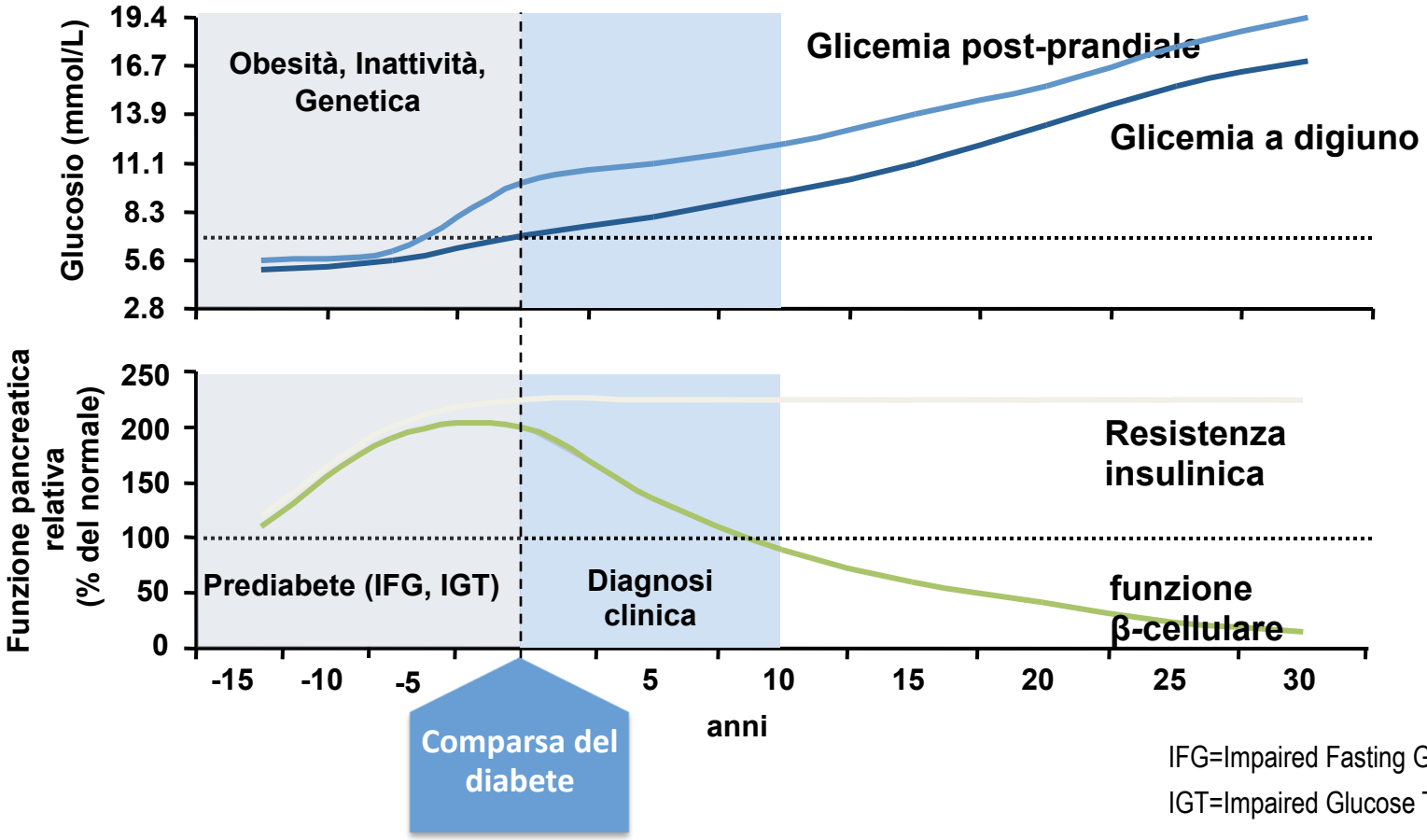
Diabete Mellito: nuove acquisizioni nella terapia insulinica

Paola Romagni
UOC Medicina Interna
Endocrinologia - Teramo

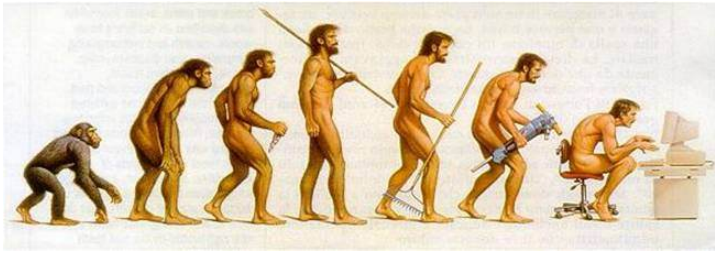
Storia naturale del diabete mellito di tipo 2

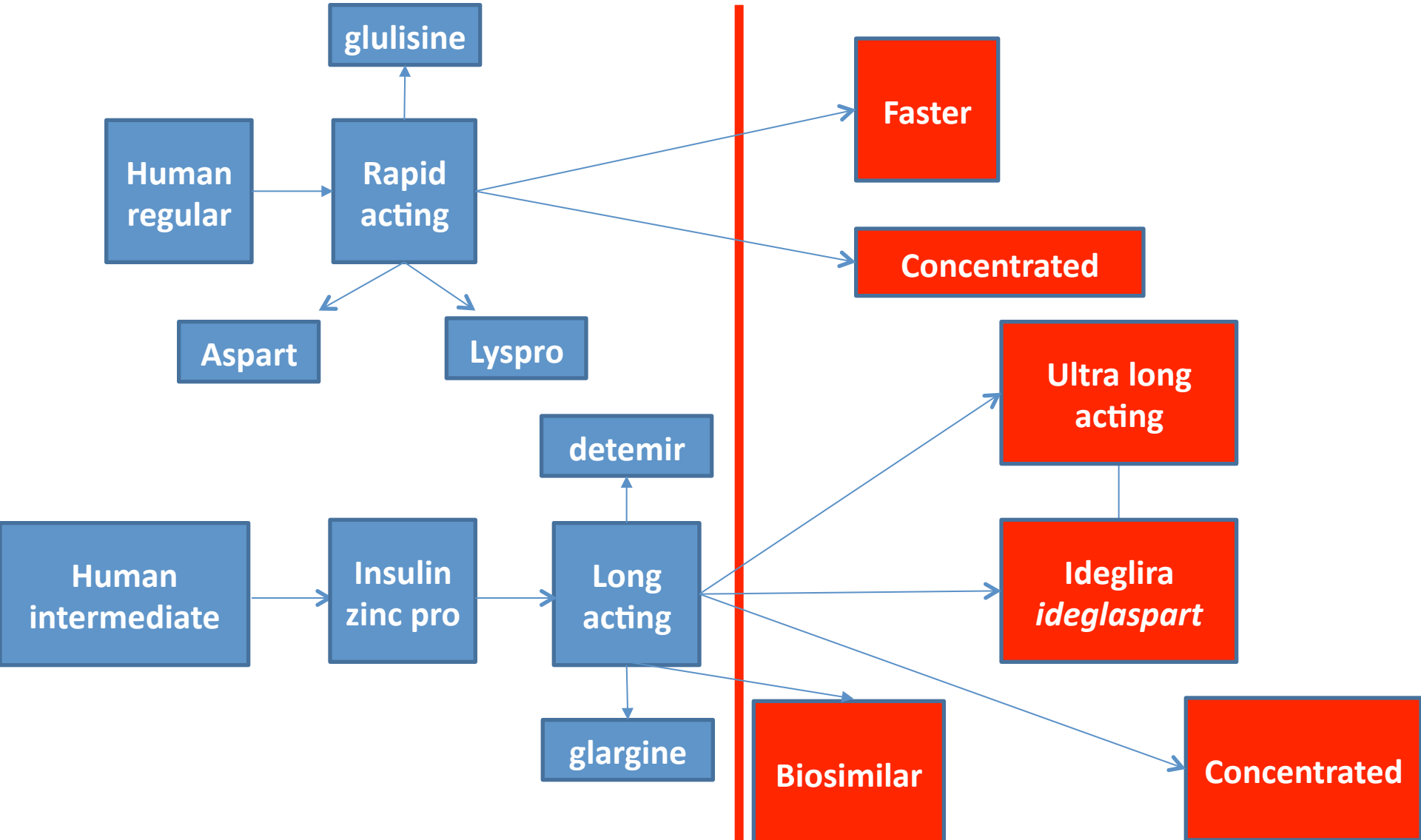


IFG=Impaired Fasting Glucose;
IGT=Impaired Glucose Tolerance

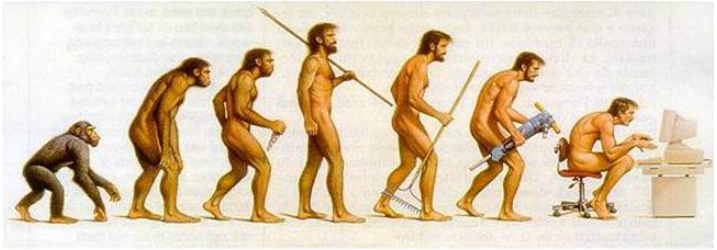
Adattato da : Simonson GD and Kendall DM. *Coron Artery Dis* 2005;16:465-7; Zimmet P et al. *Nature* 2001;414:782-7

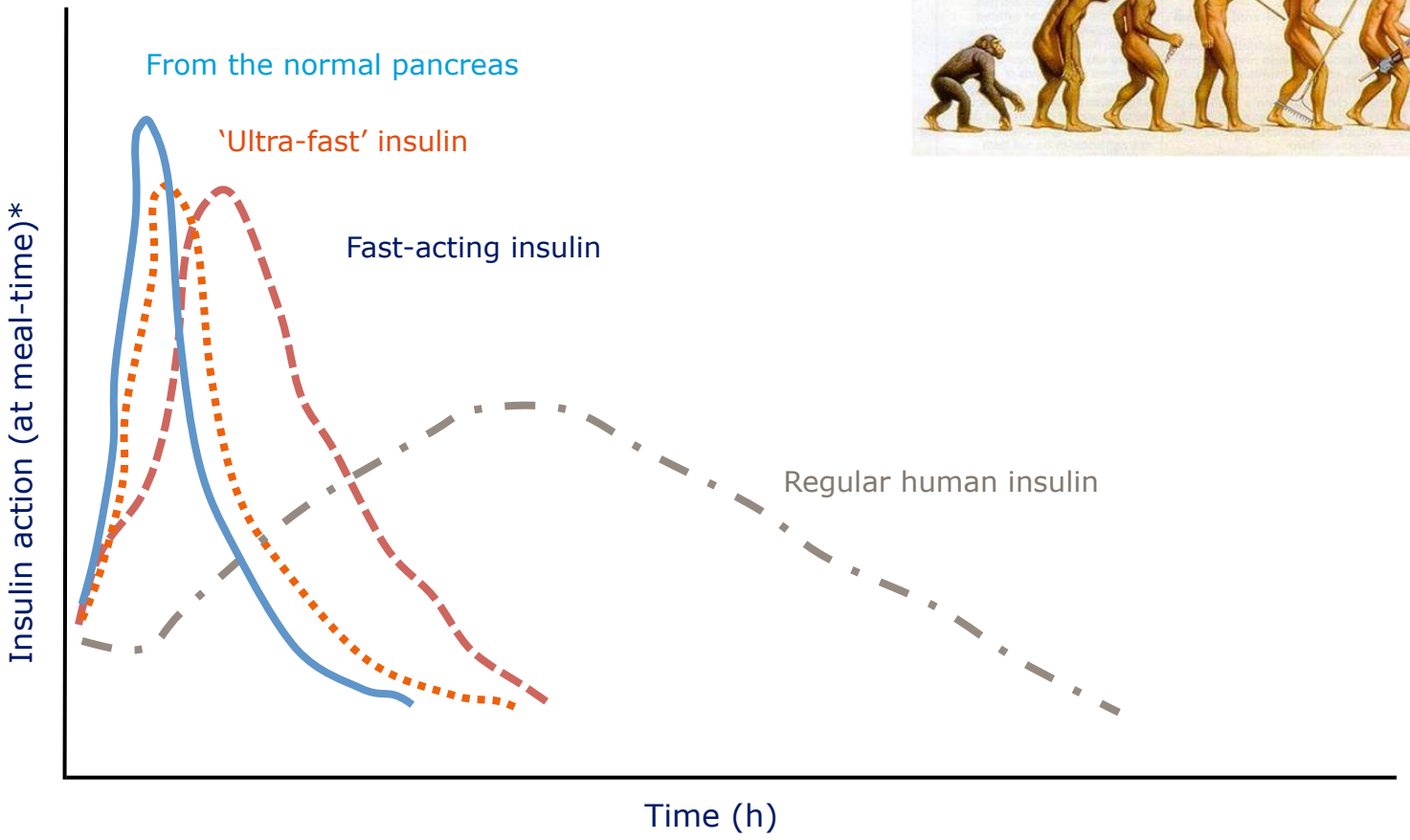
Evolution of Insulin





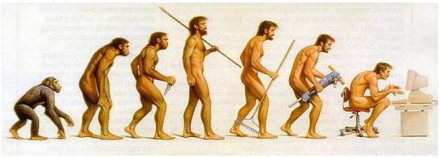
Dall’insulina umana regolare all’ultra fast



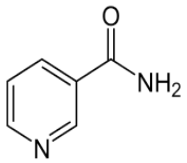


*Schematic representation

Faster Aspart

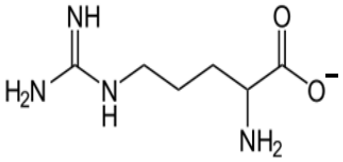


Niacinamide*: modificatore dell'assorbimento

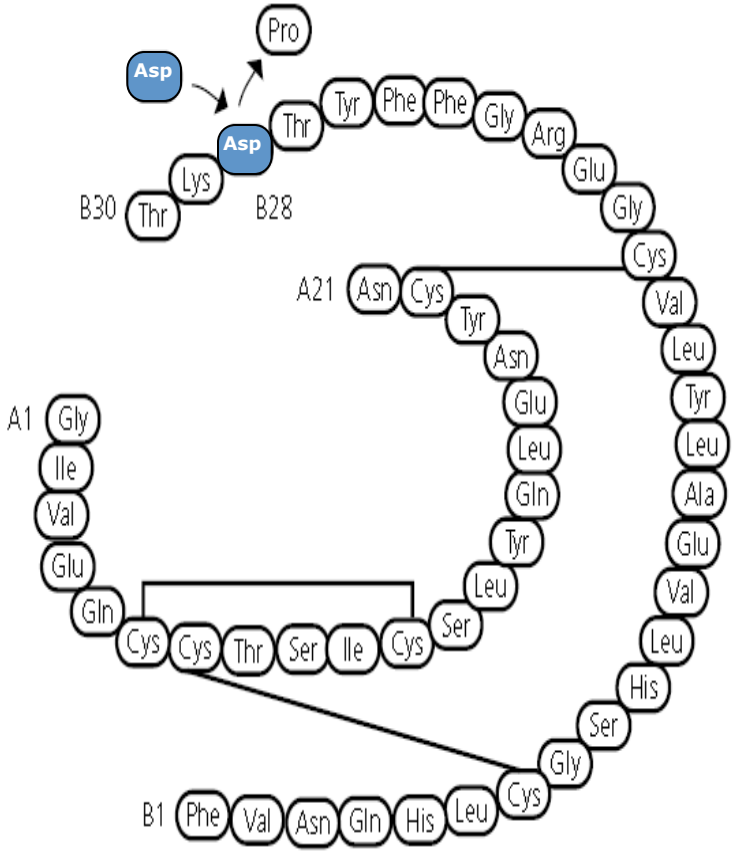


Responsabile dell'assorbimento più veloce

Arginina: potenziatore di stabilità



Aumenta la stabilità molecolare



*also known as nicotinamide – the amide form of vitamin B3
Adapted from Brange J et al. *Diabetes Care* 1990;13:923–954

original article

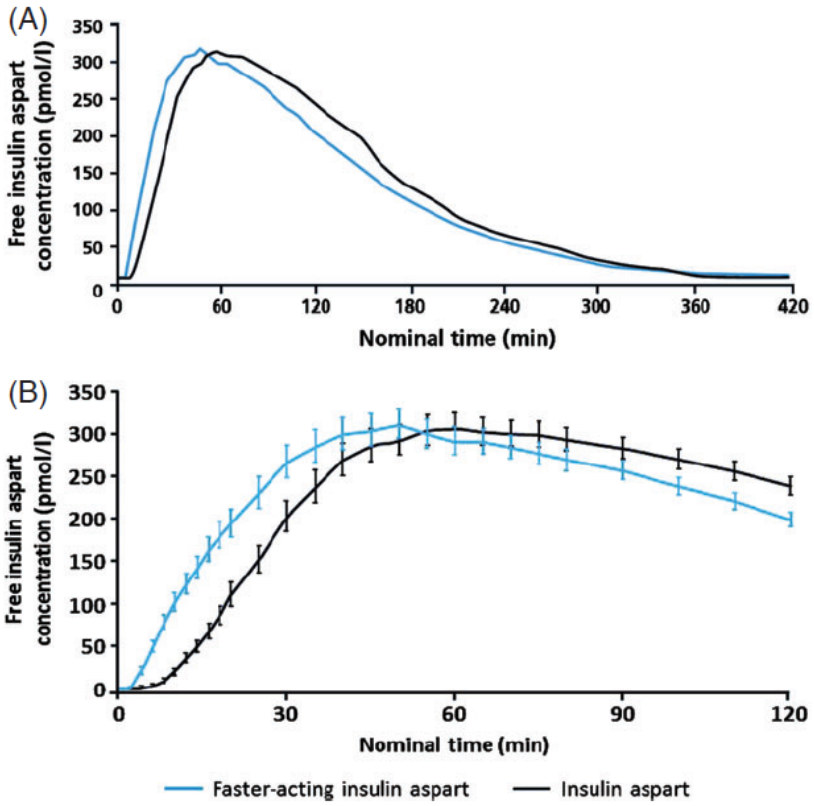
Diabetes, Obesity and Metabolism 2015.

Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart

ORIGINAL ARTICLE

T. Heise[1], U. Hövelmann[1], L. Brøndsted[2], C. L. Adrian[2], L. Nosek[1] & H. Haahr[2]

[1] *Profil, Neuss, Germany*
[2] *Novo Nordisk A/S, Søborg, Denmark*



Pharmacokinetics

Insulin Concentration Profiles. The mean concentration–time profiles for serum insulin aspart after administration of faster-acting insulin aspart were shifted to the left, compared with those after administration of insulin aspart, indicating a faster onset and greater early insulin exposure with faster-acting insulin aspart (Figure 1A, B).

Inizio di comparsa in circolo due volte più veloce
Esposizione insulinica due volte maggiore

original article

Diabetes, Obesity and Metabolism 2015.

Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart

ORIGINAL ARTICLE

T. Heise[1], U. Hövelmann[1], L. Brøndsted[2], C. L. Adrian[2], L. Nosek[1] & H. Haahr[2]

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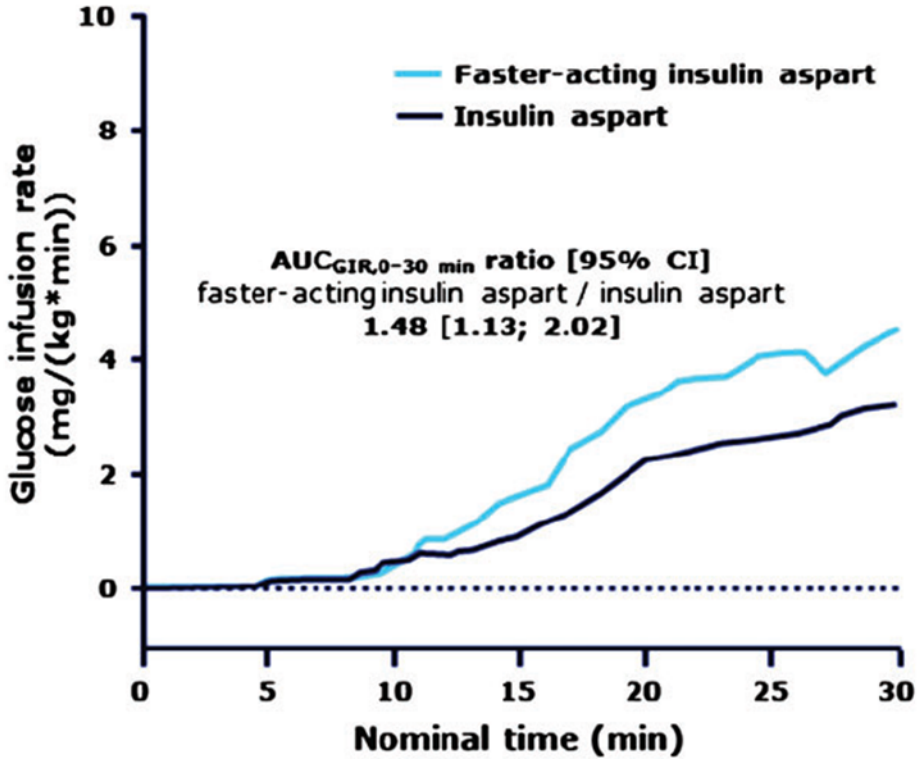


Azione 50% maggiore entro i primi 30 minuti

IL PROGRAMMA ONSET

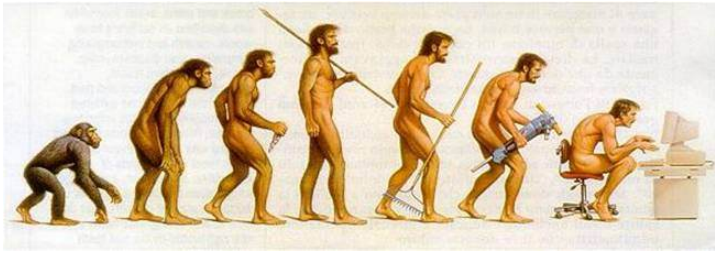
- Trial onset 1 (1,143 soggetti randomizzati): faster-acting insulin aspart vs Aspart, entrambe in associazione a detemir in DM di tipo 1.

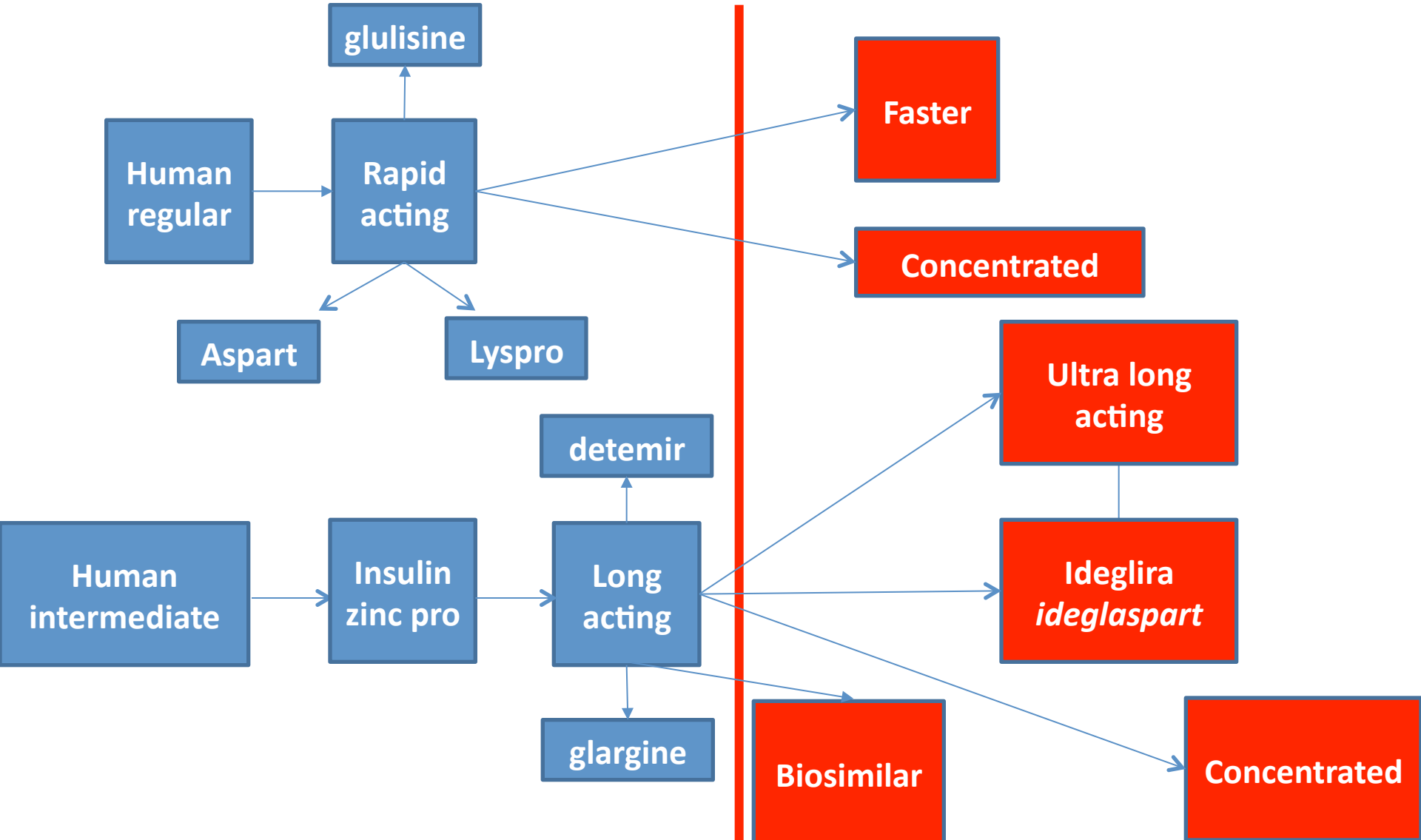
- Trial Onset 2 (689 soggetti randomizzati): faster-acting insulin aspart vs Aspart, entrambe in associazione a glargine in DM di tipo 2.

- Trial Onset 3 (236 soggetti randomizzati): basalbolus vs insulina basale ha confermato la superiorità (in termini di HbA1c) di faster-acting aspart vs terapia insulinica basale, entrambe in associazione a metformina.

- Trial Onset 4 (37 soggetti randomizzati): ha confermato compatibilità e sicurezza di faster-acting insulin aspart e Aspart in DM di tipo 1 trattato con microinfusore.

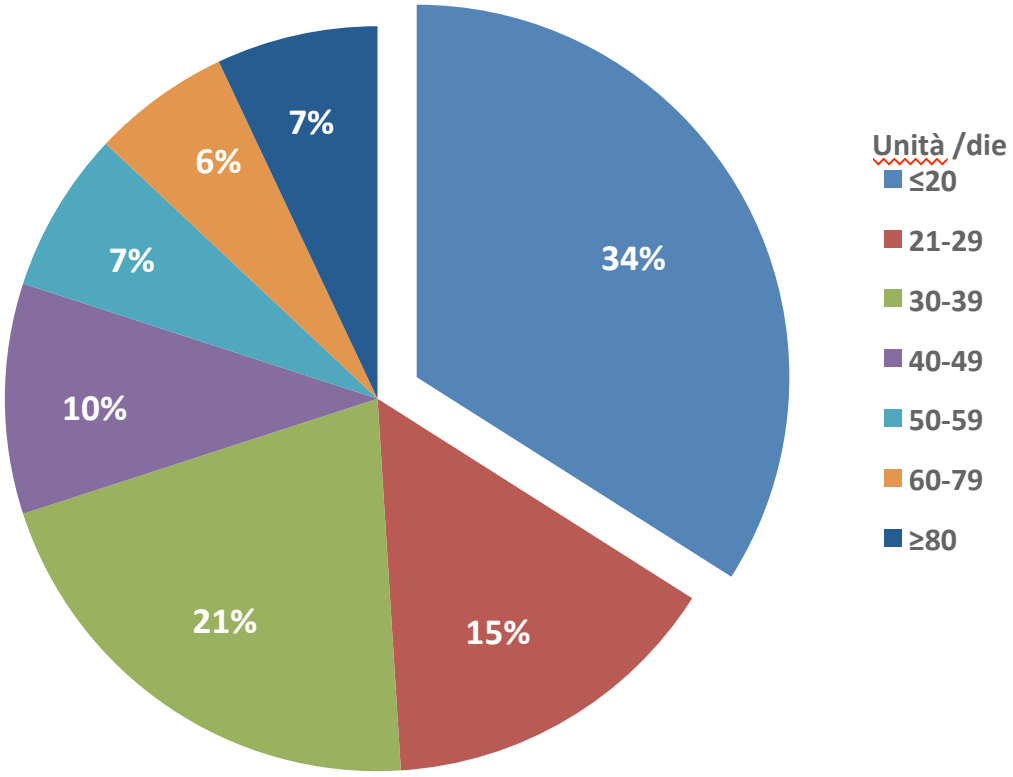
Evolution of Insulin



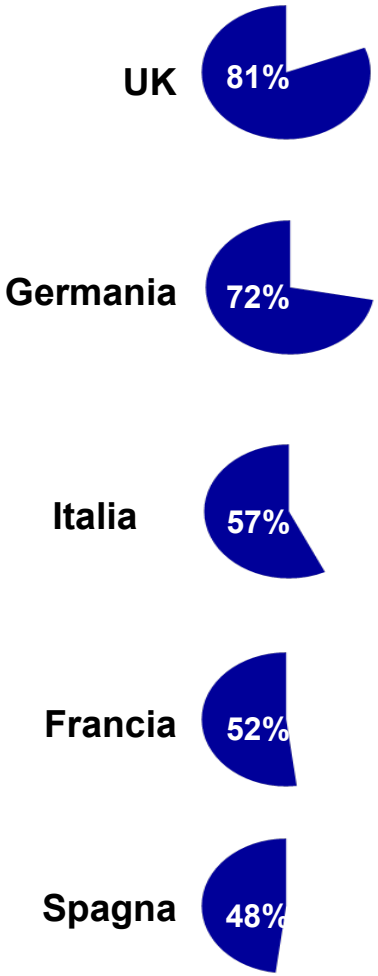


T2DM: 66% dei pazienti che utilizzano insulina ai pasti in Europa, assumono più di 20 U/Die

% di pazienti per dose di insulina prandiale



% di pazienti che usano >20 U/Die



Insulina Lispro 100 U/ml vs. 200 U/ml

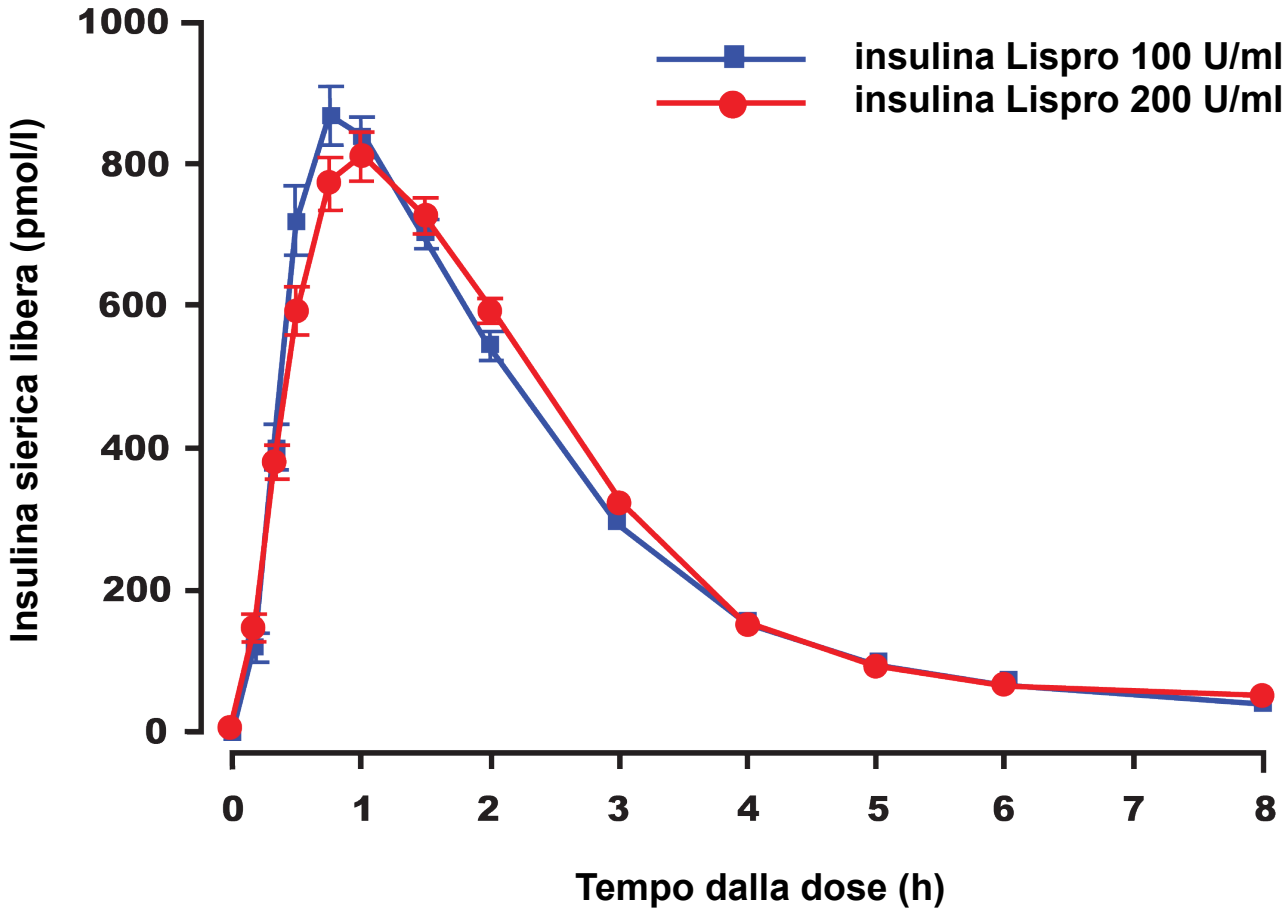
Ingredienti per ml:

Insulina Lispro 100 U/ml	Insulina Lispro 200 U/ml
Principio attivo: 100 unità insulina lispro	Principio attivo: 200 unità insulina lispro
Tampone: 1.88 mg fosfato di sodio dibasico	tampone: 5 mg trometamolo
Zinco: 0.0197 mg/100 unità	Zinco: 0.023 mg/100 unità

1. EMA. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000088/WC500176634.pdf

Profili farmacocinetici (media ± SE)

SE=Standard Error



Adattato da: de la Pena A. et al. Clinical Pharmacology in Drug Development, Wiley online, DOI 10.1002/cpdd.221 – August 2015

Studio di comparazione della Glide Force (GF)

- La penna preriempita con insulina Lispro 200 U/ml è associata a valori di GF significativamente più bassi rispetto alla penna preriempita con insulina Lispro 100 U/ml.

- Una GF più bassa può essere preferita da pazienti che richiedono più di 20 U di insulina prandiale/die ed in particolare da quelli che hanno ridotta funzionalità delle mani a causa di complicanze del diabete.

Rees T et al. *Journal of Diabetes Science and Technology* 2015

Informazioni cliniche importanti relativamente ad insulina Lispro 200 U/ml

- Non devono essere eseguite conversioni della dose quando si passa da insulina Lispro 100 U/ml a insulina Lispro 200 U/ml

- Insulina Lispro 200 U/ml non deve essere prelevata dal suo specifico device per essere utilizzata con altri sistemi di infusione di insulina (siringhe, microinfusori, cateteri e.v.)

- Dovrebbe essere riservata agli adulti che richiedono più di 20 U/die di insulina rapida; questo assicura che l'insulina non venga sprecata o venga utilizzata oltre i 28 giorni di utilizzo una volta aperta la confezione.

- **I Pazienti possono trarre beneficio da una migliore esperienza dell'iniezione/ ridotto numero di penne per insulina**

Differenze tra Generico, Bioequivalente, Biosimilare

Farmaci di sintesi chimica

Molecola chimica originaria

Generici o equivalenti: Copie di farmaci a basso peso molecolare che derivano da processi di produzione chimici[1] facilmente riproducibili

Farmaci di origine biologica

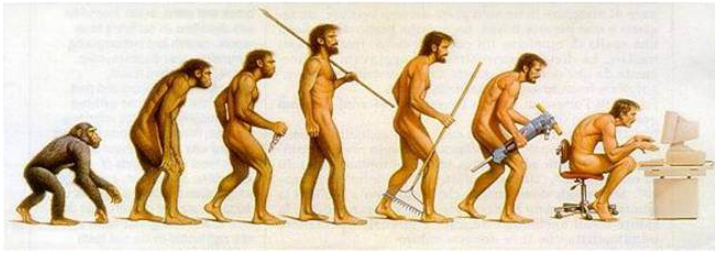
Molecola biologica originaria

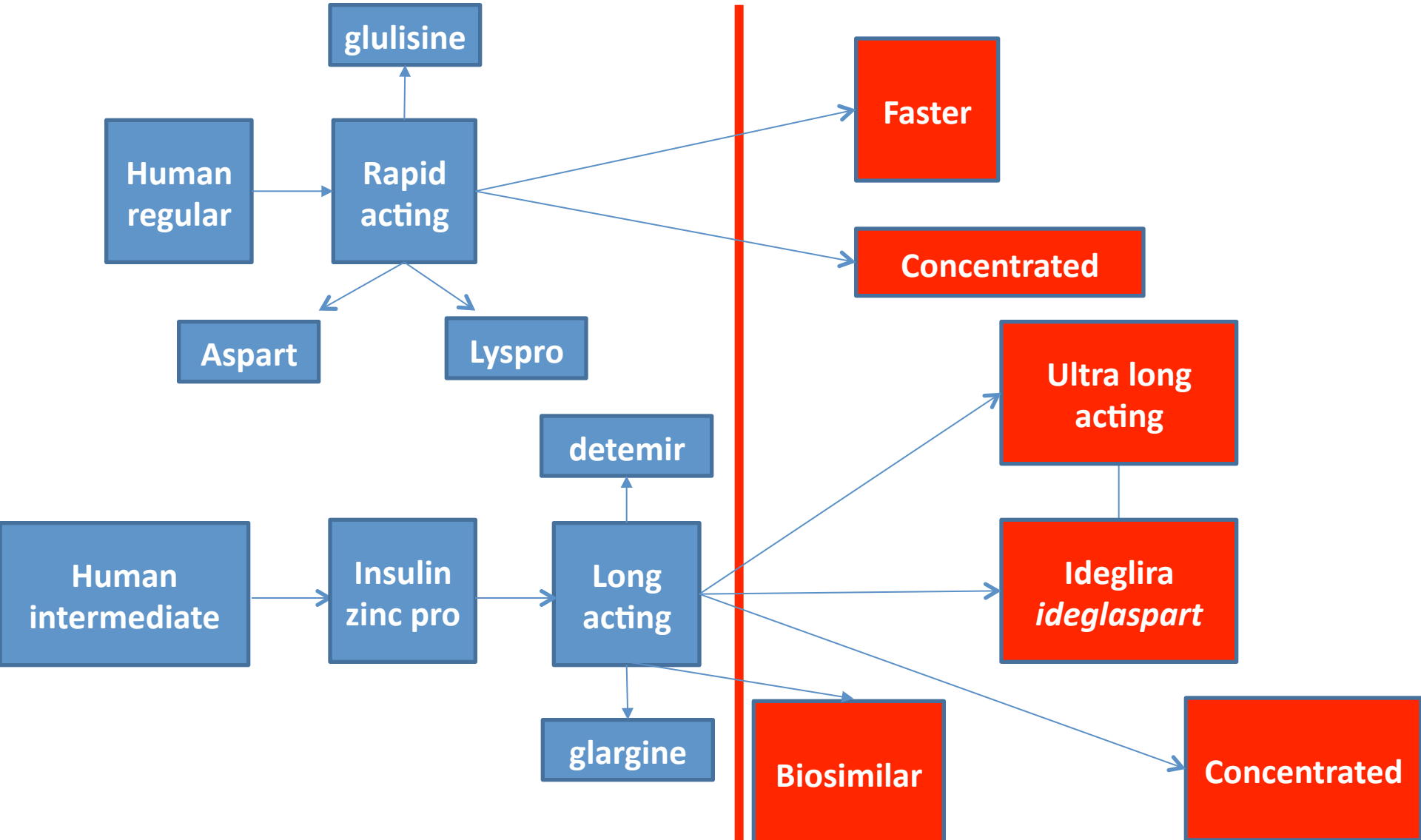
Bioequivalenti: identico principio attivo di biologici prodotti dalla stessa azienda derivanti da DIVERSI processi di produzione biotecnologici[1]

Biosimilari: versione simile dell'originator biologico prodotti da aziende differenti e con differenti processi biotecnologici [1-3]

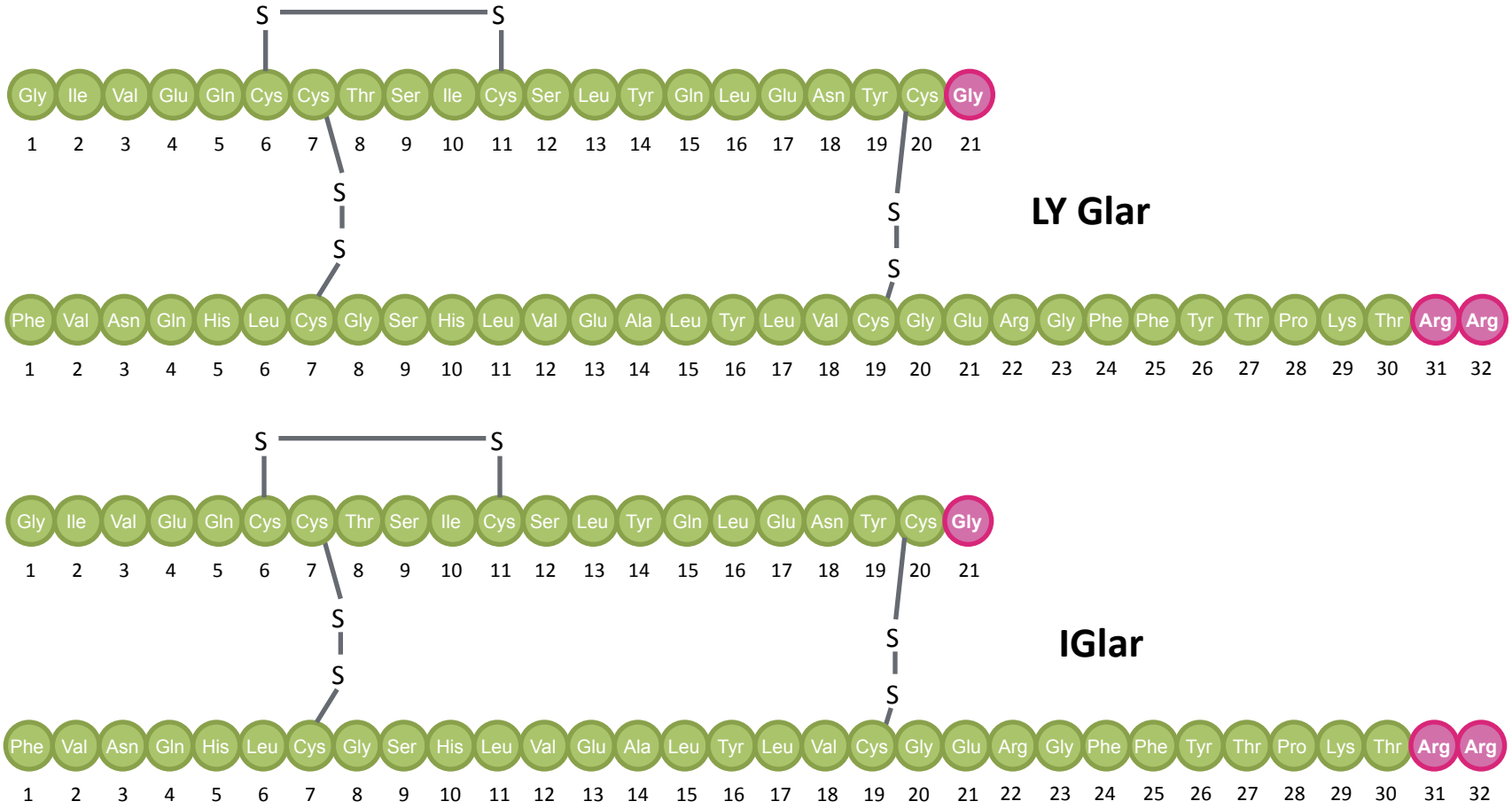
1. Sekhon BS, Saluja V. Biosimilars 2011;1:1–11;
2. EMA. Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Quality Issues (Revision 1). 2012;
3. Owens DR et al. Diabetes Technol Ther 2012;14:989–996

Evolution of Insulin





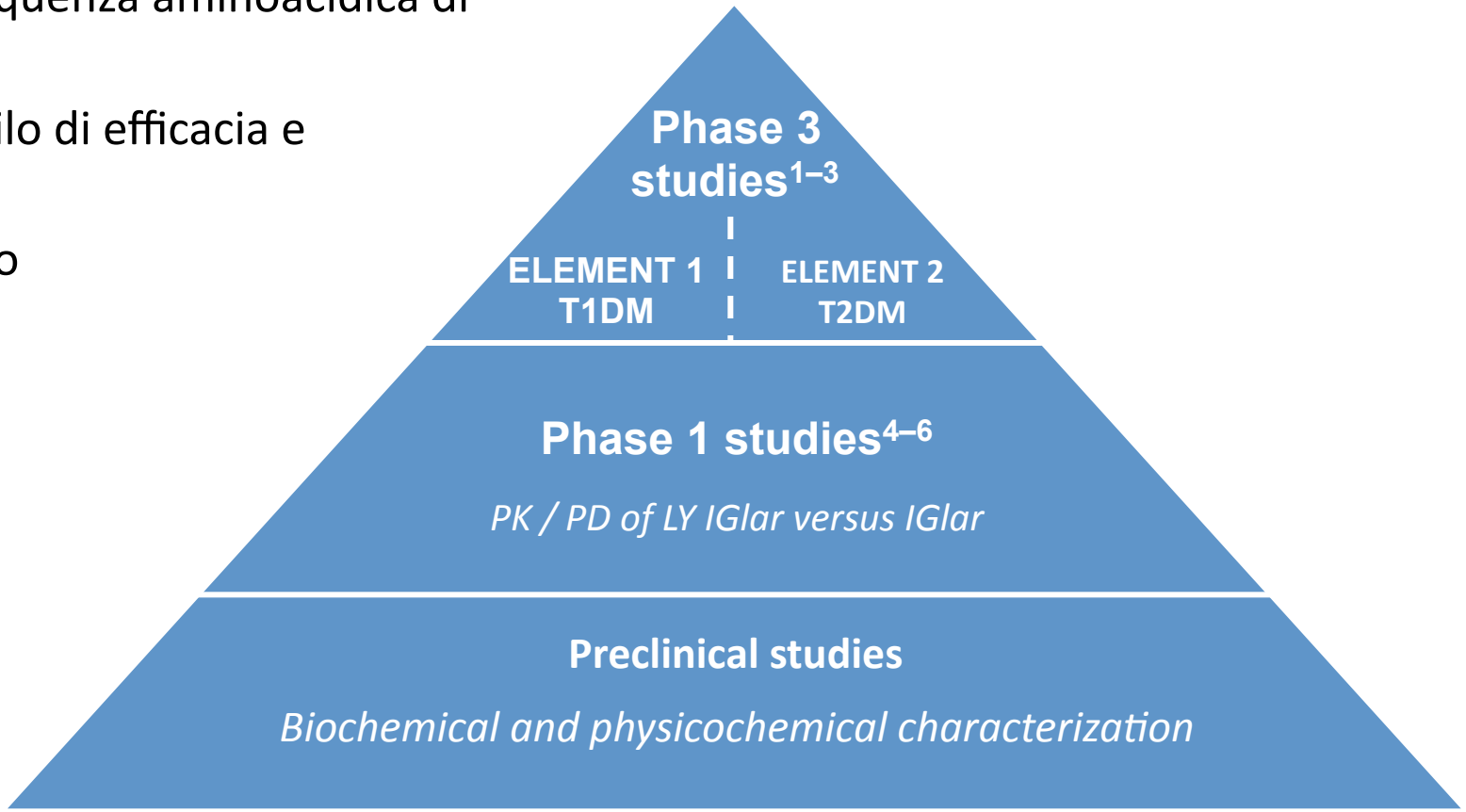
LYGlar



1 EPAR PI EMA. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000284/WC500036082.pdf
2 EPAR PI EMA. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002835/WC500175381.pdf

LY IGlar Development Program

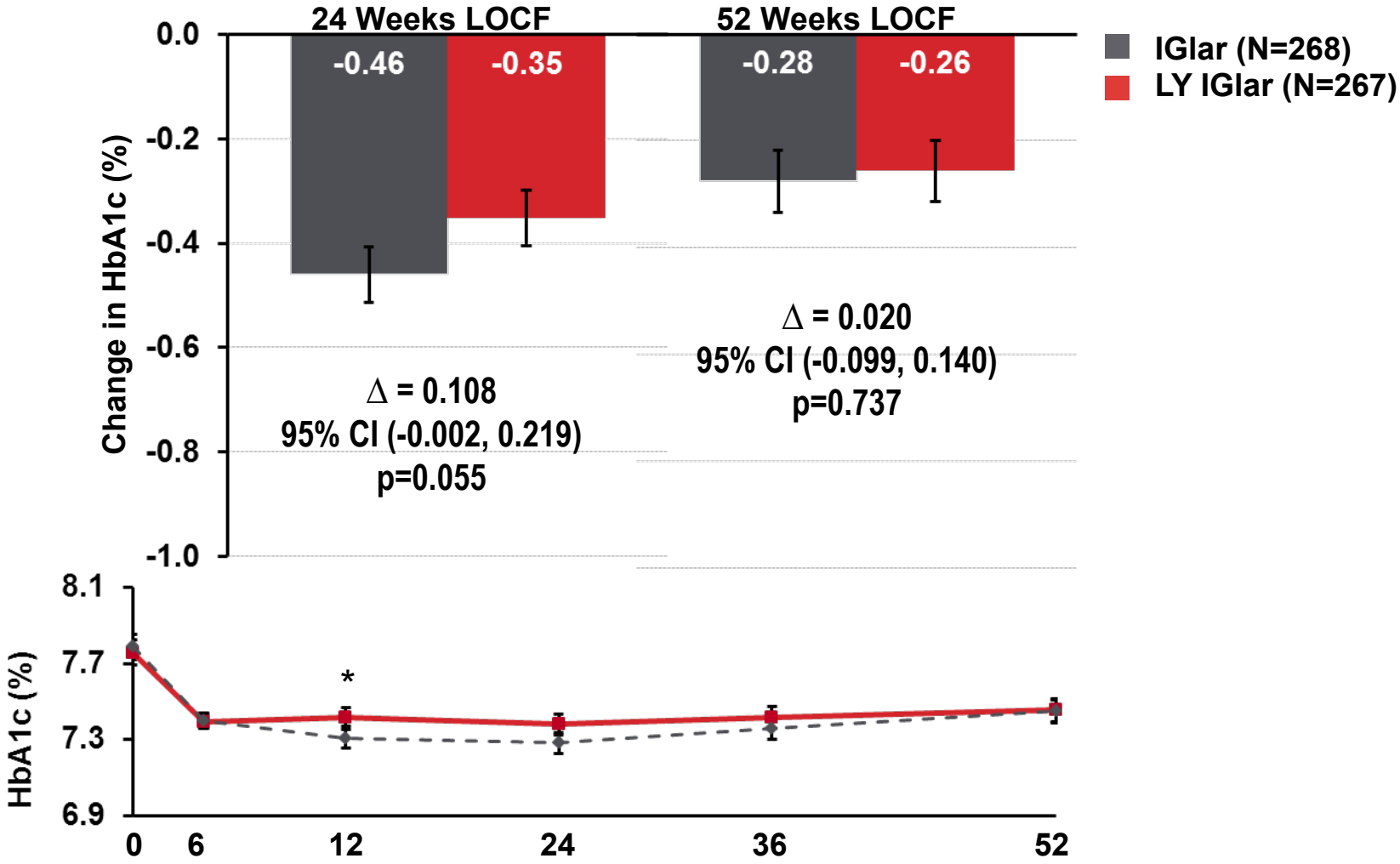
- Identica sequenza aminoacidica di Glargine
- Simile profilo di efficacia e sicurezza
- Minor costo



1. Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33; 2. Rosenstock et al., Diabetes Obes Metab. 2015 Aug;17(8):734-41;
3. Ilag et al, Diabetes Obes Metab. 2015 Oct 5, [Epub ahead of print]; 4. Linnebjerg et al., Diabetes Care. 2015 Dec;38(12):2226-33
5. Zhang et al. *ADA 2014*: 890-P; 6. Heise et al. *ADA 2014*: 891-P

PD=pharmacodynamic; PK=pharmacokinetic;
T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus

ELEMENT 1: HbA_{1c} Change from Baseline and over Time with LY IGlar and IGlar

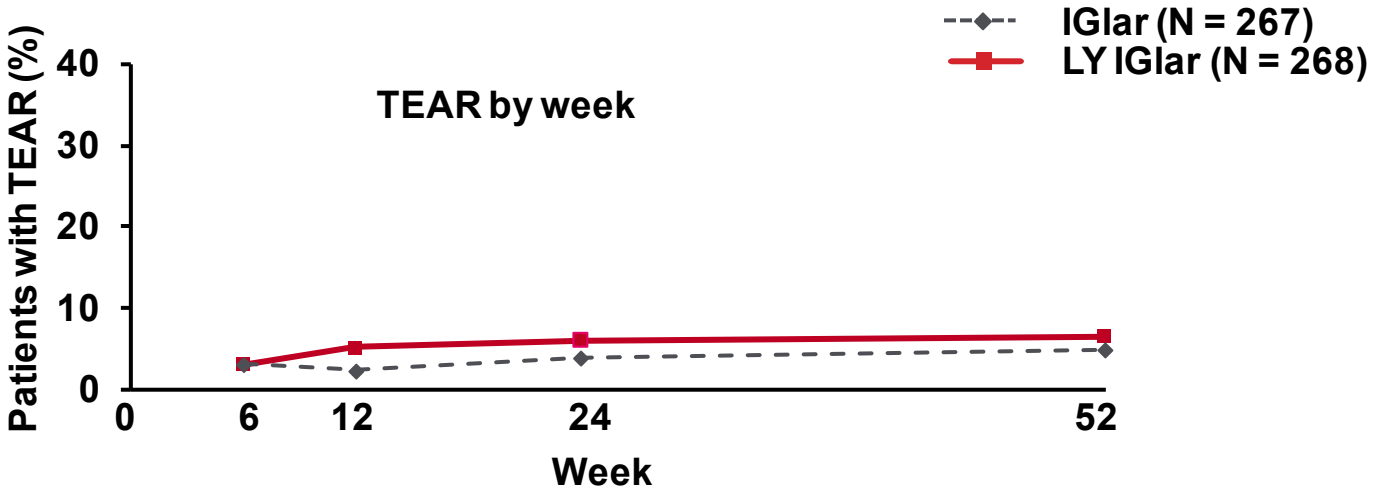


Data are least squares mean ± standard error
*p = 0.03; no significant differences between treatment at any other time point
CI=confidence interval; HbA_{1c}=glycosylated hemoglobin; LOCF=last observation carried forward

Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33

ELEMENT 1: Incidence of Treatment-emergent Antibody Response (TEAR)

TEAR criteria	
If antibody was not detected at baseline	% antibody binding ≥1.26%
If antibody was detected at baseline	Absolute increase in % antibody binding of 1% AND 30% relative increase from baseline

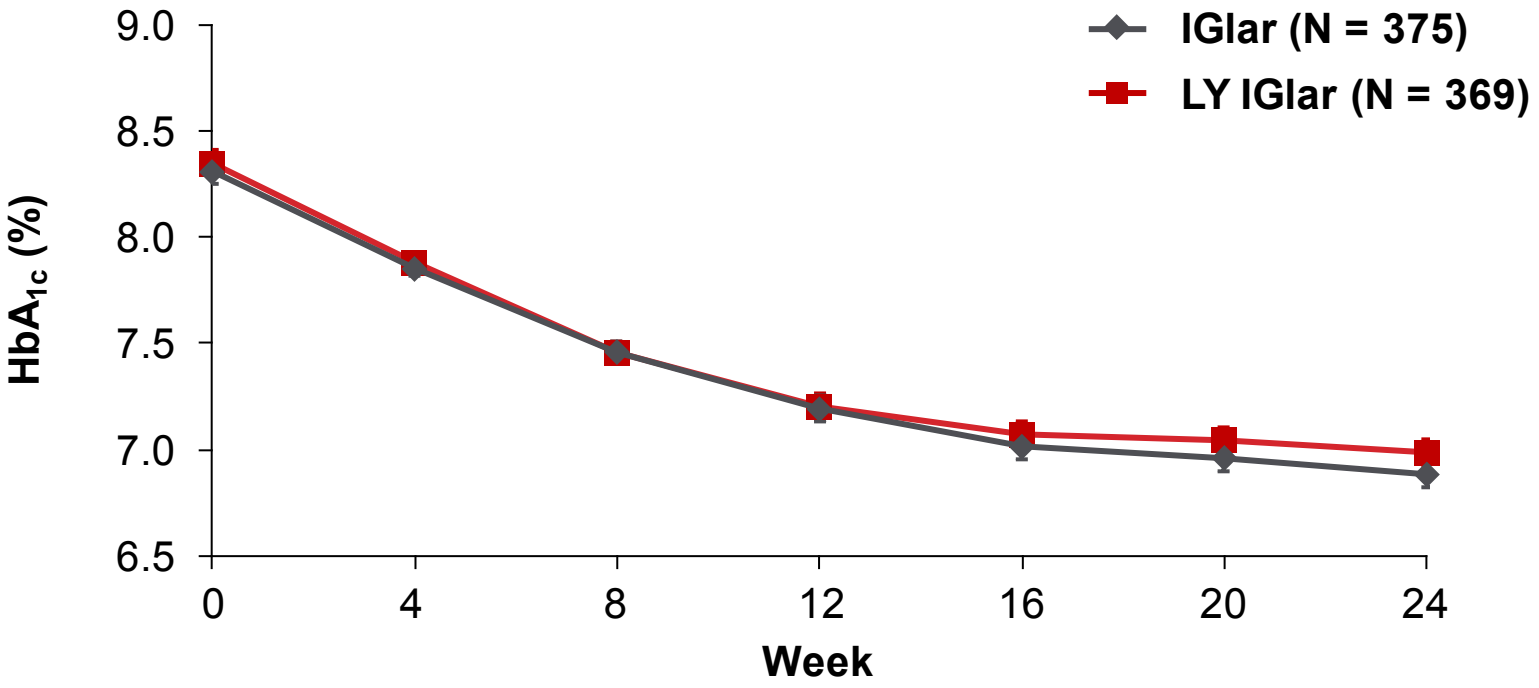


		IGlar	LY IGlar	p value
Patients with TEAR, n (%)	Week 52 (LOCF)	12 (5)	18 (7)	0.27
	Overall 24 weeks	17 (6)	25 (9)	0.20
	Overall 52 weeks	25 (9)	29 (11)	0.57

LOCF=last observation carried forward

Blevins et al., Diabetes Obes Metab. 2015 Aug;17(8):726-33

ELEMENT 2: HbA_{1c} Changes over Time



		IGlar	LY IGlar	p value
HbA_{1c}, % LSM ± SE	Baseline	8.31 ± 0.06	8.35 ± 0.06	0.61
	Endpoint LOCF	6.99 ± 0.06	7.04 ± 0.06	0.40

HbA_{1c}=glycosylated hemoglobin; LOCF=last observation carried forward; LSM=least squares mean; SE=standard error

Rosenstock et al., Diabetes Obes Metab. 2015 Aug;17(8):734-41

ELEMENT 2: Incidence of Treatment-emergent Antibody Response (TEAR)

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If antibody was not detected at baseline	% antibody binding ≥1.26%
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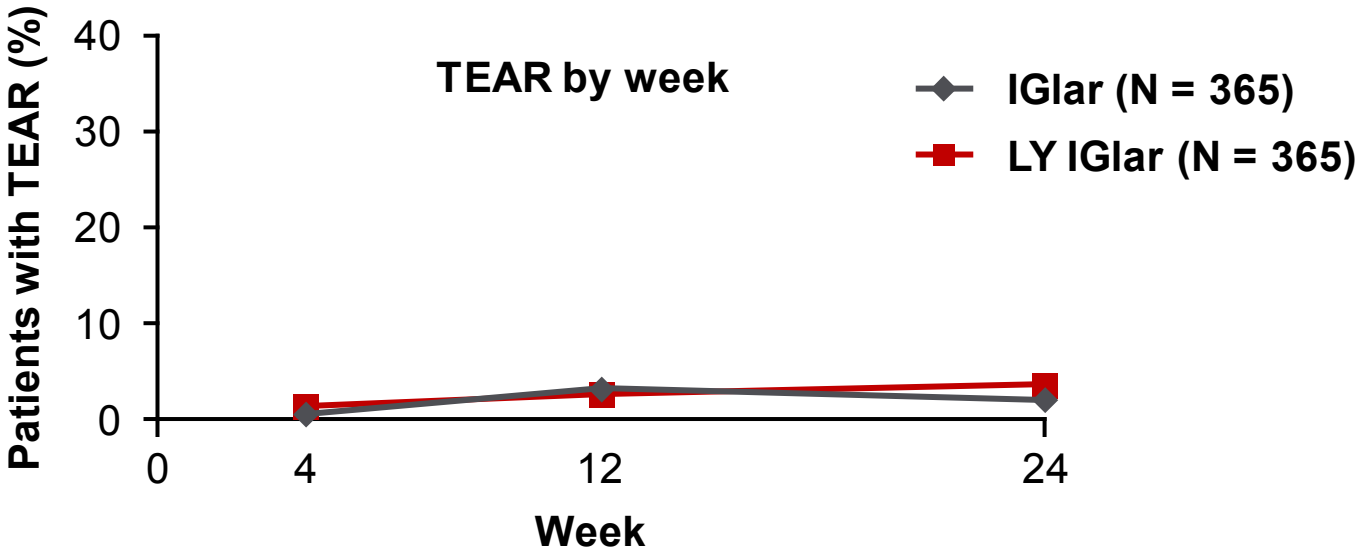
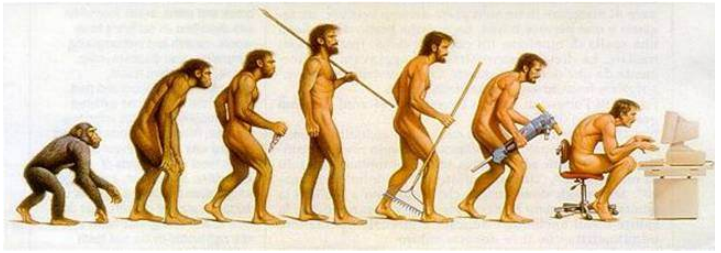


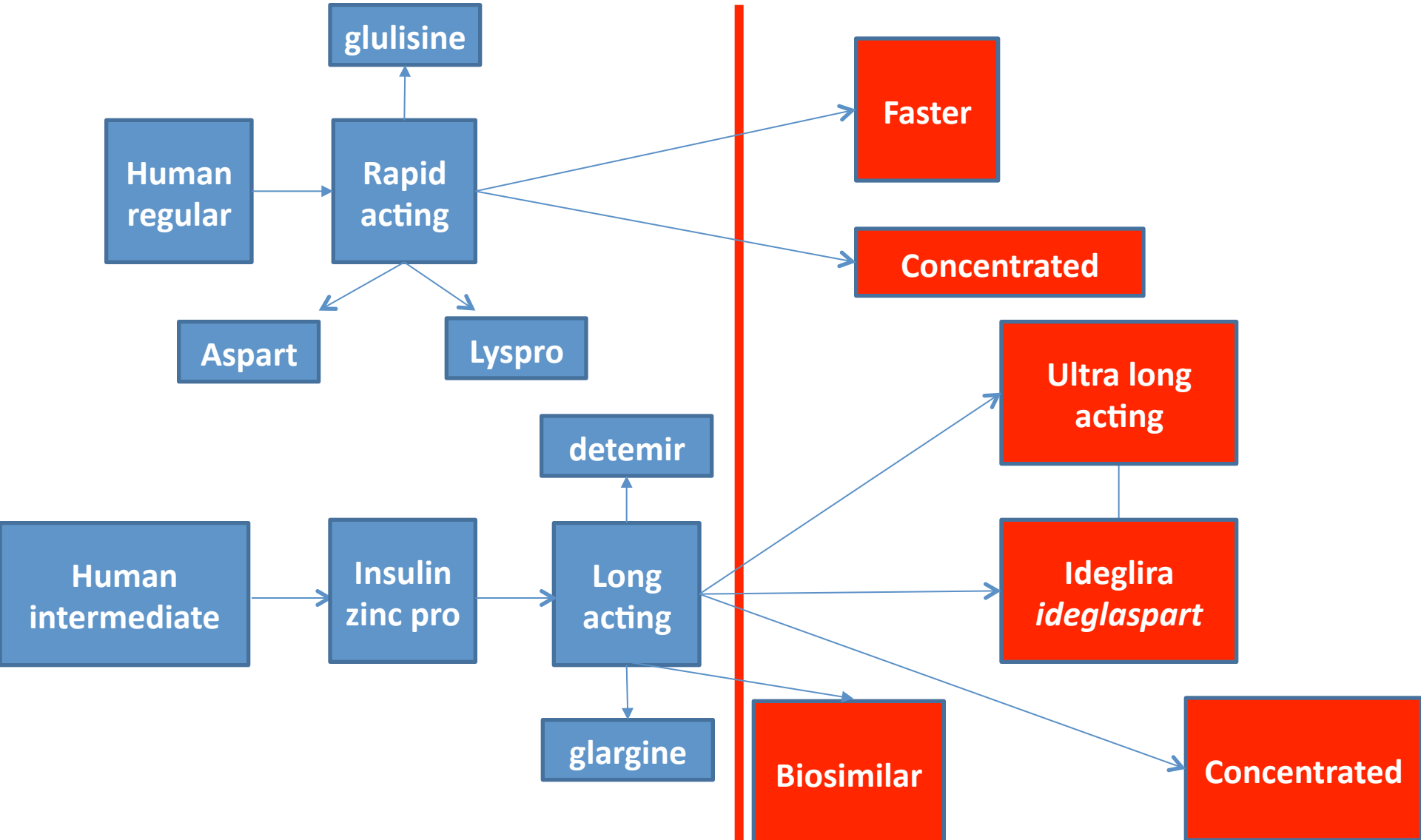
		IGlar	LY IGlar	p value
Patients with TEAR, n (%)	Week 24 (LOCF)	7 (2)	12 (3)	0.35
	Overall	14 (4)	14 (4)	>0.99

LOCF=last observation carried forward

Rosenstock et al., Diabetes Obes Metab. 2015 Aug;17(8):734-41

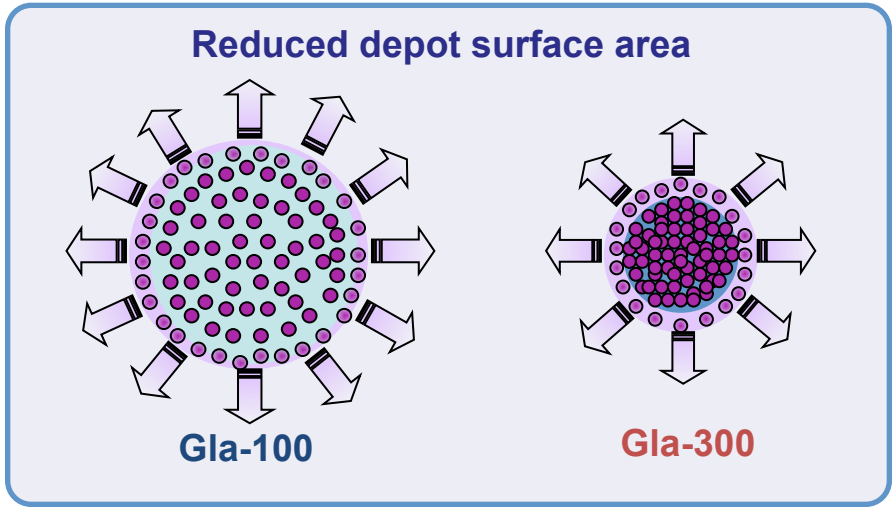
Evolution of Insulin





Gla-300

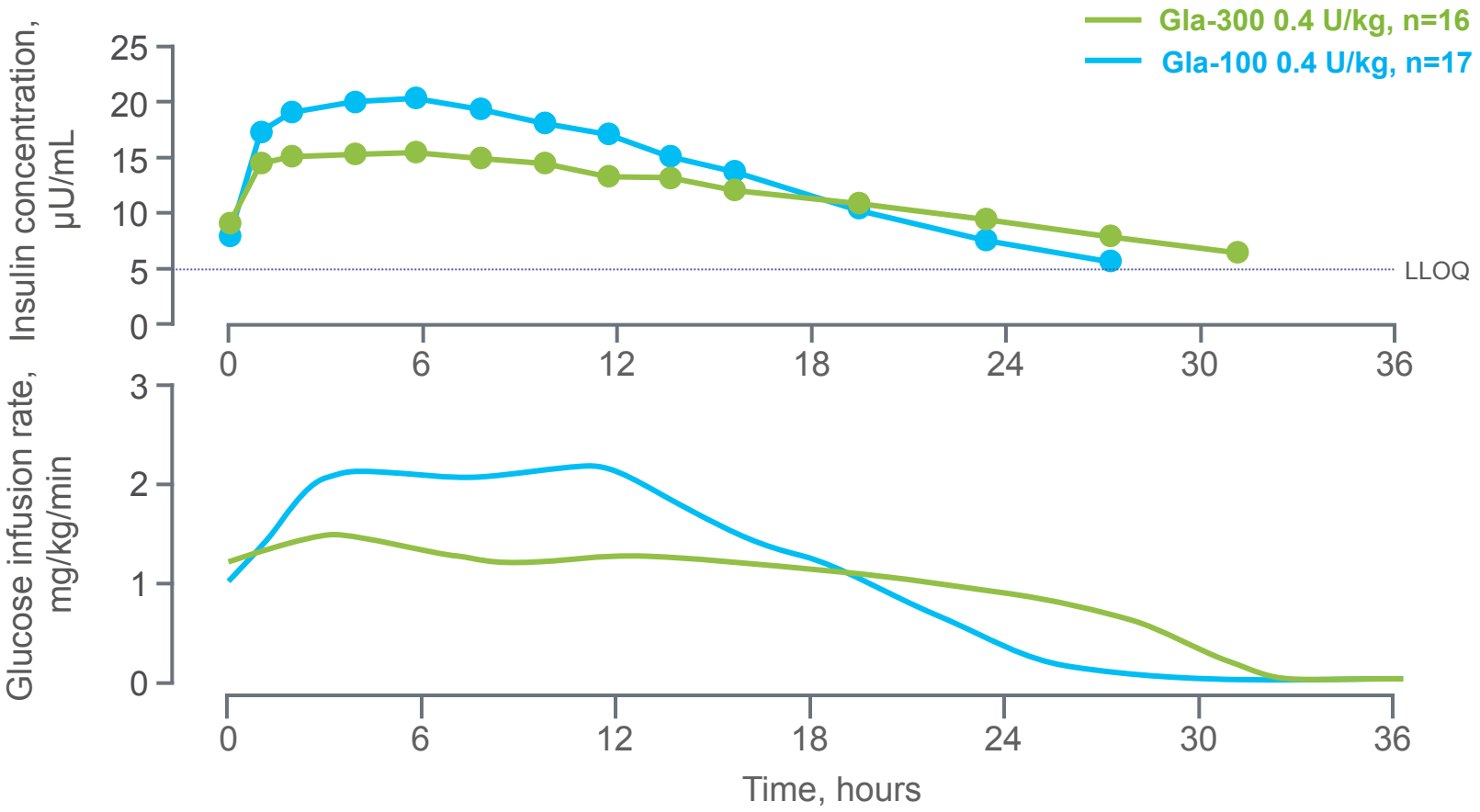
- Gla-300 contiene lo stesso numero di UI di Gla-100 in un terzo del volume
- Gla-300 forma dei microprecipitati come Gla-100, ma con un'area di superficie ridotta



La riduzione del volume diminuisce la superficie depot, con un rallentato tasso di cessione di glargine

Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000309/WC500047935.pdf
Accessed June 2015; Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6

More stable and prolonged (beyond 24 hours) PK/PD profile with Gla-300 vs Gla-100



- Double-blind, crossover euglycemic clamp study of Gla-300 vs Gla-100 in 30 patients with T1DM

LLOQ, lower limit of quantification; PD, pharmacodynamic; PK, pharmacokinetic; T1DM, type 1 diabetes mellitus
Further details on study design can be found in the back-up slides

Becker RH et al. Diabetes Care. 2015;38:637-43

EDITION program

Gla-300 vs Gla-100 studies in different populations

T2DM

EDITION 1
N=807
BB
Basal insulin (≥42 U/day) plus mealtime bolus insulin (fast-acting analogue)

EDITION 2
N=811
BOT
Basal insulin (≥42 U/day) plus OAD (excl. SU)

EDITION 3
N=878
BOT
Basal insulin plus OAD (excl. SU) and/or GLP-1 receptor agonists

EDITION JP 2
N=241
BOT
Basal insulin plus OAD Japanese patients

T1DM

EDITION 4
N=549
BB
Basal insulin plus mealtime bolus insulin (fast-acting analogue)

EDITION JP 1
N=243
BOT
Basal insulin plus mealtime bolus insulin (fast-acting analogue) Japanese patients

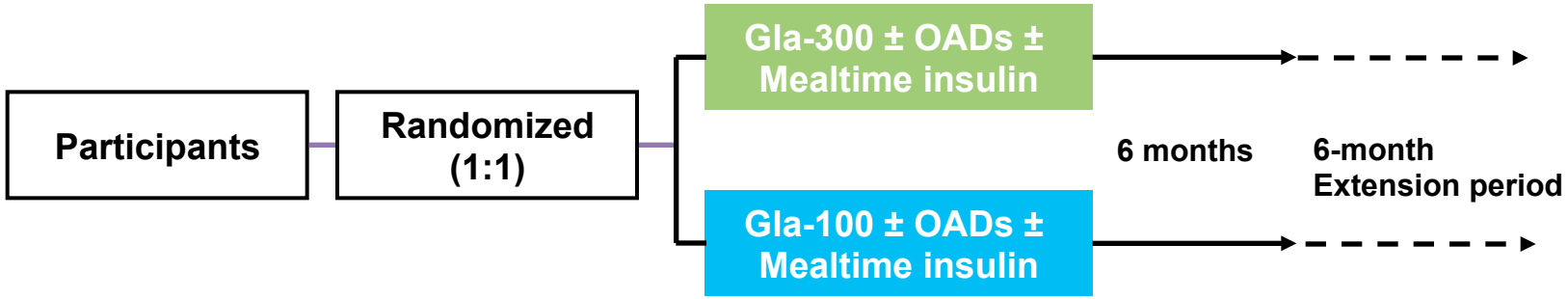
All Phase 3, age of participants ≥18 years, randomization ratio 1:1
Data from the worldwide EDITION studies (EDITION 1–4) will be presented in this slide deck

BB, basal-bolus therapy; BOT, basal only therapy; GLP-1, glucagon-like peptide-1; OAD, oral antihyperglycemic drug; SU, sulfonylurea; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43;
Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print];
Terauchi Y et al. Poster presentation at EASD 2014; Abstract 976; Matsuhisa M et al. Poster presentation at EASD 2014; Abstract 975

EDITION study design consistent across the program

- Randomized 1:1, open-label, parallel-group, multicenter studies
- EDITION program built with similar study design across trials to confirm results
- Comparator: Gla-100



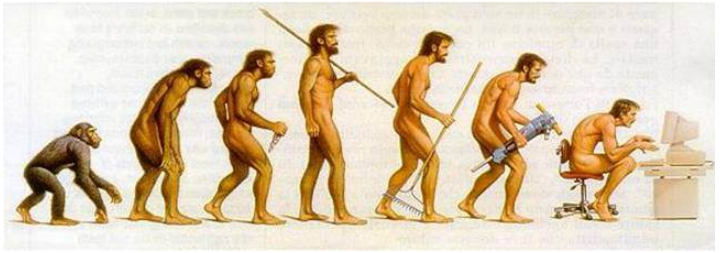
Non-inferiority to Gla-100 in HbA_{1c} reduction at 6 months was the primary endpoint in all trials

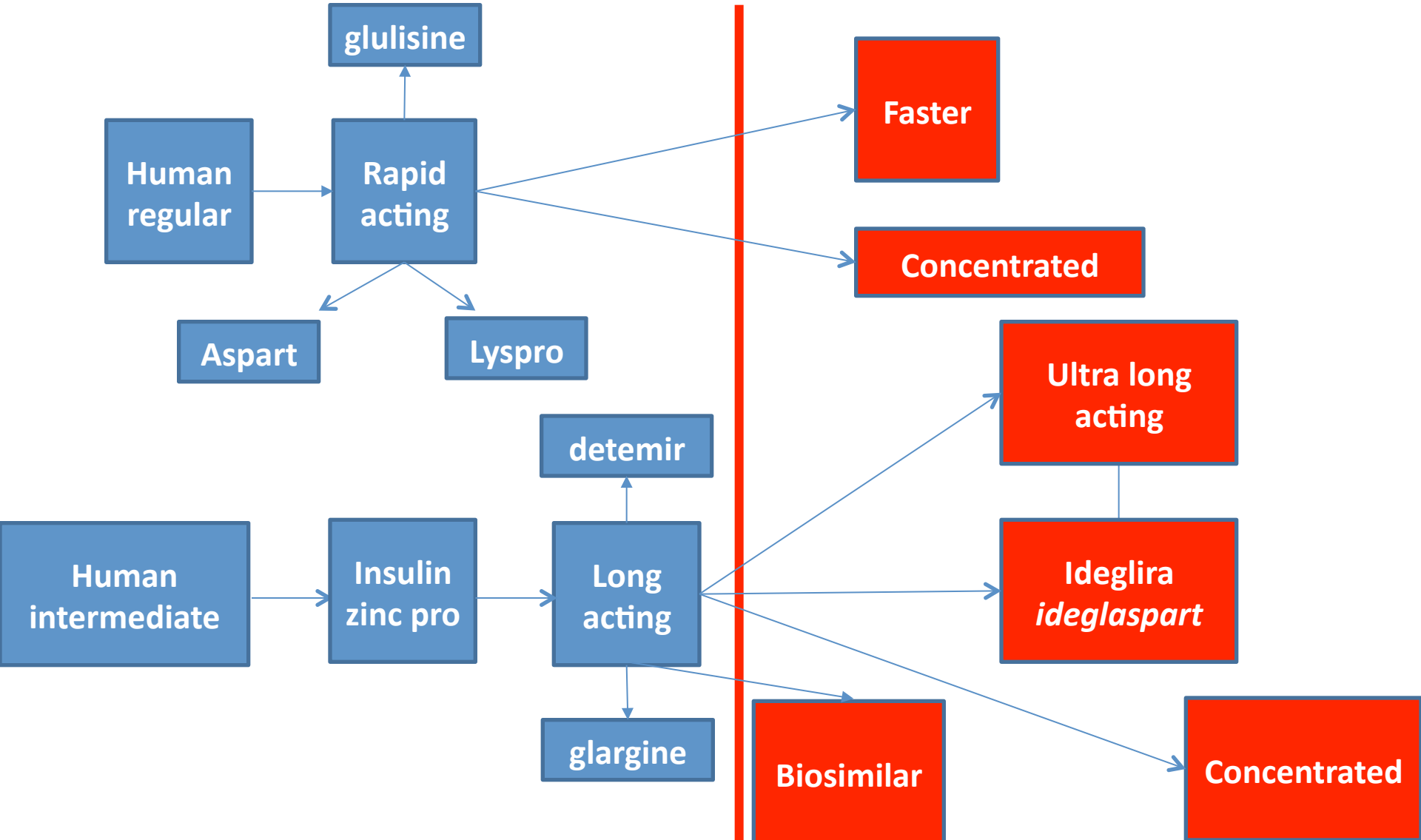
Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43;
Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print]

Gla-300: risultati degli studi e prospettive cliniche

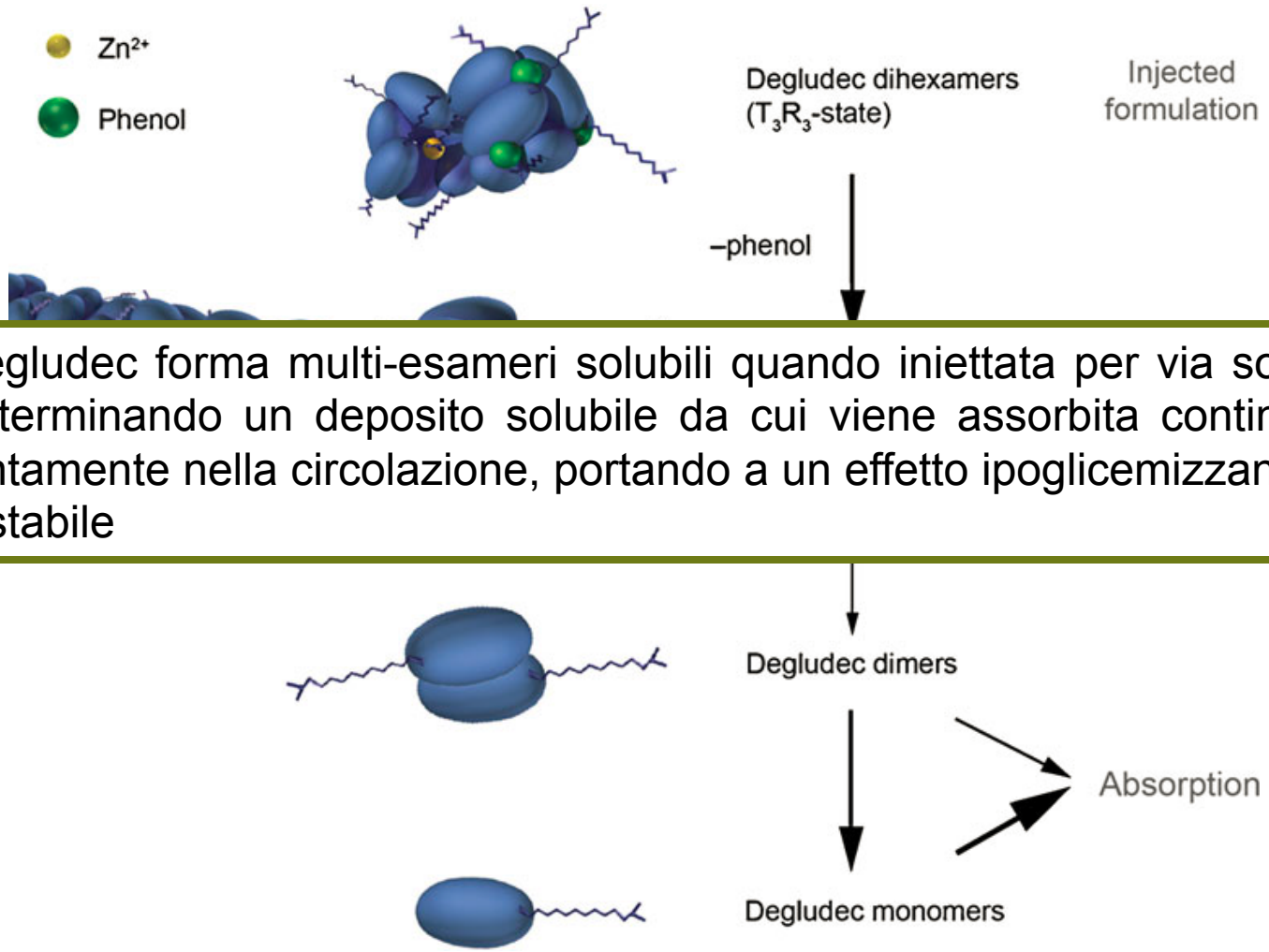
- Simile efficacia di glargine in termine di riduzione di Hba1c in DM tipo 2 e 1
- Simile sicurezza e tollerabilità di glargine
- Minor rischio di ipoglicemie severe notturne e diurne in DM di tipo 2 e quindi maggiore aderenza al target glicemico nella titolazione
- Un profilo PK/PD più prolungato con un controllo glicemico > 24h e minor variabilità glicemica

Evolution of Insulin





Degludec: Proprietà Farmacologiche



Degludec forma multi-esameri solubili quando iniettata per via sottocutanea, determinando un deposito solubile da cui viene assorbita continuamente e lentamente nella circolazione, portando a un effetto ipoglicemizzante uniforme e stabile

Degludec RCP
Jonassen et al. Pharm Res 2012;29:2104–14

Degludec: Proprietà Farmacologiche (RCP)

L'emivita dopo somministrazione sottocutanea di degludec è determinata dal grado di assorbimento dai tessuti sottocutanei. L'emivita di degludec è di circa 25 ore indipendentemente dalla dose.

Durante un periodo di 24 ore con trattamento una volta al giorno, l'effetto ipoglicemizzante di degludec, contrariamente all'insulina glargine, era distribuito in modo uniforme tra le prime e le seconde 12 ore ($AUC_{GIR,0\text{-}12h,SS}$/ $AUC_{GIR,totale,SS}$ = 0,5)

Lo steady state si raggiunge dopo 2-3 giorni dalla somministrazione della dose.

L'azione ipoglicemizzante dell'insulina degludec allo steady state mostra una variabilità da giorno a giorno quattro volte inferiore in termini di coefficienti di variazione (CV)

Degludec RCP
Heise et al. Diabetologia 2011;54(Suppl. 1):S425; Heise et al. Diabetes 2012;61(Suppl. 1):A259; Heise et al. Diabetes Obes Metab 2012;14:859-64

Insulin degludec once daily (BEGIN)

All studies with active comparator

Type 1 diabetes

BB T1 LONG
Basal–bolus
n=629
Heller, 2012; *Lancet*
Bode, 2013; *Diabet Med*

FLEX T1
Flexible basal therapy
n=493
Mathieu, 2013; *J Clin Endocrinol Metab*

BB T1
Basal–bolus
n=456
Davies, 2014; *Diabetes Obes Metab*

Type 2 diabetes

BB
Basal–bolus
Met ± TZD, n=1006
Garber, 2012; *Lancet*

FLEX
BOT
Met ± OADs, n=687
Meneghini, 2013; *Diabetes Care*

ONCE LONG
Basal start
Met ± DPP-4, n=1030
Zinman, 2012; *Diabetes Care*
Rodbard, 2013; *Diabet Med*

EARLY
Basal start
Met ± SU/TZD, n=458
Philis-Tsimikas, 2013;
Diabetes Obes Metab

LOW VOLUME
U200 Basal start
Met ± DPP-4, n=460
Gough, 2013; *Diabetes Care*

ONCE ASIA
Basal start
Met ± SU/α-gluc, n=435
Onishi, 2013; *J Diabetes Investig*

vs. insulin detemir

vs. DPP-4 inhibitors

T1D and T2D vs. insulin glargine

α-gluc, alpha glucosidase inhibitor; BB, basal–bolus; BOT, basal–oral therapy; DPP-4, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione

Degludec: risultati degli studi e prospettive cliniche

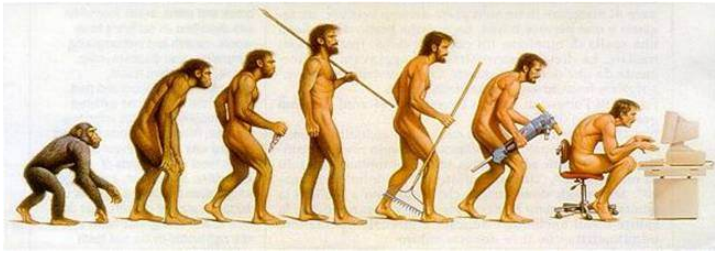
- Simile efficacia in termini di riduzione di Hba1c in DM tipo 2 e 1 con un dosaggio significativamente inferiore rispetto a glargine

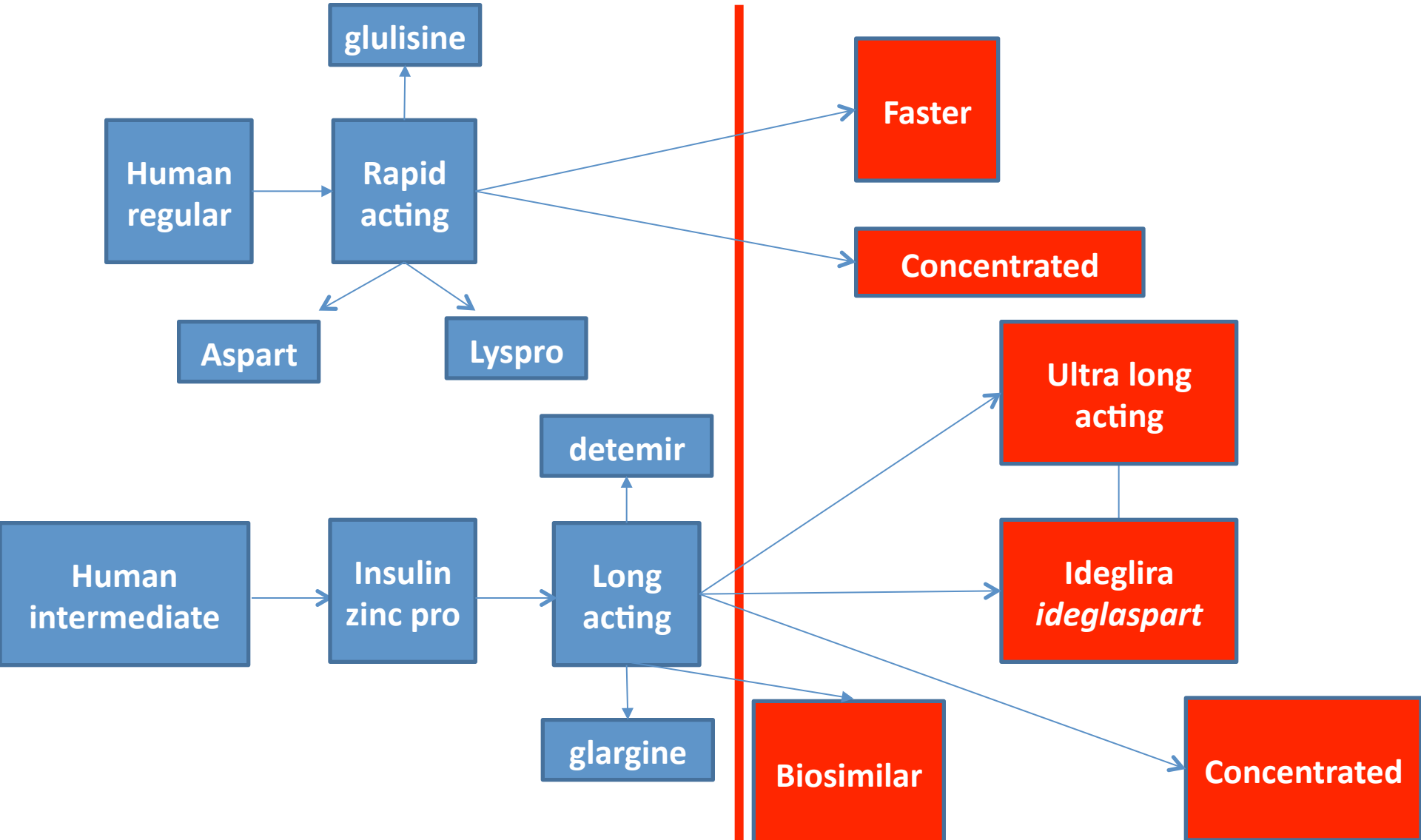
- Minor rischio di ipoglicemie severe notturne sia nello schema ideg fixed che ideg flexible, quindi maggiore aderenza al target glicemico nella titolazione

- Un profilo PK/PD più prolungato con un'emivita di circa 25 h e minor variabilità glicemica

- Maggiore flessibilità

Evolution of Insulin





La complessità della fisiopatologia del diabete può avvalersi di un approccio terapeutico diretto verso differenti organi - bersaglio

GLP-1 analogue

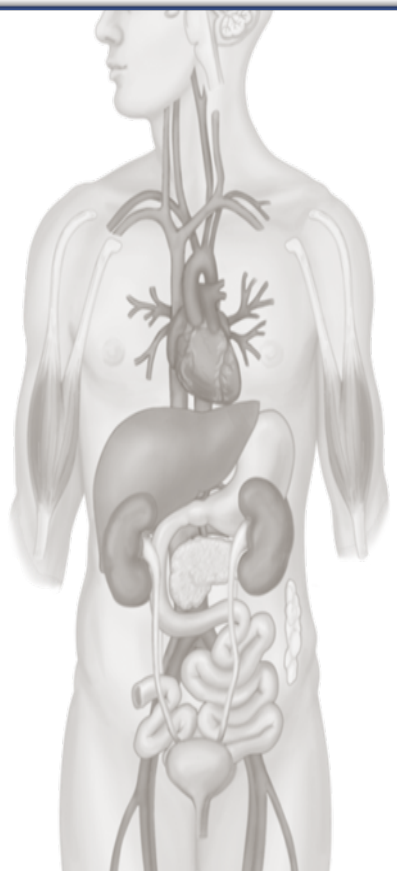
Brain
Energy intake
Satiety
Learning and memory*
Neuroprotection

Heart
Cardioprotection
Cardiac function

Pancreas
Glucose-dependent insulin and glucagon secretion
Insulin synthesis
Beta-cell mass*

Liver
Hepatic glucose output

GI tract
Gastric emptying



Basal insulin

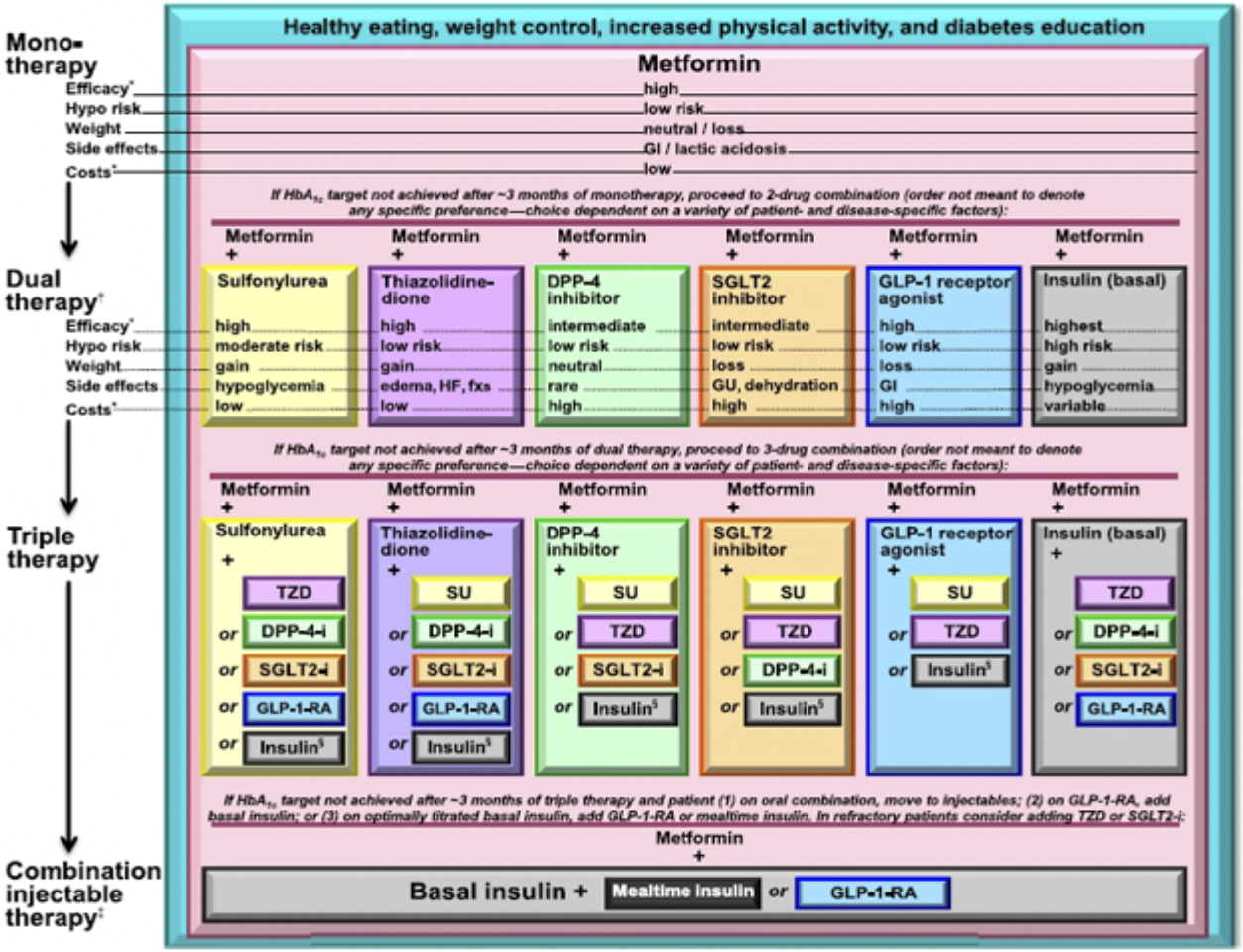
Skeletal muscle
Glucose disposal

Liver
Hepatic glucose production

Adipose tissue
Insulin receptor activation

GLP-1, glucagon-like peptide-1; *in animal studies
Baggio, Drucker. *Gastroenterol* 2007;132:2131–57

ADA EASD GUIDELINES 2015



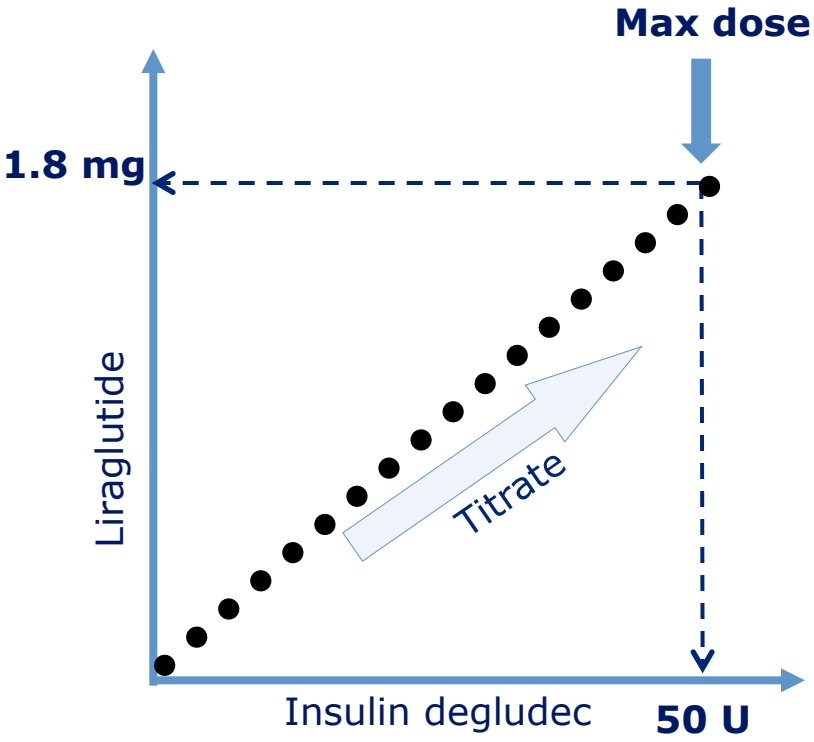
IDegLira

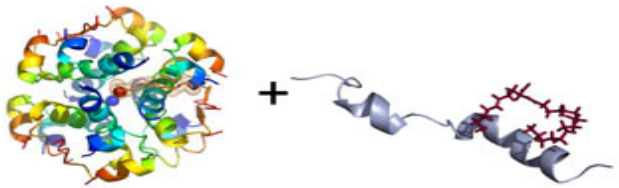
- Subcutaneous injection
  - 3 mL pre-filled pen
  - Fixed ratio of insulin degludec (100 U/mL) and liraglutide (3.6 mg/mL)

Insulin titration to achieve glycaemic control

50 dose steps

50 U insulin degludec + 1.8 mg liraglutide





IDegLira: Phase 3 Clinical Development Plan

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

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

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

DUAL IV
IDegLira add-on to SU vs. placebo

DUAL V
IDegLira vs. basal insulin optimisation

DUAL VI
Easy Titration

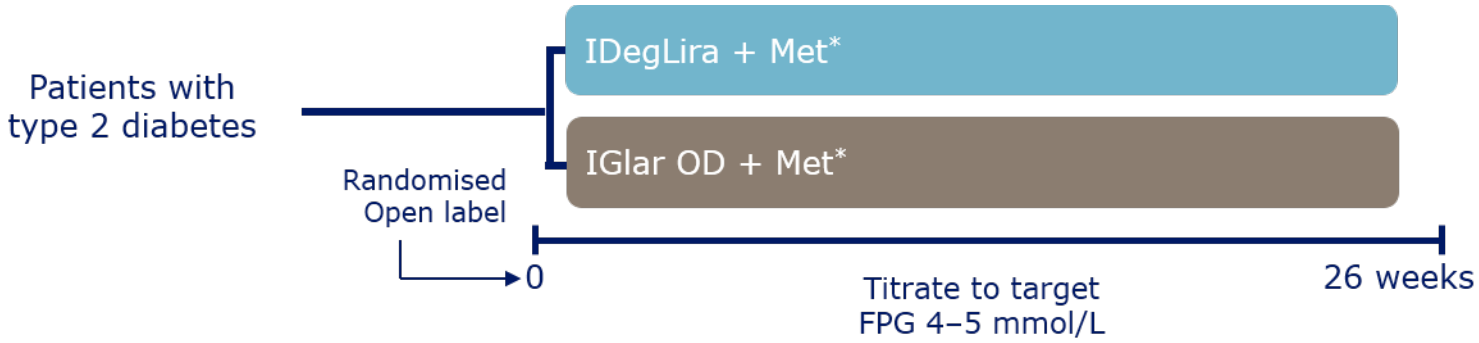
DUAL VII
IDegLira vs. BB (glargine + aspart)

DUAL VIII
IDegLira vs. glargine (durability - 104 months)

....DUAL IX, DUAL X

www.clinicaltrials.gov

DUAL™ V: Basal insulin switch



Inclusion criteria

- Type 2 diabetes currently on Met and IGlar (20–50 U)
- HbA_{1c} 7–10%
- BMI ≤40 kg/m^2
- Age ≥18 years

IGlar; insulin glargine; IDegLira, insulin degludec/liraglutide
*Met dose must be unchanged throughout the trial

- La riduzione di Hba1c è risultata significativamente maggiore in Ideglira vs Iglar (-1.81% vs -1.13%; pvalue < .001)
- Perdita di peso in ideglira vs incremento ponderale in Iglar(-1.4 Kg vs 1.8 Kg)
- Minori episodi ipoglicemici in Ideglira
- Maggior numero di eventi avversi GI non gravi con Ideglira

Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The DUAL V Randomized Clinical Trial; ***JAMA ,*** *March 1, 2016, Vol 315, No. 9*

Conclusioni

- Nuove insuline più rapide e più concentrate saranno a disposizione per il controllo delle glicemie post-prandiali ed una maggiore aderenza alla terapia;

- Nuove insuline basali sono e saranno a disposizione per il controllo della glicemia a digiuno ed anche delle glicemie post-prandiali (ideglira)

- Minor rischio di ipoglicemie notturne e diurne, maggiore flessibilità, minore variabilità glicemica, differenze nei device, compliance e farmaco-economia devono guidarci nella scelta dell'insulina più adatta al nostro paziente