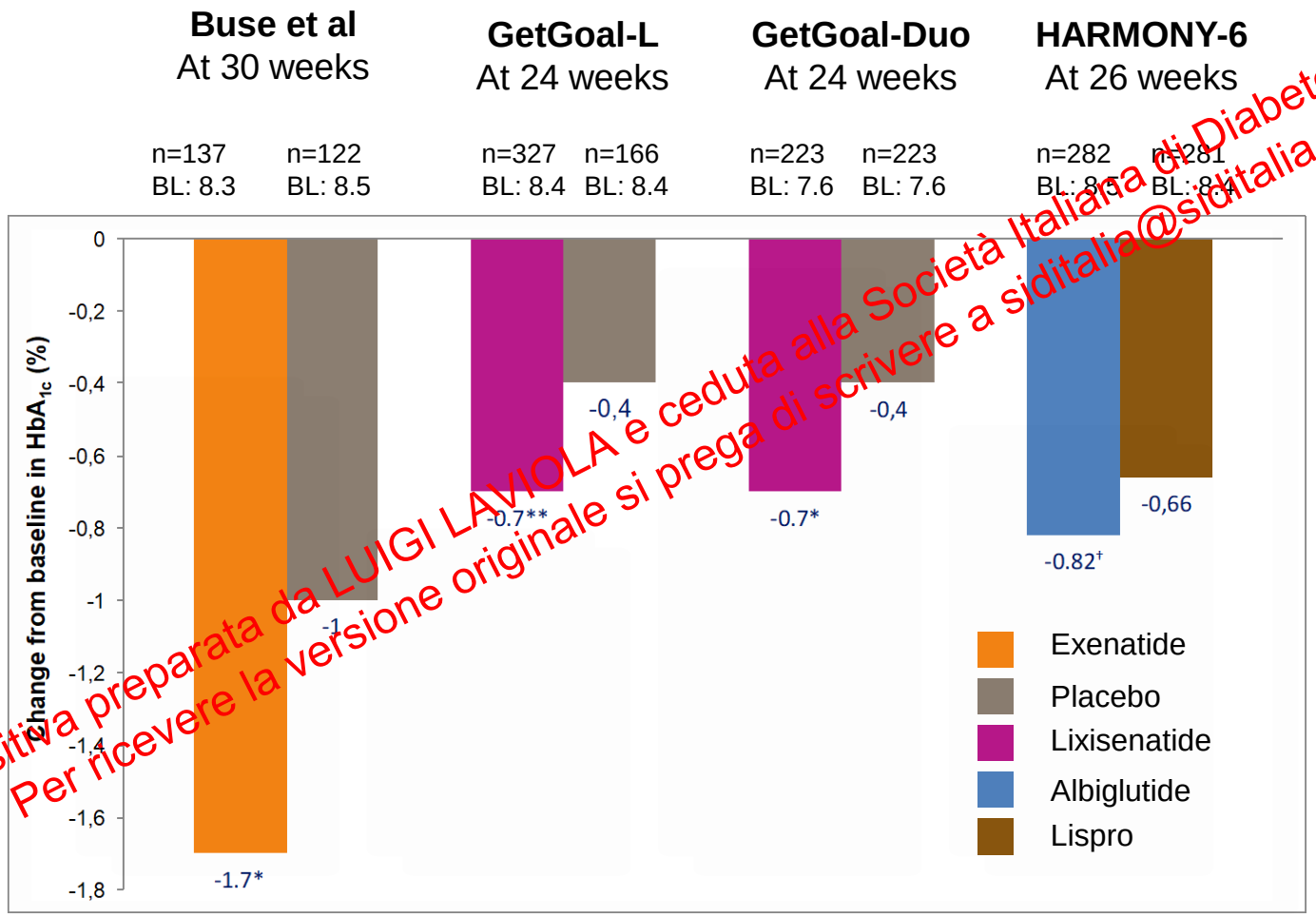
Uso di degludec in combinazione con gli agonisti del recettore del GLP-1 in pazienti con diabete mellito di tipo 2

- Quando si aggiunge degludec agli agonisti del recettore del GLP-1, la dose giornaliera iniziale raccomandata è di 10 unità seguita da aggiustamenti della dose individuali.

- Quando si aggiungono gli agonisti del recettore del GLP-1 a degludec, si raccomanda di ridurre del 20% la dose di degludec per minimizzare il rischio di ipoglicemia. Successivamente la dose può essere aggiustata individualmente.

Addition of GLP-1 analogues to basal insulin:

Change from baseline in HbA1c



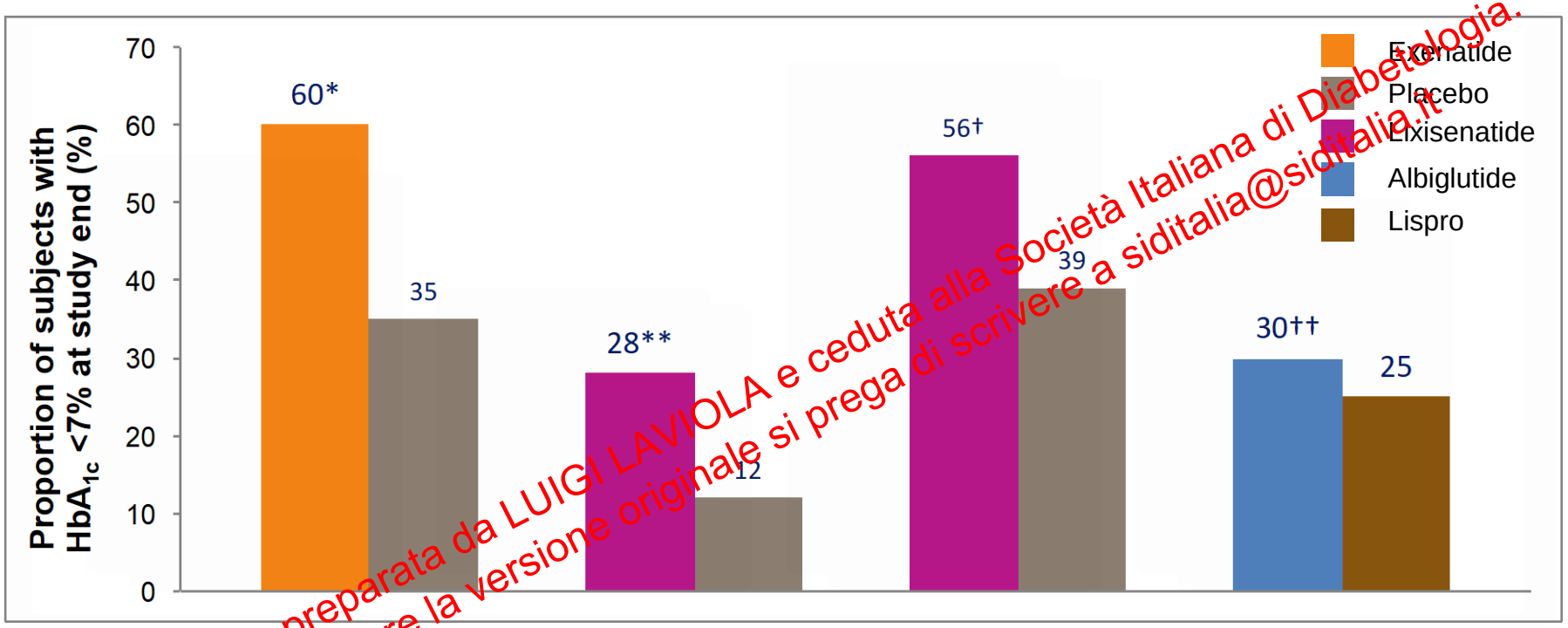
Treatment difference for GLP-1 vs. comparator: **p*<0.001; ***p*=0.0002; †*p=NS*

Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496; Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. Diabetes Care 2014; Published online 04 June. DOI: 10.2337/dc14-0001

Addition of GLP-1 analogues to basal insulin:

Proportion of subjects achieving HbA1c <7%



Buse et al	GetGoal-L	GetGoal-Duo	HARMONY-6
At 30 weeks	At 24 weeks	At 24 weeks	At 26 weeks
n=137 BL: 8.3	n=327 BL: 8.4	n=223 BL: 7.6	n=282 BL: 8.5
n=122 BL: 8.5<	n=166 BL: 8.4	n=223 BL: 7.6	n=281 BL: 8.4

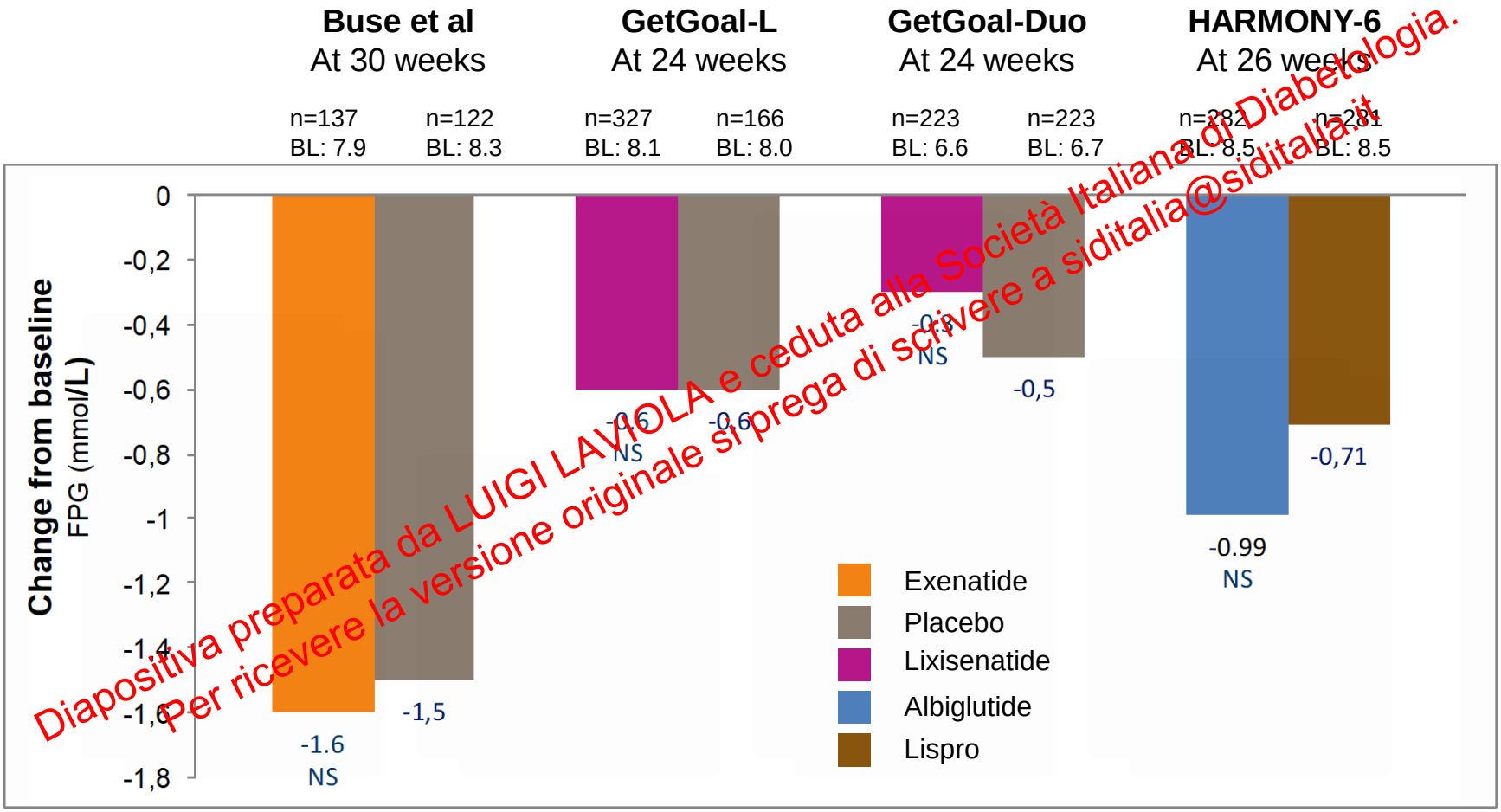
Treatment difference for GLP-1 vs. comparator: **p*<0.001; ***p*<0.0001; †*p*=0.0001 ††*p*=NS

Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496; Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. Diabetes Care 2014; Published online 04 June. DOI: 10.2337/dc14-0001

Addition of GLP-1 analogues to basal insulin:

Change from baseline in FPG



Treatment difference for GLP-1 vs. comparator: NS = not significant

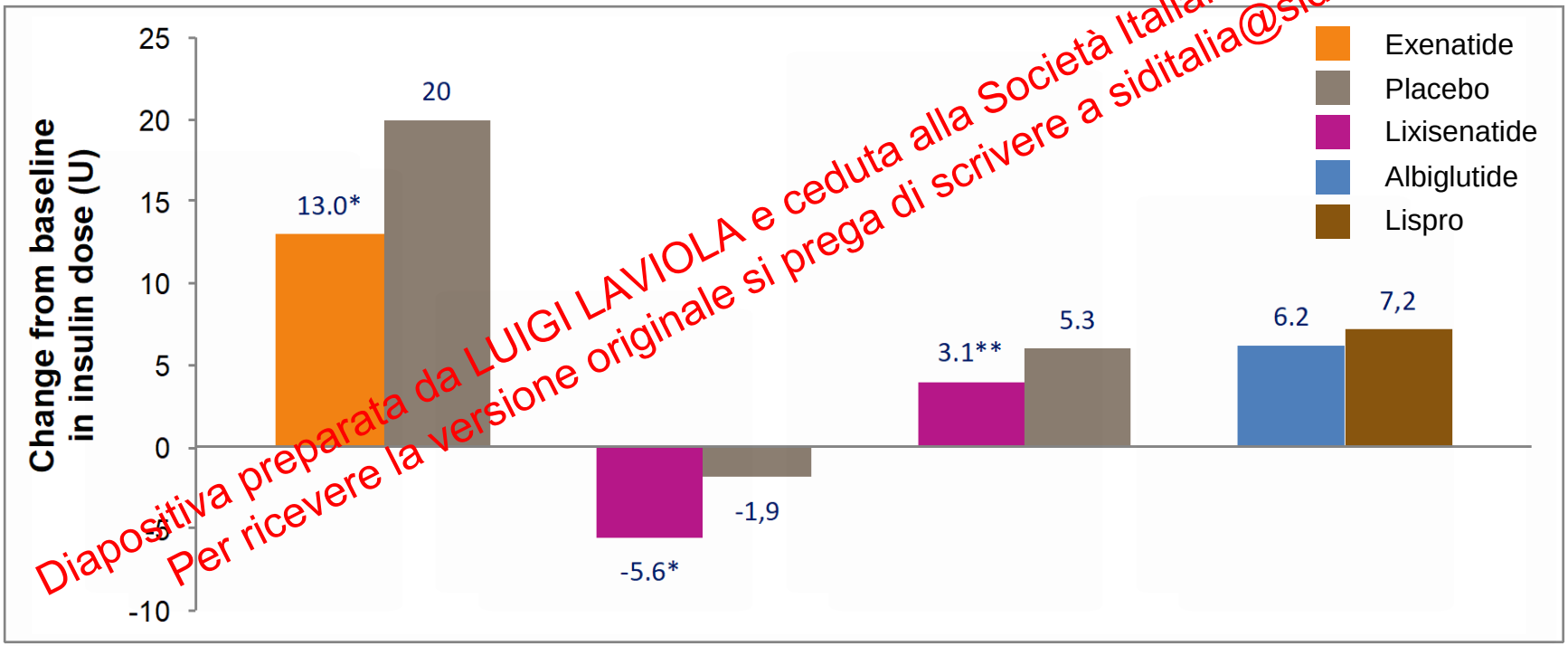
Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496; Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. Diabetes Care 2014; Published online 04 June. DOI: 10.2337/dc14-0001

Addition of GLP-1 analogues to basal insulin:

Change from baseline in insulin dose

Buse et al At 30 weeks		GetGoal-L At 24 weeks		GetGoal-Duo At 24 weeks		HARMONY-6 At 26 weeks	
n=137 BL: 49.5	n=122 BL: 47.4	n=327 BL: 54	n=166 BL: 58	n=223 BL: 43	n=223 BL: 44	n=282 BL: 47	n=281 BL: 43.4



Treatment difference for GLP-1 vs. comparator: *p<0.05

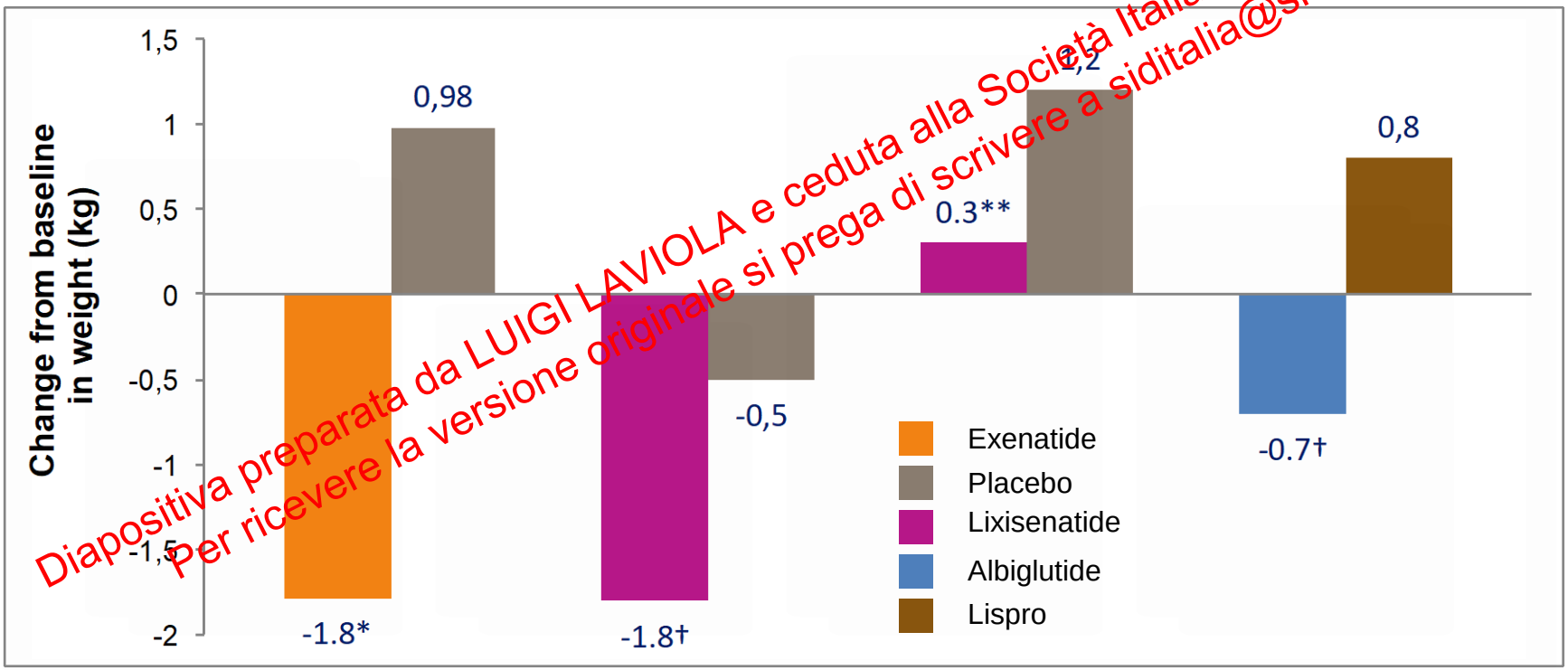
Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496;
Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. Diabetes Care 2014; Published online 04 June. DOI: 10.2337/dc14-0001

Addition of GLP-1 analogues to basal insulin:

Change from baseline in body weight

Buse et al At 30 weeks		GetGoal-L At 24 weeks		GetGoal-Duo At 24 weeks		HARMONY-6 At 26 weeks	
n=137 BL: 95.4	n=122 BL: 93.4	n=327 BL: 87.4	n=166 BL: 89.1	n=223 BL: 87.5	n=223 BL: 86.7	n=282 BL: 92.5	n=281 BL: 91.6



Treatment difference for GLP-1 vs. comparator: **p*<0.001; ***p*=0.0012; †*p*<0.0001

Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496; Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. Diabetes Care 2014; Published online 04 June. DOI: 10.2337/dc14-0001

Addition of GLP-1 analogues to basal insulin:

Hypoglycaemia

Hypoglycaemia	Buse *et al**		GetGoal-L**		GetGoal-Duo†		HARMONY-6††	
	EXEN + IGlar (n=137)	PLBO + IGlar (n=122)	LIXI + basal insulin (n=328)	PLBO + basal insulin (n=167)	LIXI + IGlar (n=223)	PLBO + IGlar (n=223)	ALBI + IGlar (n=282)	Lispro + IGlar (n=281)
Proportion of subjects experiencing hypoglycaemia (%)	25	29	26.5	21.0	20.2	11.7	23.2	39.1
Hypoglycaemia rate/patient year	1.1	1.2	NR	NR	0.80	0.44	0.94	2.33

*Minor hypoglycaemia (signs or symptoms associated with hypoglycaemia and fingerstick blood glucose level <3 mmol/L (54 mg/dL) that were either self-treated or resolved on their own)

**Symptomatic hypoglycaemia with blood glucose <3.3 mmol/L (60 mg/dL); †BG < 3.3 mmol/L (60 mg/dL)

††Documented symptomatic with BG < 3.9 mmol/L (70 mg/dL)

EXEN = exenatide; PLBO = placebo; LIXI = lixisenatide; IGlar = insulin glargine; ALBI = albiglutide; NR = not reported

Buse et al. Ann Intern Med 2011;154:103–12 ; Riddle et al. Diabetes Care 2013;36:2489–2496; Riddle et al. Diabetes Care 2013;36:2497–2503

Rosenstock et al. Diabetes Care 2014; Published online 04 June. DOI: 10.2337/dc14-0001

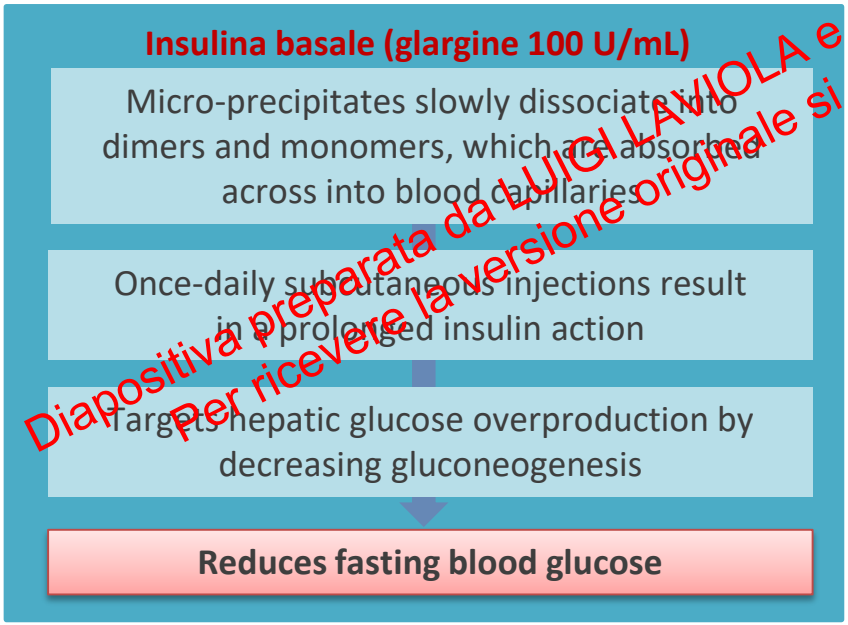
4.1 Indicazioni terapeutiche

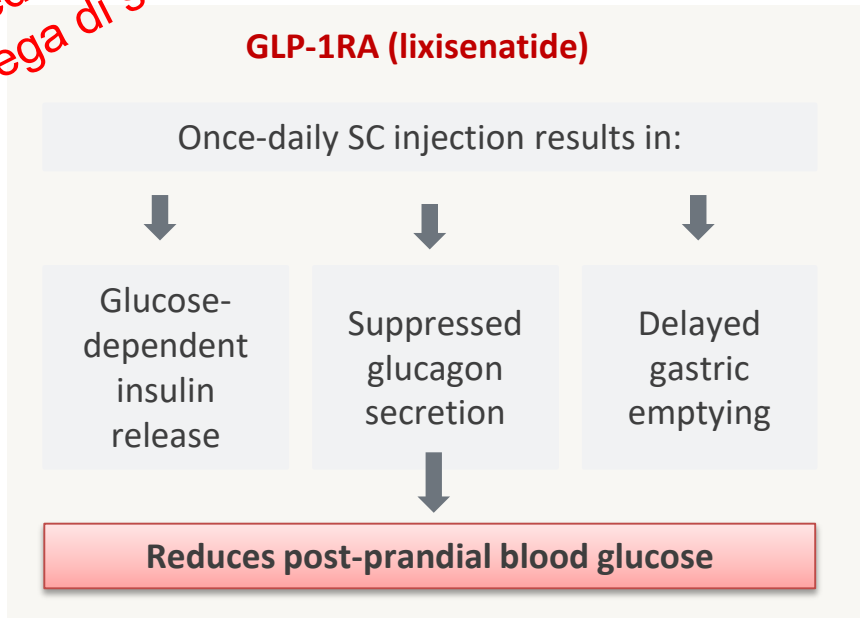
IDegLira è indicato per il trattamento di adulti affetti da diabete mellito di tipo 2 per migliorare il controllo glicemico in associazione con medicinali ipoglicemizzanti orali quando questi in monoterapia o in associazione con agonisti del recettore del GLP-1 o con insulina basale non permettano un controllo glicemico adeguato

FIXED RATIO COMBINATION
IGlarLixi

Cos'è iGlarLixi
Caratteristiche dei componenti

iGlarLixi è una nuova combinazione a rapporto fisso, titolabile, di insulina basale (Lantus®, glargine 100 U/mL) + l'agonista recettoriale GLP-1RA (Lyxumia®; lixisenatide) disponibile in un'unica somministrazione giornaliera per il trattamento di pazienti adulti con T2DM





LixiLan-L: Demographic and baseline characteristics

	iGlarLixi (n=367)	iGlar (n=369)
Age (years)	59.6	60.3
Female (%)	55.0	51.5
Caucasian/Black (%)	91.8/4.6	91.6/5.7
Body weight (kg) at baseline	87.7	87.1
BMI (kg/m^2) at baseline	31.3	31.0
Patients with BMI ≥30 kg/m^2 (%)	57.5	57.2
Diabetes duration (years)	12.0	12.1
Duration of basal insulin treatment (years)	3.4	3.3
Basal insulin type at screening (%)		
iGlar	63.5	65.3
Detemir	13.1	15.2
NPH	23.4	19.5
OAD use at screening (%)		
None	4.9	5.1
Metformin	46.3	51.5
SU	4.4	3.8
DPP-4 inhibitor	0.5	1.1
Metformin + SU	37.3	32.0
Metformin + DPP-4 inhibitor	5.4	4.9

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; SU, sulfonylurea

Aroda VR, et al. Diabetes Care 2016

LixiLan-L: Demographic and baseline characteristics

	iGlarLixi (n=367)	iGlar (n=366)
HbA1c (%)		
Screening	8.5	8.5
Baseline	8.1	8.1
Fasting plasma glucose (mmol/L [mg/dL])		
Screening	7.9 (143.1)	8.0 (144.7)
Baseline	7.3 (132.0)	7.3 (131.9)
iGlar dose (U)		
Start of run in	28.4	29.0
Baseline	35.0	35.2

Aroda VR, et al. Diabetes Care 2016

LixiLan-O: Demographic and baseline characteristics

	iGlarLixi (n=469)	iGlar (n=467)	Lixisenatide (n=234)	All (N=1,170)
Age (years)	58.2	58.3	58.7	58.4
Male/Female (%)	47.3/52.7	50.7/49.3	56.8/43.2	50.6/49.4
Caucasian/Black (%)	88.9/7.0	90.1/7.1	92.3/5.1	90.1/6.7
Diabetes duration (years)	8.9	8.7	8.8	8.8
BMI (kg/m^2)	31.6	31.7	31.9	31.7
Patients with BMI ≥30 kg/m^2 (%)	62.9	61.7	67.9	63.4
HbA1c (%) at screening	8.2	8.2	8.3	8.2
HbA1c (%) at baseline	8.1	8.1	8.1	8.1
Patients with HbA1c ≥8% (%)	55.9	55.7	56.0	55.8
Fasting plasma glucose (mmol/L, [mg/dL])	9.9 (177.9)	9.8 (175.7)	9.8 (175.7)	9.8 (176.6)
Metformin dose (baseline) (mg)	2246.1	2244.7	2267.3	2249.8
Second OAD use at screening (%)	58.4	57.8	56.8	57.9
Sulfonylurea	55.2	53.3	52.6	53.9
Glinide	0.6	2.1	2.1	1.5
SGLT-2 inhibitor	0.4	0.4	0	0.3
DPP-4 inhibitor	2.6	2.4	2.1	2.4

BMI; body mass index; DPP-4; dipeptidyl peptidase-4
SGLT-2, sodium-glucose co-transporter-2

Rosenstock J, et al. Diabetes Care 2016

Meta-analysis of clinical trials comparing basal insulin/GLP-1 RA and basal/bolus insulins

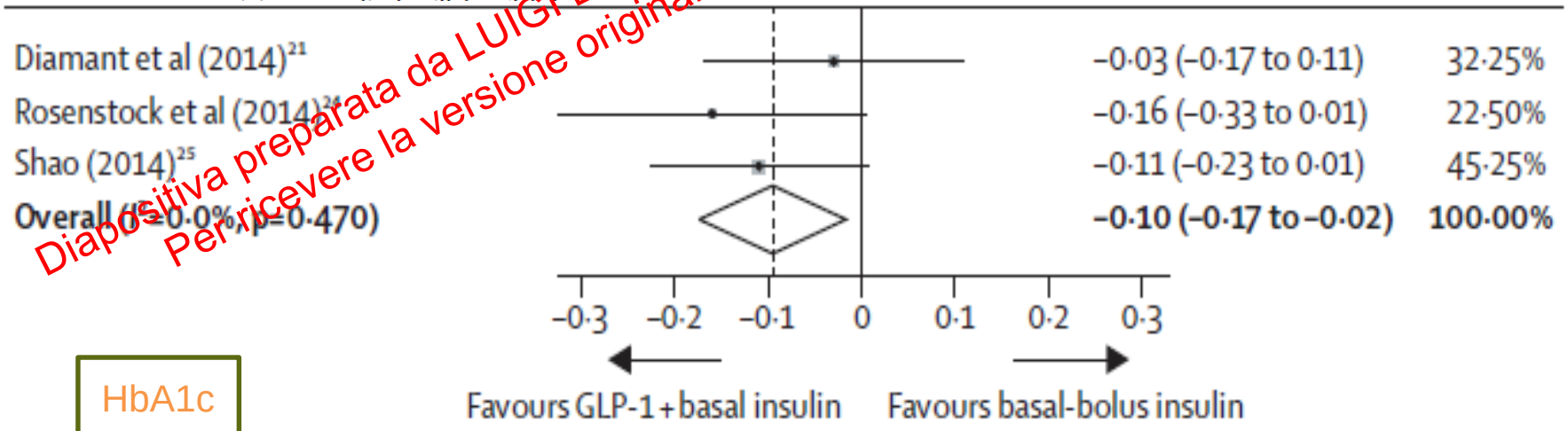
Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Conrad Eng*, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran

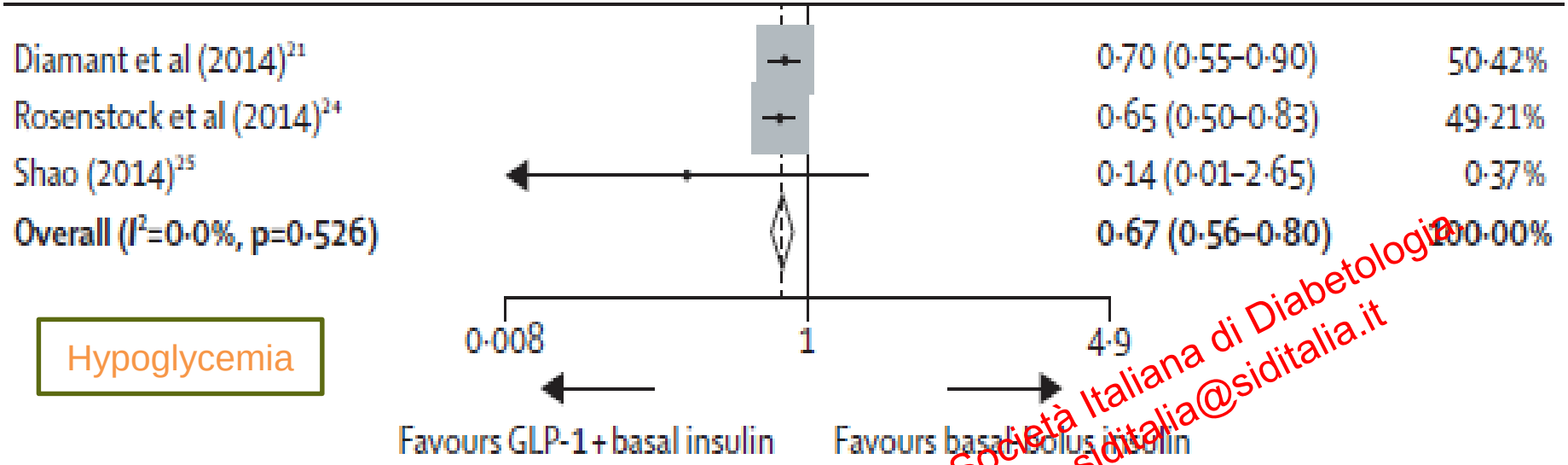
Lancet 2014; 384: 2228–34
Published Online September 12, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61335-0

Summary

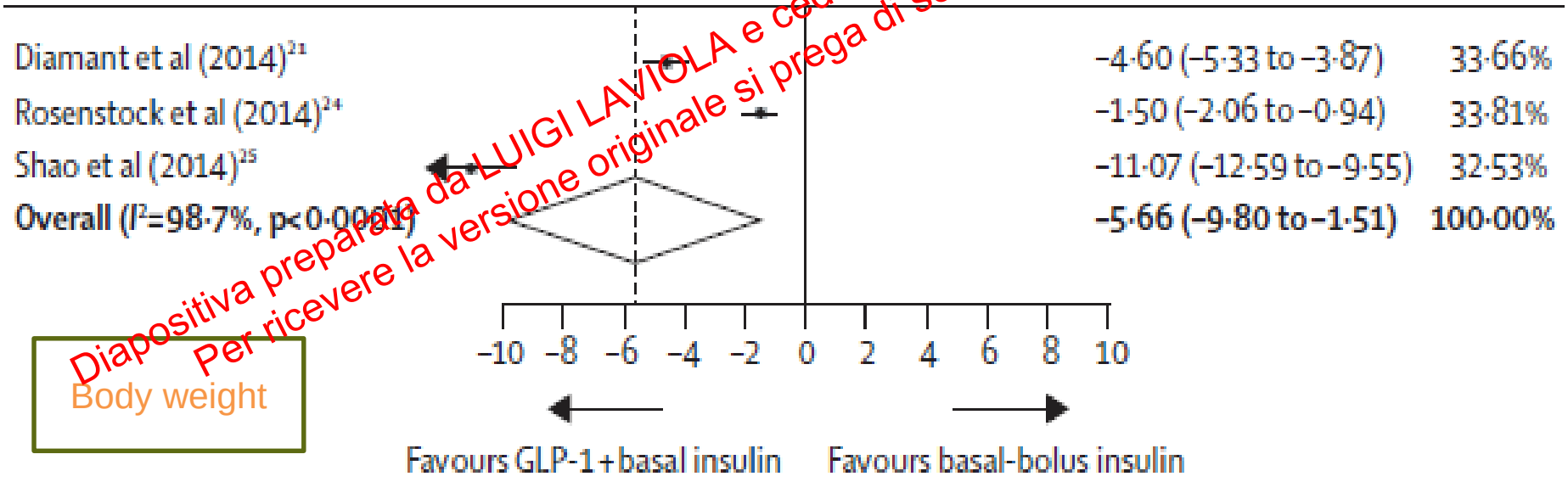
Background Combination treatment with a glucagon-like peptide-1 (GLP-1) agonist and basal insulin has been proposed as a treatment strategy for type 2 diabetes that could provide robust glucose-lowering capability with low risk of hypoglycaemia or weight gain. We thus did a systematic review and meta-analysis of randomised controlled trials to assess the effect of this combination treatment on glycaemic control, hypoglycaemia, and weight gain in



HbA1c



Hypoglycemia



Body weight

Basal i therap recept the tre guide t

Gerhard H. Sc

Comorbid conditions which may affect the use of GLP-1RA

Obesity (BMI ≥ 30 kg/m²) Preferred, if of android origin with visceral/liver fat accumulation Reduction in liver fat correlated with improvement in HbA1c	
Enhanced risk of hypoglycemia (older age, renal failure, medication) or need to avoid hypoglycemia (e.g. professional reasons)	
Age No use below 18 years, in older patients preferred use in 'young old' (65-79 years), no data in 'old old' (80-89 years) and older	
Previous macro- and microvascular diseases Until now, no additional risks observed, protective effects possible, Caution: preexisting maculopathy, higher grade retinopathy, longer diabetes duration	
Renal failure Use with care (lixisenatide: CrCl < 50 ≥ 30 ml/min), dose reduction (exenatide: CrCl < 60 ≥ 30 ml/min), not suggested (liraglutide: CrCl < 60 ml/min, exenatide and lixisenatide: CrCl < 30 ml/min).	
Liver disease Exenatide/lixisenatide: side effects not expected but no conclusive information, liraglutide: not suggested in mild, severe and very severe liver failure	
Gastrointestinal and pancreatic diseases Exenatide, liraglutide and lixisenatide are not recommended in patients with severe gastrointestinal diseases and contraindicated in patients with previous pancreatitis and pancreas carcinoma	

Figure 2. Comorbid conditions which may affect the use of GLP-1 RAs. BMI, body mass index; CrCl, creatinine clearance; GLP-1 RA, glucagon-like protein 1 receptor agonist; HbA1c, hemoglobin A1c.

IDegLira: Phase 3 Clinical Development Plan

Uncontrolled on OADs

DUAL I
IDegLira compared with the mono-components added on to OAD

DUAL IV
IDegLira add-on to SU vs. placebo

Uncontrolled on GLP-1RA

DUAL III
Switch from (daily) GLP-1RA therapy vs. unchanged GLP-1RA therapy

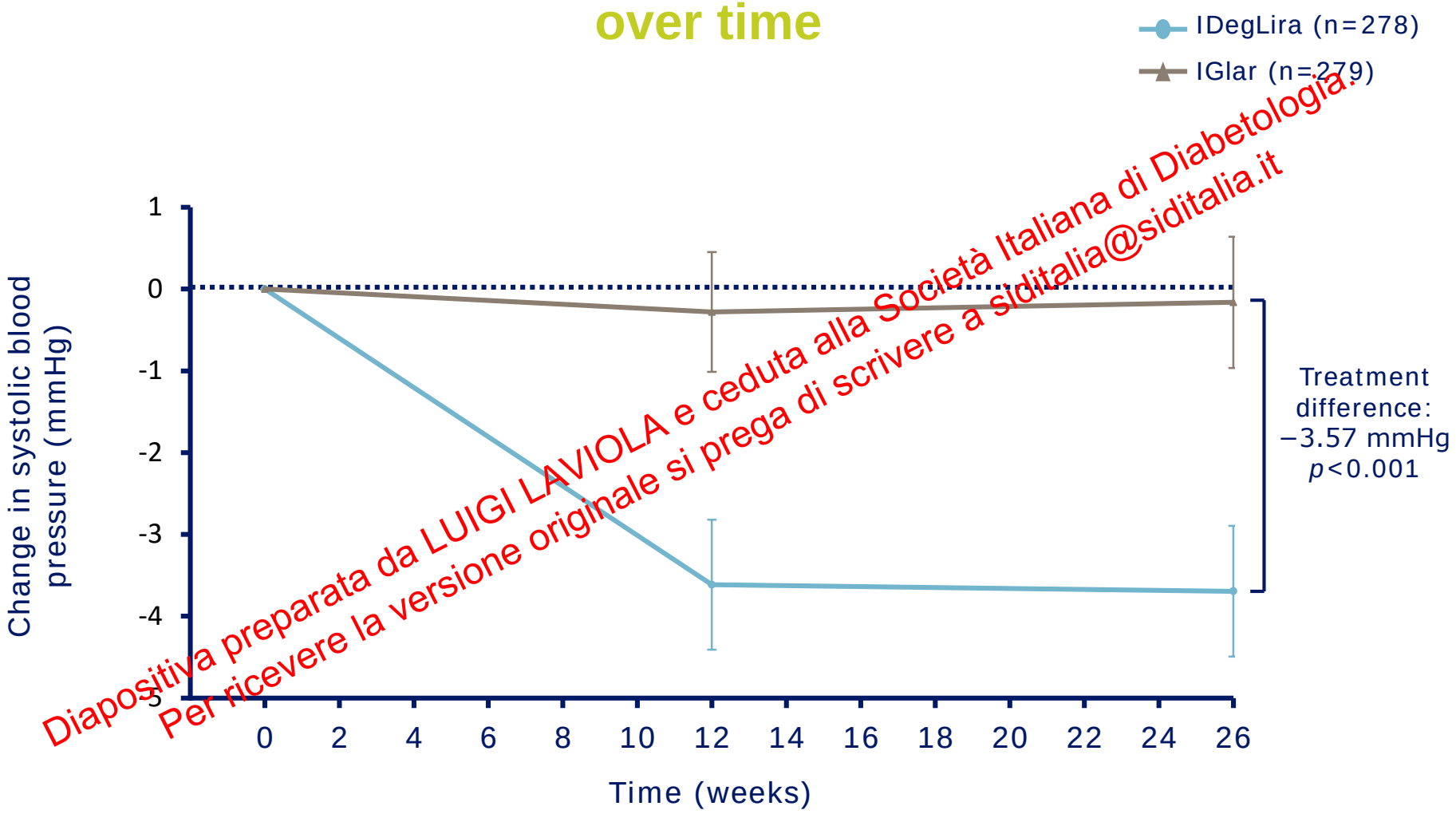
Uncontrolled on basal insulin

DUAL II
IDegLira compared with IDeg in patients previously treated with basal insulin

DUAL V
IDegLira vs. basal insulin optimisation

www.clinicaltrials.gov

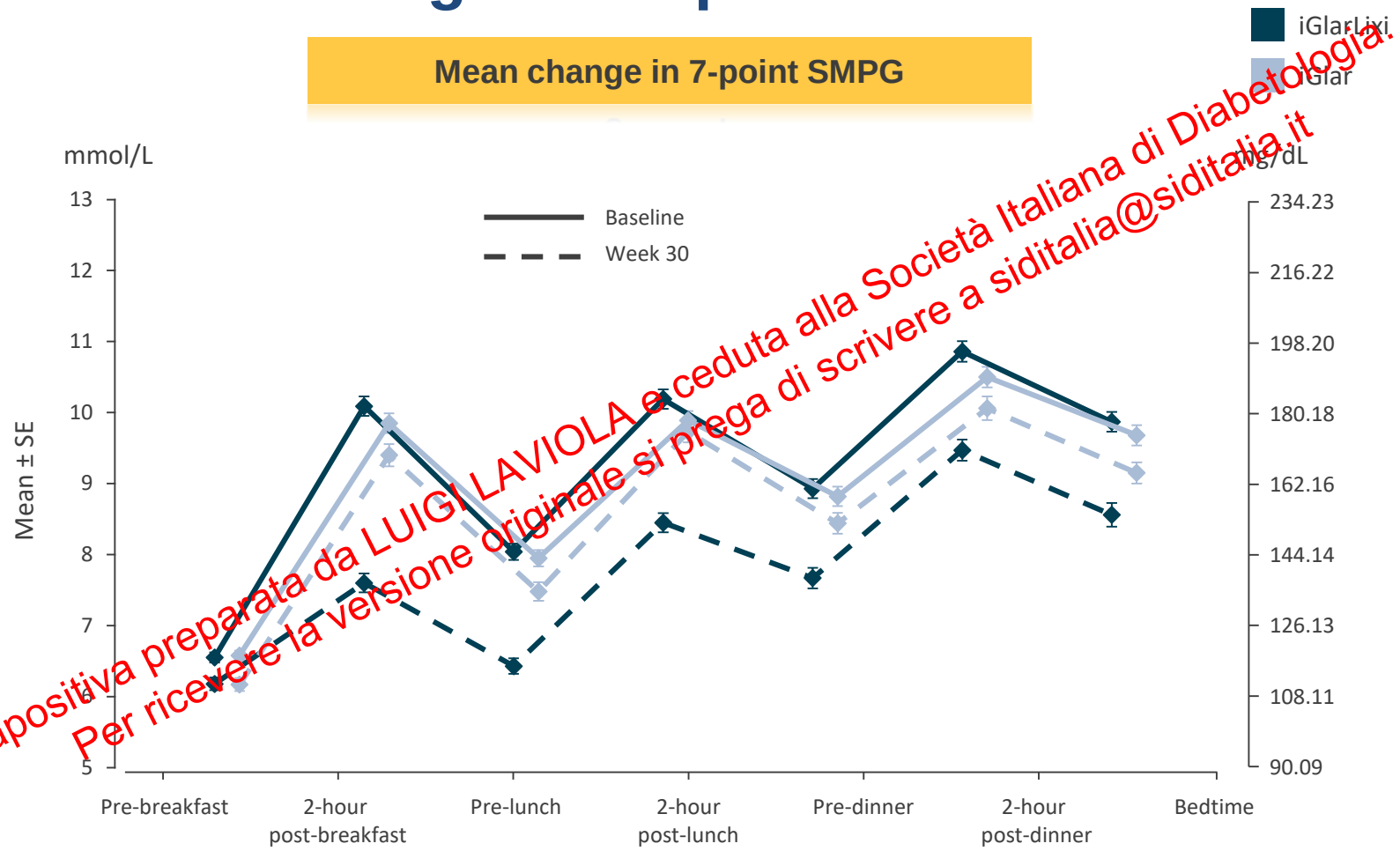
Change in systolic blood pressure over time



Mean observed values with error bars (standard error mean) based on FAS and LOCF imputed data
Treatment difference is estimated from an ANCOVA analysis
NN9068-3952; IDegLira vs. IGlar

LixiLan-L: 7-point self-measured glucose profiles

Mean change in 7-point SMPG



mITT population

Aroda VR, et al. Diabetes Care 2016

LixiLan-L: Overview of adverse events profile

Patients, n (%), with at least one:	iGlarLixi (n=365)	iGlar (n=365)
TEAE		
Any	195 (53.4)	191 (52.3)
Serious	20 (5.5)	18 (4.9)
Leading to death	1 (0.3)	2 (0.5)
Leading to discontinuation	10 (2.7)	3 (0.8)
GI TEAEs		
Nausea	38 (10.4)	2 (0.5)
Leading to discontinuation	*4 (1.1)*	*0*
Vomiting	13 (3.6)	2 (0.5)
Leading to discontinuation	*0*	*0*
Diarrhea	16 (4.4)	10 (2.7)
Leading to discontinuation	*0*	*0*

The incidence of documented symptomatic hypoglycemia (≤70 mg/dL) was similar in the iGlarLixi and iGlar treatment groups

Overall, iGlarLixi was well tolerated with a safety profile reflecting those of iGlar and lixisenatide

- Nausea and vomiting were reported less frequently with iGlarLixi compared with what is usually reported with a GLP-1 RA, including lixisenatide, when used as a stand-alone treatment

Three suspected allergic events from 3 patients were reported by investigators; of these, one event (allergic rhinitis; iGlar group) was adjudicated as an allergic reaction by the Allergic Reaction Assessment Committee

Safety population
GI, gastrointestinal; TEAE, treatment emergent adverse event

Aroda VR, et al. Diabetes Care 2016

IGlarLixi: Phase 3 summary of key results

	HbA1c reduction	Body weight change	Hypo* incidence	Incidence of GI events
LixiLan-O[1]	Superiority of iGlarLixi over iGlar and lixisenatide achieved	iGlarLixi associated with body weight reduction vs. iGlar; weight loss significantly greatest with lixisenatide	Incidence comparable between iGlarLixi and iGlar, lower with lixisenatide	Low incidence overall; significantly lower than with lixisenatide
LixiLan-L[2]	Superiority of iGlarLixi over iGlar achieved	iGlarLixi associated with weight reduction vs. iGlar	Incidence comparable between iGlarLixi and iGlar	Incidence of events higher with iGlarLixi than iGlar

Overall, the fixed-ratio combination was well tolerated with a safety profile reflecting those of iGlar and lixisenatide

*Documented (≤70 mg/dL) symptomatic hypoglycemia

1- Rosenstock J, et al. Diabetes Care 2016
2- Aroda VR, et al. Diabetes Care 2016

LixiLan-O: Summary

- The primary objectives of the study were met as superiority of iGlarLixi in HbA1c change from baseline was shown versus both iGlar and lixisenatide
- iGlarLixi added to metformin:
  - Improved HbA1c from 8.1% to 6.5%
  - Reduced 2 hour-PPG and glucose excursions vs. iGlar
  - Prevented body weight gain seen at insulin introduction (−0.3 kg) with a significant difference of 1.4 kg versus iGlar (p<0.0001)
  - Allowed 74% of patients to reach HbA1c <7%
    - 43% with HbA1c <7% and no weight gain
    - 32% with HbA1c <7%, no weight gain and no documented hypoglycemia
- The incidence of documented symptomatic hypoglycemia (≤70 mg/dL) was similar in the iGlarLixi and iGlar treatment groups and lower in the lixisenatide group, as expected
- Overall, iGlarLixi was well tolerated with a safety profile reflecting those of iGlar and lixisenatide
  - Nausea and vomiting were reported considerably less frequently with iGlarLixi compared with lixisenatide

Rosenstock J, et al. Diabetes Care 2016