



2ND SUMMIT
RARE
DISEASES
C O P A C

Safety and Efficacy in therapeutical options for Gaucher Disease

Nicolás Fernández Escobar
Hematólogo
Hospital Gutiérrez, BsAs, Argentina

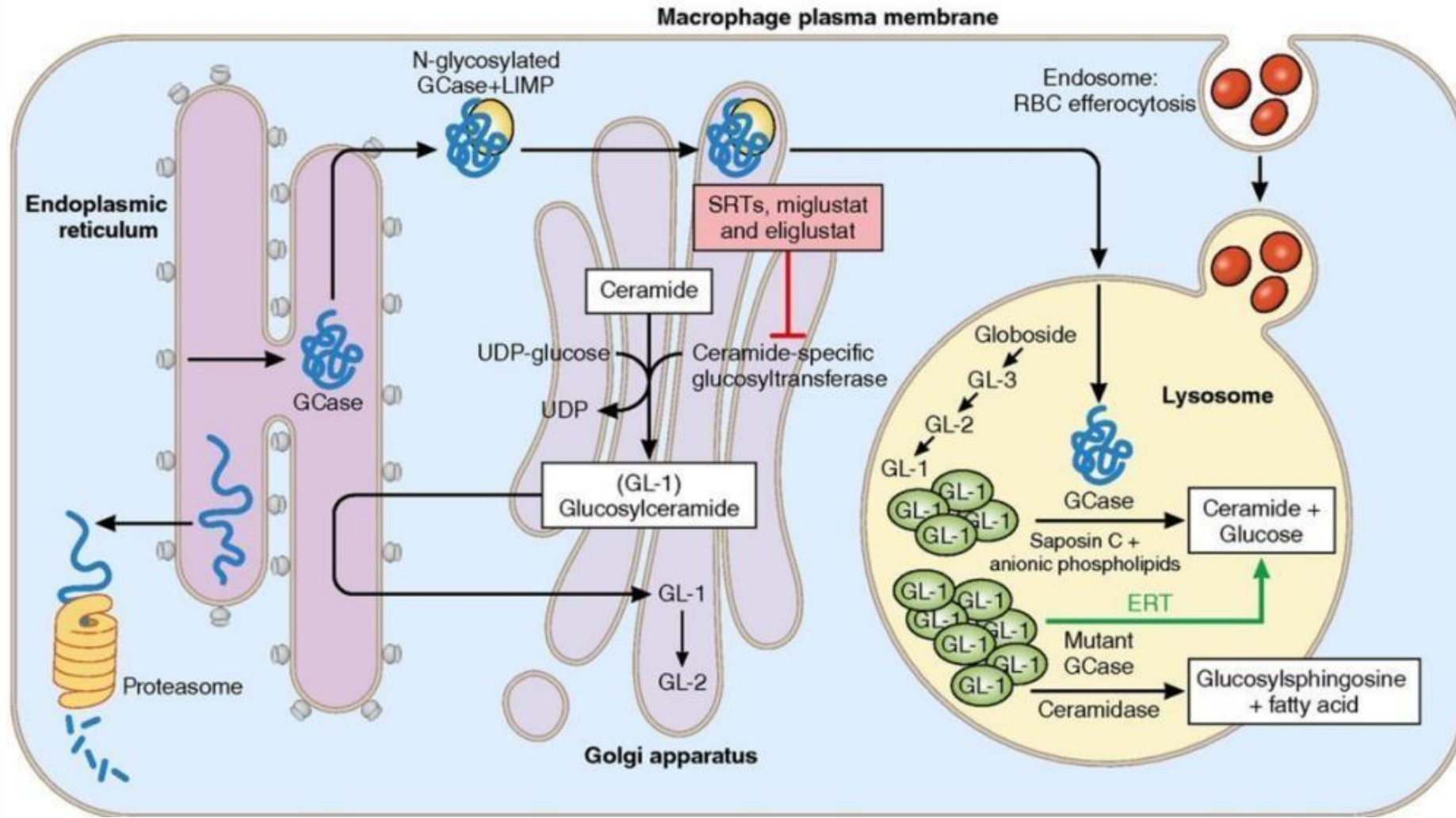
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Declaración Conflicto de Interés

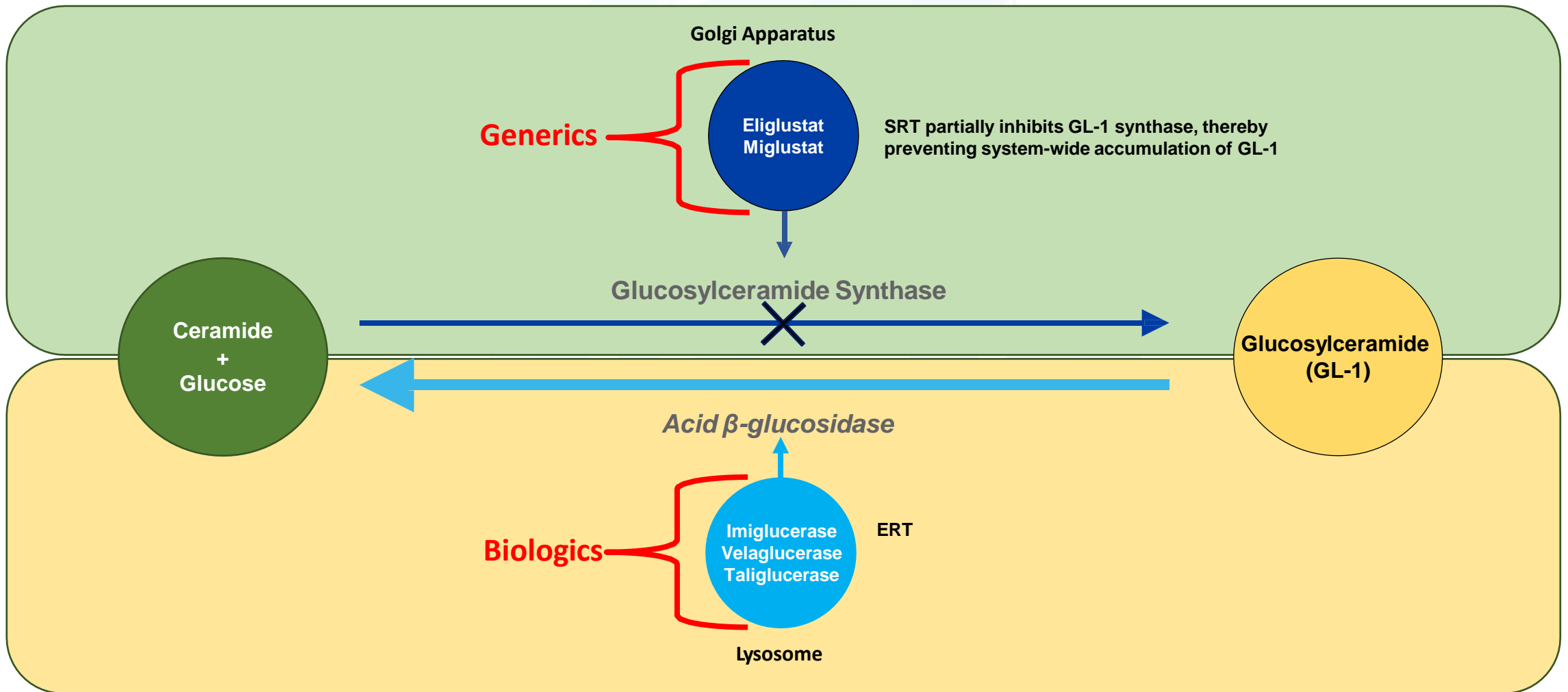
- He recibido honorarios por parte de Sanofi por esta conferencia.

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Therapeutical options for Gaucher Disease



SRT and ERT - Synthesis and Degradation



GL-1 synthase=glucosylceramide synthase. Figure is adapted from Shayman JA. *Drugs Future*. 2010;35:613-620.

1. Cerdelga Summary of Product Characteristics (SmPC); Genzyme Europe B.V.; January 2020.
2. Shayman JA. *Drugs Future*. 2010;35:613-620.
3. Mistry PK, et al. *Am J Hematol*. 2011;86(1):110-115.

SRT and ERT

What are we talking about when we talk about generic drugs or biological drugs?

Generics

Eliglustat
Miglustat

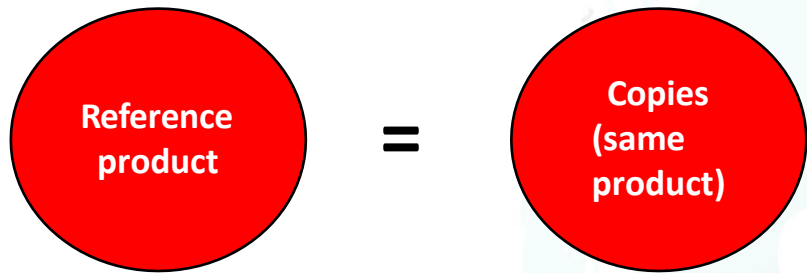
Biologics

Imiglucerase
Velaglucerase
Taliglucerase

Drugs or medicines (generics or biologics)

Generics (small molecules drugs)

Chemically synthesized medicines are small molecular structures made by combining specific chemical “ingredients”



Following the same “recipe” yields exactly the same product (molecular “sameness” is possible) with comparable quality (content, purity + limited bioequivalence clinical studies).

Example:
eliglustat
miglustat

Biologics (large and complex proteins)

Biologics are grown from living organisms.



Proving molecular “sameness” is not possible because changes in cell lines, different manufacturing processes, formulation, delivery devices may result in altered PK/PD and/or immune response.

Example:
Imiglucerase
Velaglucerase
Taliglucerase

Safety and Efficacy in Gaucher Disease

Timeline



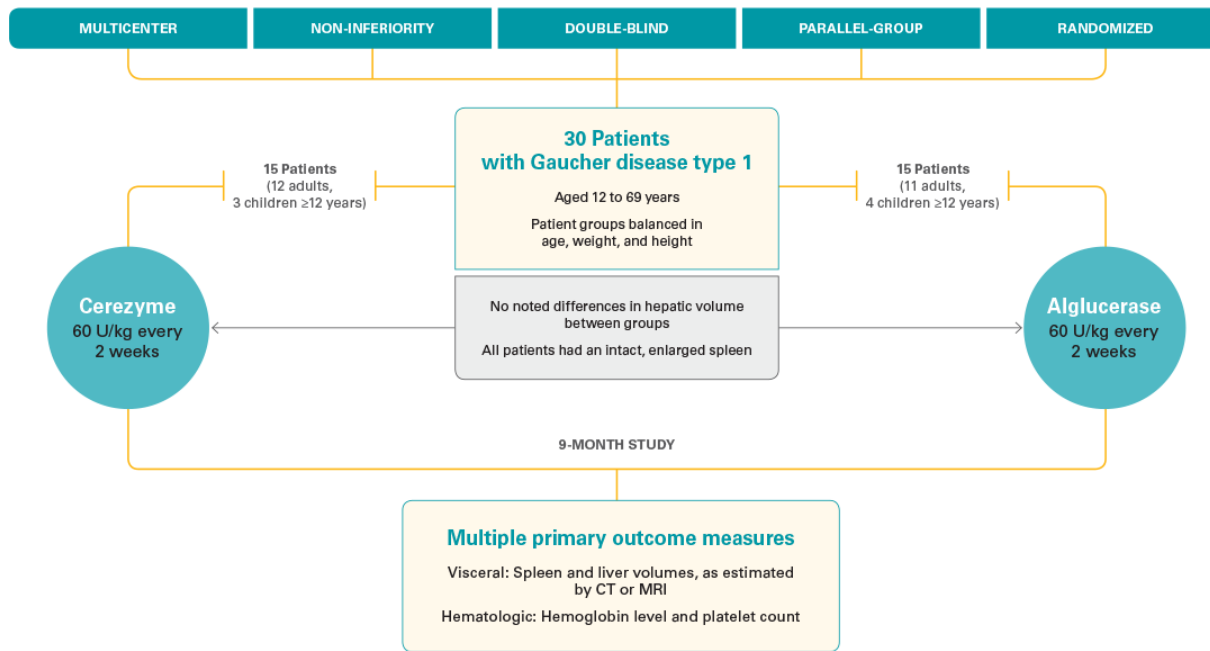
1. BartonNW, FurbishFS, MurrayGJ, GarfieldM, BradyRO. Therapeutic response to intravenous infusions of glucocerebrosidase in a patient with Gaucher disease. *Proc Natl Acad Sci U S A.* 1990;87(5):1913–1916.
2. BartonNW, BradyRO, DambrosiaJM, et al. Dose-dependent responses to macrophage-targeted glucocerebrosidase in a child with Gaucher disease. *J Pediatr.* 1992;120(2 Pt 1):277–280.
3. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency – macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med.* 1991;324(21): 1464–1470.
4. Grabowski G, Brady RO, et al. Enzyme Therapy in Type 1 Gaucher Disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. *Annals of Int Med.* 1995; 122 (1): 33-39

Safety and Efficacy in Gaucher Disease

Pivotal
Phase 3 trial
Multicenter
Non inferiority
Double blind
Randomized
n = 30
9 months



ERT timeline: Pivotal, phase 3 Study



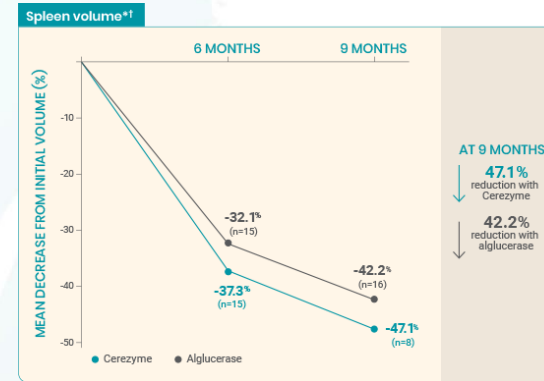
CT=computed tomography;
MRI=magnetic resonance imaging.

Results:

No significant differences were found in the rate or extent of improvement in hemoglobin levels, platelet counts, serum acid phosphatase or angiotensin-converting enzyme activities, or hepatic or splenic volumes between either treatment group. The incidence of IgG antibody formation was greater in the Ceredase group (40%) than in the Cerezyme group (20%). No major immunologic adverse events occurred in either group.

Conclusions:

Our study shows the therapeutic similarity of Ceredase and Cerezyme. Cerezyme has the advantage of being theoretically unlimited in supply and free of potential pathogenic contaminants.

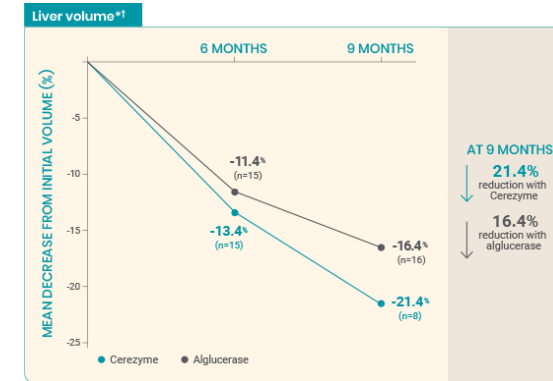


The mean baseline spleen volume was 19.3 MN for Cerezyme patients and 23.7 MN for alglucerase patients.

MN=multiples of normal.

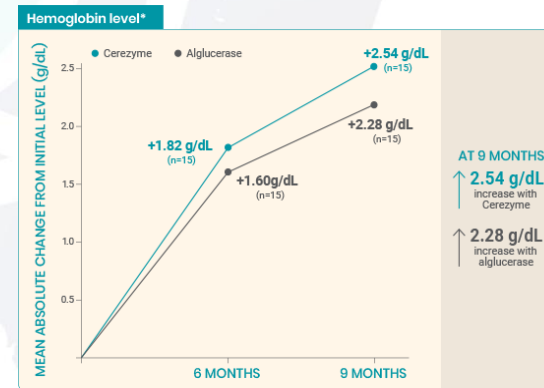
*P values for all comparisons were >0.2.

†Percentage changes refer to changes from the initial volume.



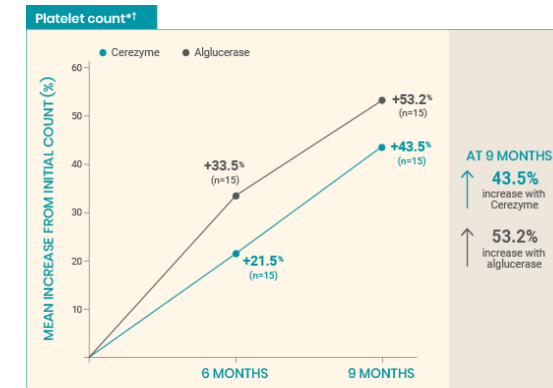
The mean baseline liver volume was 1.65 MN for Cerezyme patients and 1.83 MN for alglucerase patients.

Evaluación de 4 metas en 9 meses



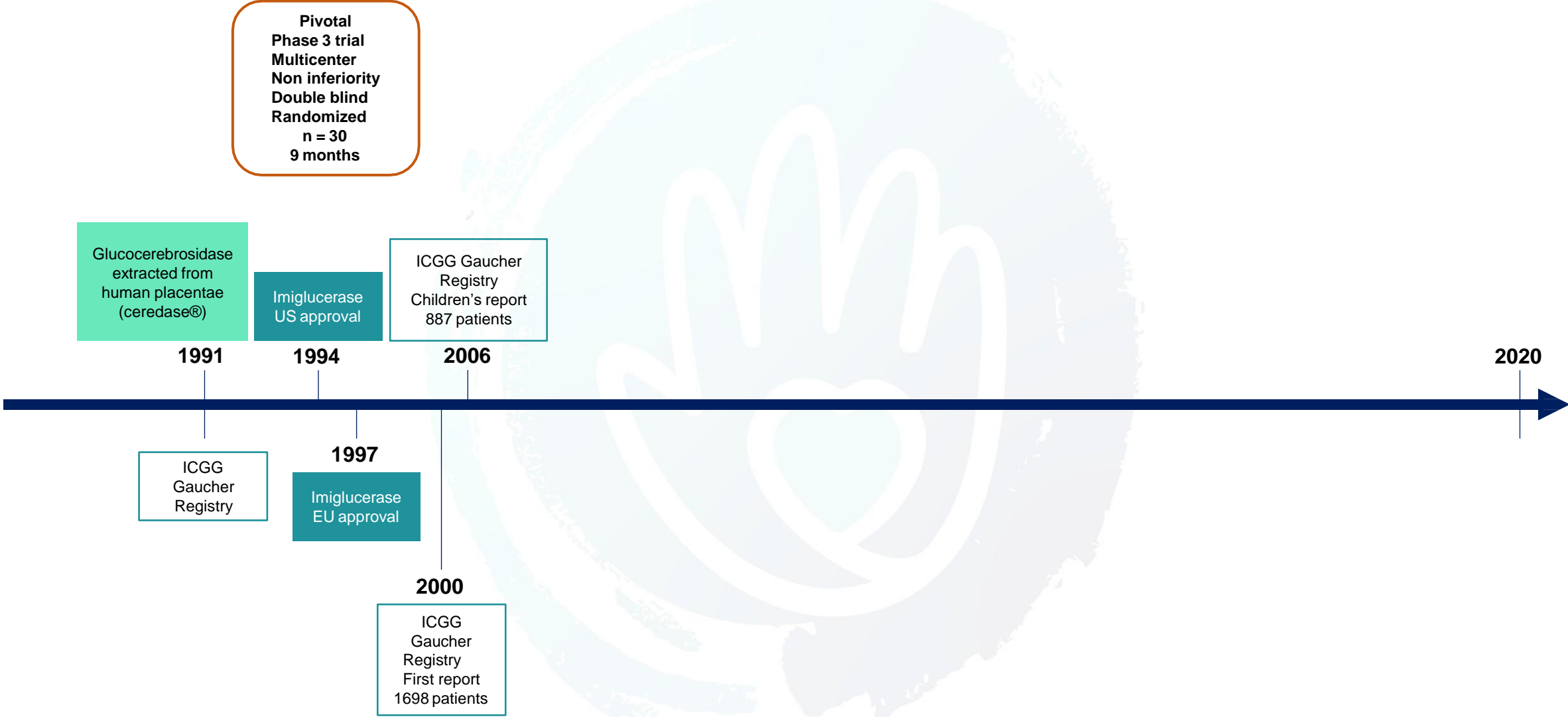
The mean baseline hemoglobin level was 10.71 g/dL for Cerezyme patients and 10.77 g/dL for alglucerase patients.

*P values for all comparisons were >0.2.



The mean baseline platelet count level was 72.1 x 10⁹/L for Cerezyme patients and 70.9 x 10⁹/L for alglucerase patients.

Safety and Efficacy in Gaucher Disease



6. Paige Kaplan, Hans C Anderson et al. The Clinical and Demographic Characteristics of Nonneuronopathic Gaucher Disease in 887 Children at Diagnosis. *Arch Pediatr Adolesc Med.* 2006 Jun;160(6):603-8.

ERT timeline: GD in 887 children at diagnosis

Which is the importance of include children with GD in these reports?
Do you think we have any other special populations?

6. Paige Kaplan, Hans C Anderson et al. The Clinical and Demographic Characteristics of Nonneuronopathic Gaucher Disease in 887 Children at Diagnosis. *Arch Pediatr Adolesc Med.* 2006 Jun;160(6):603-8.

ERT timeline: GD in 887 children at diagnosis

Table 1. Patient Demographics at Diagnosis*

Demographic Variables	No. (%) of Patients (N = 887)
Age at diagnosis, y	
0 to <6	425 (48)
6 to <12	274 (31)
12 to <18	188 (21)
Sex	
Male	454 (51)
Female	433 (49)
Ethnicity	
White, non-Jewish	262 (30)
Jewish, Ashkenazi	207 (23)
Unknown	118 (13)
African American/Caribbean	102 (11)
Hispanic	91 (10)
Other†	57 (6)
Arab	50 (6)
Geographic region	
United States	253 (29)
Latin America	222 (25)
Europe	165 (19)
Israel	130 (15)
Asian Pacific‡	46 (5)
Middle East§	38 (4)
Canada	33 (4)

Table 3. Patient Hematologic and Organ Volume Characteristics at Diagnosis*

	Age at Diagnosis, y				P Value†
	0 to <6	6 to <12	12 to <18	All Ages	
Hemoglobin, patient population	n = 287	n = 184	n = 131	n = 602	<.05
Anemic‡	128 (45)	62 (34)	49 (37)	239 (40)	
Not anemic	159 (55)	122 (66)	82 (63)	363 (60)	
Thrombocytopenia with spleen intact (platelet count, $\times 10^3/\mu\text{L}$),§ patient population	n = 277	n = 176	n = 117	n = 570	.003
Severe (<60)	24 (9)	12 (7)	15 (13)	51 (9)	
Moderate (60 to <120)	98 (35)	75 (43)	58 (50)	231 (41)	
Mild/normal (≥ 120)	155 (56)	89 (51)	44 (38)	288 (51)	
Splenomegaly (spleen volume, MN), patient population	n = 115	n = 72	n = 54	n = 241	<.001
Severe (>15)	84 (73)	26 (36)	14 (26)	124 (51)	
Moderate (>5-15)	30 (26)	42 (58)	34 (63)	106 (44)	
Mild/normal (≤ 5)	1 (1)	4 (6)	6 (11)	11 (5)	
Hepatomegaly (liver volume, MN), patient population	n = 111	n = 68	n = 58	n = 237	<.001
Severe (>2.5)	32 (29)	4 (6)	1 (2)	37 (16)	
Moderate (>1.25 to 2.5)	74 (67)	56 (82)	38 (66)	168 (71)	
Mild/normal (≤ 1.25)	5 (5)	8 (12)	19 (33)	32 (14)	

Table 4. Patient Skeletal Manifestations at Diagnosis*

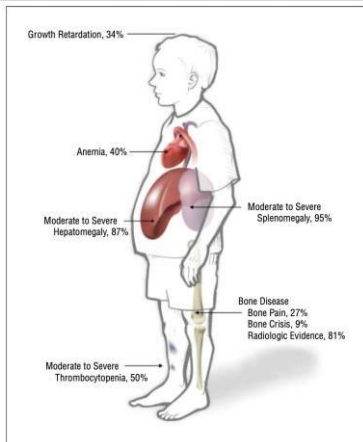
Skeletal Manifestations	Age, y				P Value†
	0 to <6	6 to <12	12 to <18	All Ages	
Bone pain, patient population	n = 214	n = 144	n = 102	n = 460	<.001
Patients reporting	33 (15)	51 (35)	40 (39)	124 (27)	
Bone crisis, patient population	n = 207	n = 143	n = 99	n = 449	<.001
Patients reporting	8 (4)	16 (11)	15 (15)	39 (9)	
Radiologic evidence of bone disease, patient population	n = 134	n = 95	n = 75	n = 304	<.001
Any evidence of radiologic bone disease‡	97 (72)	80 (84)	69 (92)	246 (81)	.06
Erlenmeyer flask deformity	59 (44)	48 (51)	43 (57)	150 (49)	.009
Marrow infiltration	40 (30)	41 (43)	35 (47)	116 (38)	.04
Osteopenia	21 (16)	20 (21)	21 (28)	62 (20)	.16
Avascular necrosis	8 (6)	6 (6)	9 (12)	23 (8)	.11
Infarction	6 (5)	11 (12)	7 (9)	24 (8)	.50
Lytic lesions	7 (5)	9 (9)	5 (7)	21 (7)	.87
New fractures	2 (1)	3 (3)	1 (1)	6 (2)	
Height, percentile, patient population	n = 245	n = 150	n = 101	n = 496	.50
<5th	79 (32)	62 (41)	26 (26)	167 (34)	
5th-25th	77 (31)	34 (23)	27 (27)	138 (28)	
>25th	89 (36)	54 (36)	48 (48)	191 (39)	

ICGG Registry
887 children

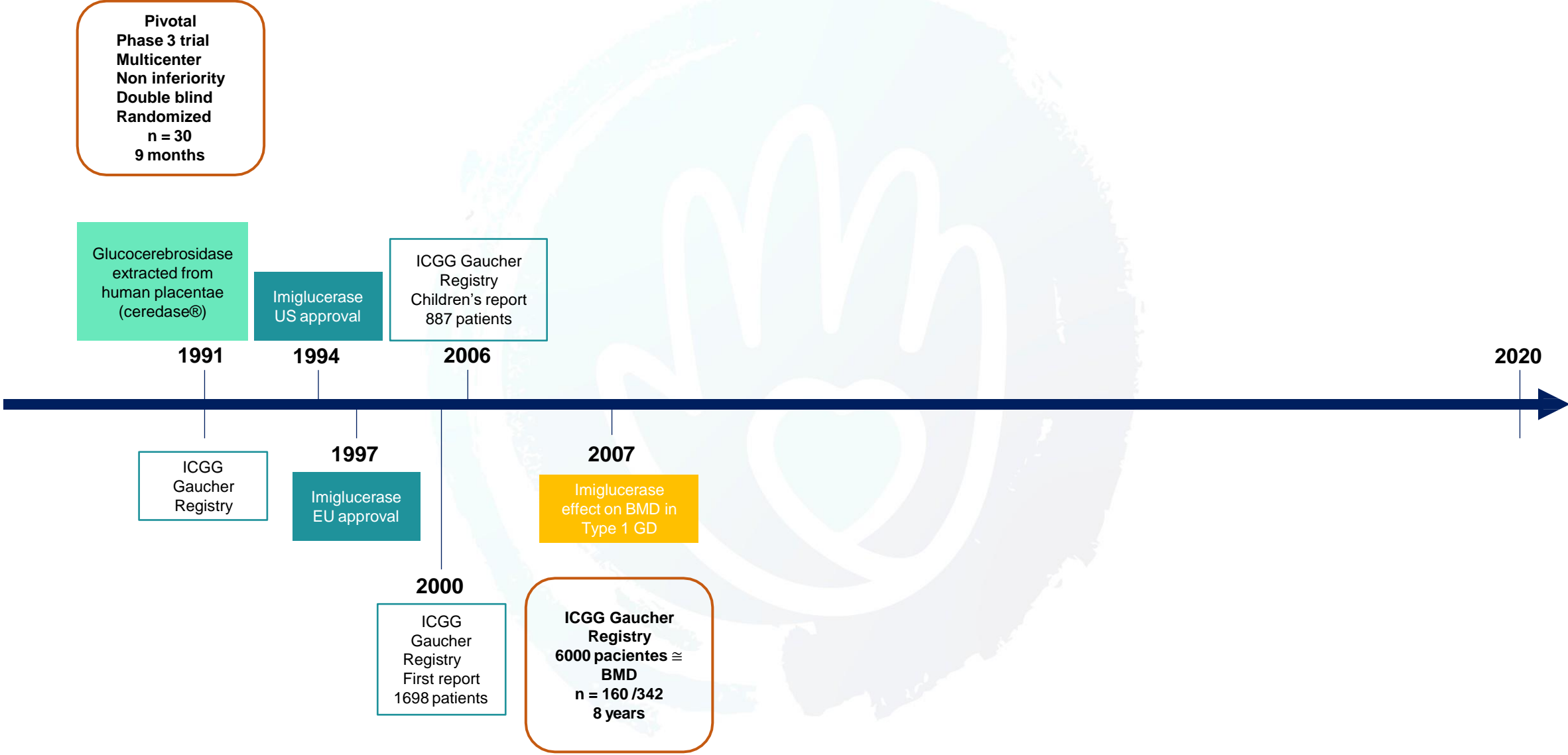
Conclusions:

Nonneuronopathic GD commonly manifests in childhood and affects many ethnic groups. The high prevalence of rare mutations may be associated with earlier onset and/or more severe disease.

6. Paige Kaplan, Hans C Anderson et al. The Clinical and Demographic Characteristics of Nonneuronopathic Gaucher Disease in 887 Children at Diagnosis. *Arch Pediatr Adolesc Med.* 2006 Jun;160(6):603-8.



Safety and Efficacy in Gaucher Disease



7. RichardJWenstrup, GregoryMPastores, Thomas N Hangartner et al. Effect of Enzyme Replacement Therapy With Imiglucerase on BMD in Type 1 Gaucher Disease. Journal of Bone and Mineral Research. Volume 22, Number 1, 2007

ERT timeline: Effect of ERT on BMD in Type 1 Gaucher Disease

TABLE 1. PATIENT DEMOGRAPHICS

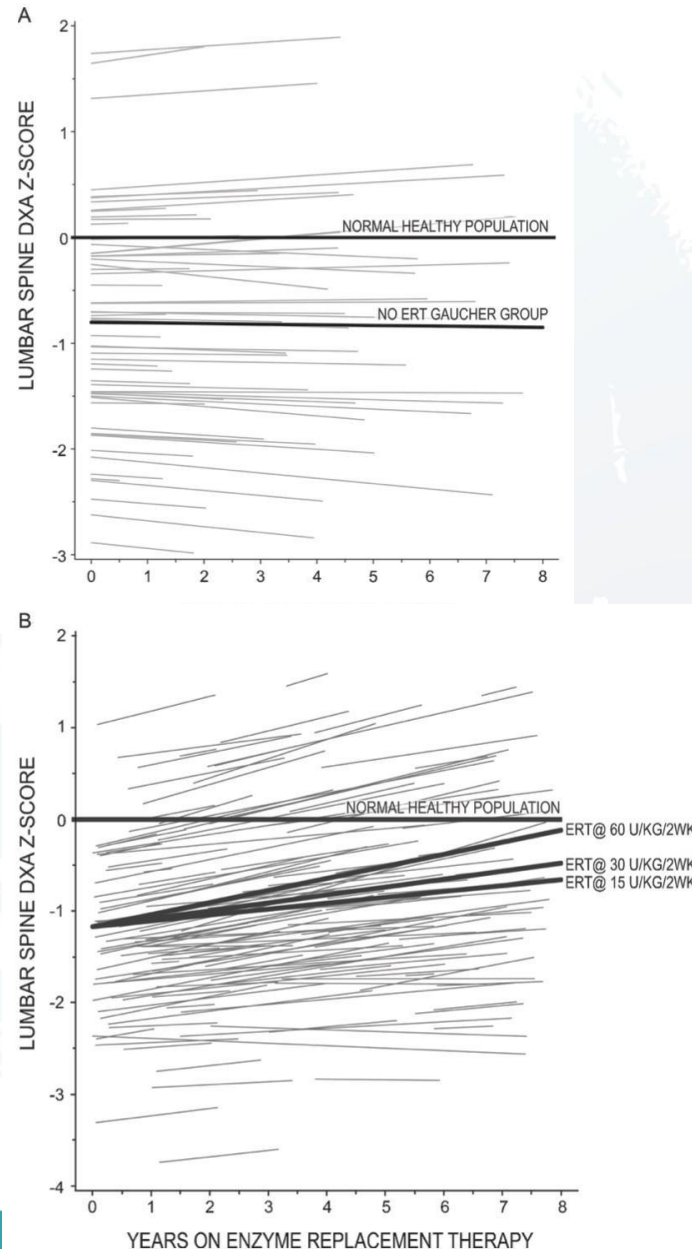
Variable	No ERT	ERT
Number of patients	N = 160	N = 342
Gender, N (%)		
Female	86 (54)	182 (53)
Male	74 (46)	160 (47)
Mean age at diagnosis in years (SD)	27 (15)	21 (15)
Mean age at first DXA for each category in years (SD)	36 (12)	38 (13)
N370S homozygous, N (%)		
Yes	110* (69)	129 (38)
No	40 (25)	189 (55)
Unknown	10 (6)	24 (7)
Geographic region, N (%)		
United States	37 (23)	198 (58)
Israel	110 (69)	90 (26)
Canada	8 (5)	21 (6)
Other [†]	5 (3)	33 (10)

* Of the 110 N370S homozygous patients, 83 (75%) were from Israel.

[†] Patients from Australia, Brazil, Colombia, Italy, Czech Republic, Serbia, and Montenegro.

TABLE 3. PATIENT CLINICAL CHARACTERISTICS AT BASELINE*[†]

Variable	No ERT	ERT
Number of patients	N = 160	N = 342
Hemoglobin [‡] (g/dl)	n = 145	n = 274
Mean (SD)	12.9 (1.5)	11.9 (1.7)
Platelet count [§] ($\times 10^3/\text{mm}^3$)	n = 134	n = 193
Mean (SD)	120 (63)	87 (53)
Spleen volume [¶] in multiples of normal	n = 95	n = 142
Mean (SD)	8.2 (3.8)	14.4 (11.3)
Liver volume ^{**} in multiples of normal	n = 102	n = 189
Mean (SD)	1.3 (0.6)	1.6 (0.7)
Number of patients with bone pain in the last 30 days, n (%)	n = 132	n = 194
46 (35)	105 (54)	
Number of patients with prior bone crisis, n (%)	n = 153	n = 321
2 (1)	35 (11)	
Body mass index ^{††} (kg/m^2)	n = 133	n = 322
Mean (SD)	23.2 (3.6)	22.6 (4.2)

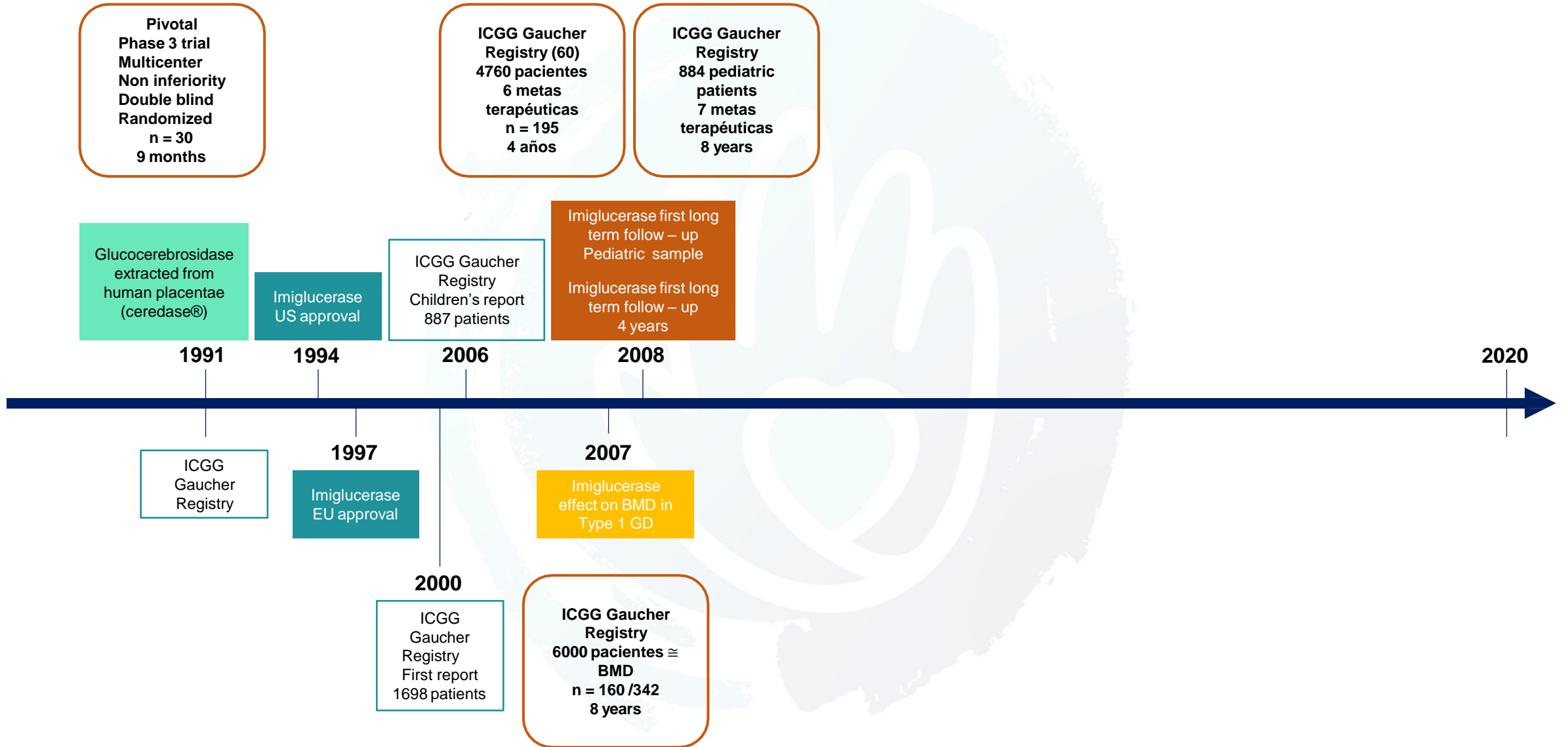


BMD
8 years

Conclusions: ERT with imiglucerase (Cerezyme) may increase BMD in patients with GD. Response to treatment with imiglucerase is slower for BMD than for hematologic and visceral aspects of GD. A normal (age- and sex-adjusted) BMD should be a therapeutic goal for patients with type 1 GD.

7. RichardJWenstrup, GregoryMPastores, Thomas N Hangartner et al. Effect of Enzyme Replacement Therapy With Imiglucerase on BMD in Type 1 Gaucher Disease. Journal of Bone and Mineral Research. Volume 22, Number 1, 2007

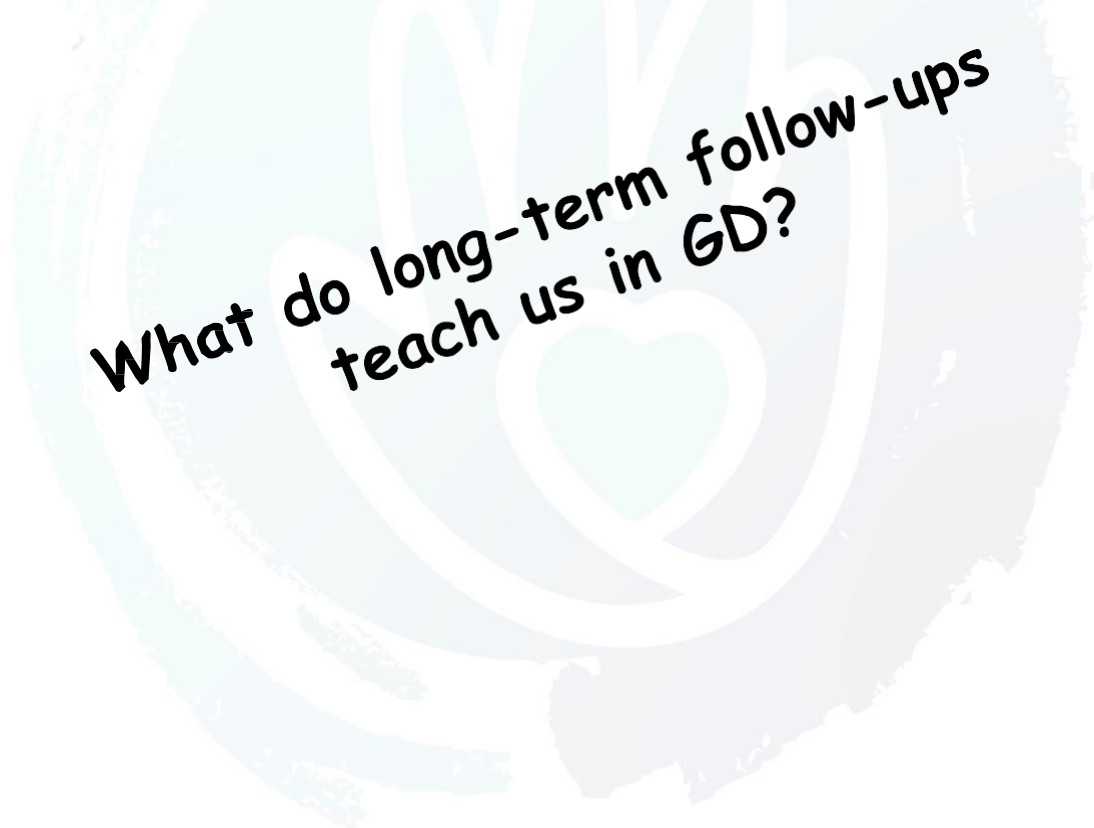
Safety and Efficacy in Gaucher Disease



8. Weinreb N, Cox T, et al. A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase. *Am J of Hematology*. Am. J. Hematol. 83:890– 895, 2008.

9. Hans Andersson, Paige Kaplan, Katherine Kacena and John Yee. Eight-Year Clinical Outcomes of Long-Term Enzyme Replacement Therapy for 884 Children With Gaucher Disease Type 1. *Pediatrics* 2008;122;1182

ERT timeline: reports with long term follow-up



8. Weinreb N, Cox T, et al. A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase. *Am J of Hematology*. Am. J. Hematol. 83:890–895, 2008.

9. Hans Andersson, Paige Kaplan, Katherine Kacena and John Yee. Eight-Year Clinical Outcomes of Long-Term Enzyme Replacement Therapy for 884 Children With Gaucher Disease Type 1. *Pediatrics* 2008;122;1182

TGs = 6
Follow up = 4 years

ERT timeline: 4 years – First long term follow-up

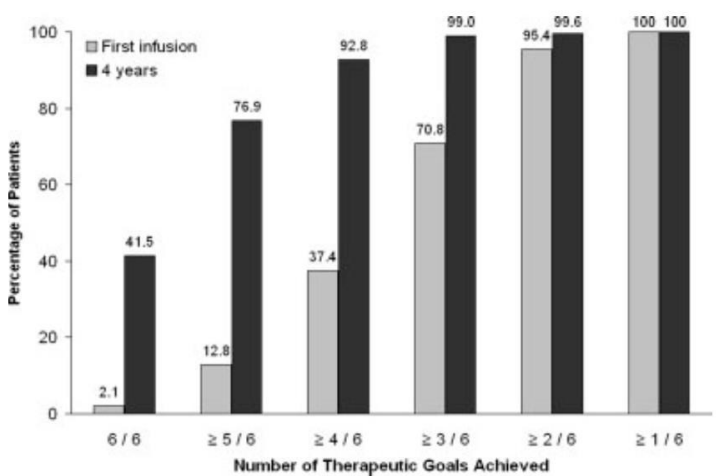
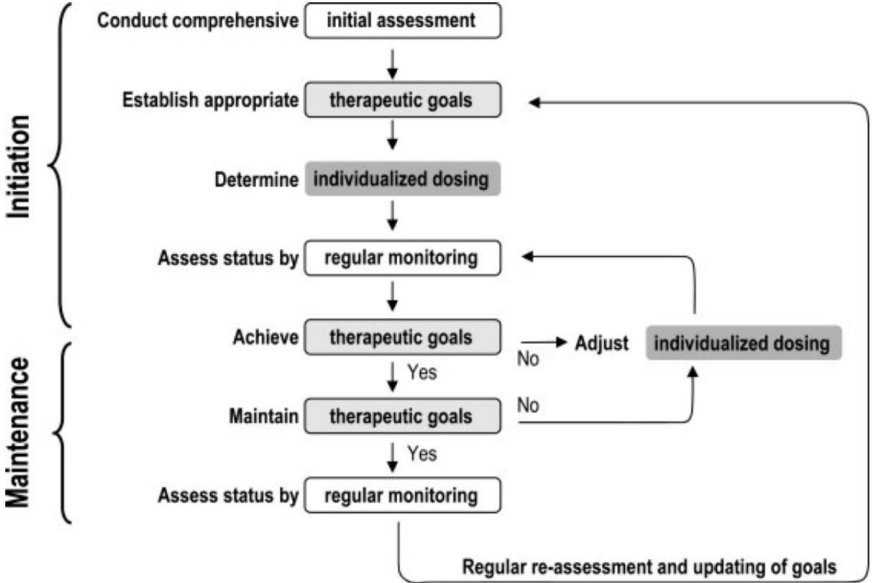


Figure 2. Cumulative achievement of therapeutic goals around initiation of imiglucerase and at 4 years after initiation of imiglucerase.

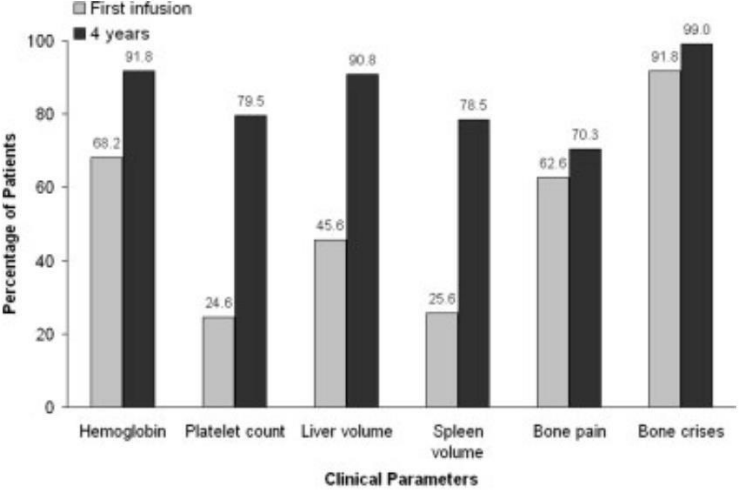


Figure 3. Proportion of patients achieving individual therapeutic goals by clinical parameter around initiation of imiglucerase and at 4 years after initiation of imiglucerase.

TABLE II. Patient Characteristics

	Analysis population
Number of Patients, n	195
Sex, n (%)	n = 195
Males	97 (49.7%)
Females	98 (50.3%)
Age at Diagnosis ^a (y)	n = 192
Median (25th, 75th)	12 (5.0, 35.0)
Mean (SD)	20.7 (19.1)
Age at First Infusion (y)	n = 195
Median (25th, 75th)	22 (7.0, 48.0)
Mean (SD)	27.7 (21.9)
Genotype, n (%)	n = 195
N370S/N370S	61 (31.3%)
N370S/Other	100 (51.3%)
Other/Other	18 (9.2%)
Unknown	16 (8.2%)
Average 4-year Dose (U/kg/4 wks)	n = 195
Median (25th, 75th)	60 (44.1, 97.3)
Mean (SD)	67.5 (31.7)

TABLE I. Definition of Therapeutic Goals for Hemoglobin, Platelets, Liver Volume, Spleen Volume, Bone Pain, and Bone Crises [18]

Parameter	Goal
1 Hemoglobin	
Children ≤ 12 years	≥11.0 g/dL
Females > 12 years	≥11.0 g/dL
Males > 12 years	≥12.0 g/dL
2 Platelets	
First infusion > 120,000/μL	>120,000/μL
First infusion 60-120,000/μL	>120,000/μL
First infusion < 60,000/μL	≥2× first infusion value
3 Liver volume (Normal = 2.5% body wt in kg)	<1.5 × normal
4 Spleen volume (Normal = 0.2% body wt in kg)	<8.0 × normal
5 Bone pain	“None” or “very mild”
6 Bone crises	No crises

8. Weinreb N, Cox T, et al. A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase. *Am J of Hematology*. Am. J. Hematol. 83:890–895, 2008.

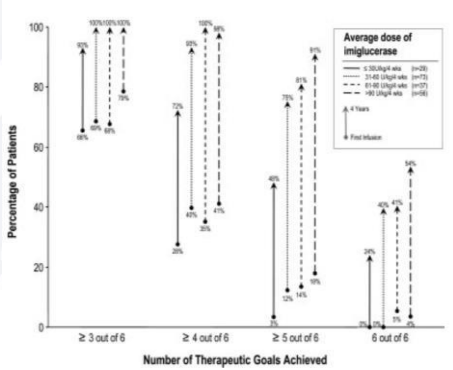


Figure 4. Achievement of therapeutic goals around initiation and at 4 years after initiation of imiglucerase, by dose category.

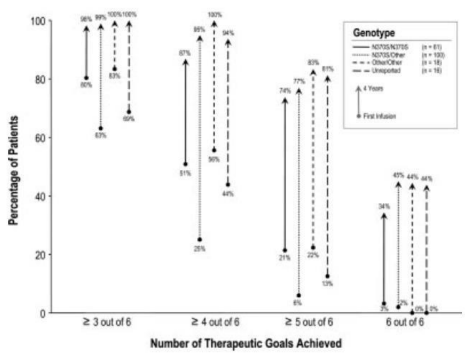


Figure 5. Achievement of therapeutic goals around initiation and at 4 years following initiation of imiglucerase, by genotype.

TGs = 7
Follow up = 8 years

ERT timeline: First pediatric report of long term follow-up

TABLE 1 Demographic Characteristics of Pediatric Patients With GD1 With Intact Spleens Who Were Receiving ERT, in the Gaucher Registry on January 6, 2006 (N = 884)

Gender, n (% of all registry patients)	
Male	463 (52.4)
Female	421 (47.6)
Age at diagnosis, n (% of all registry patients)	
In utero to <6 y	485 (54.9)
6 to <12 y	260 (29.4)
12 to <18 y	93 (10.5)
Unknown	46 (5.2)
Treatment dose, mean ± SD, U/kg per 4 wk	78.6 ± 35.0
Age at first infusion, n (% of all registry patients)	
0 to <6 y	310 (35.1)
6 to <12 y	332 (37.6)
12 to <18 y	242 (27.4)
Geographic distribution, n (% of all registry patients)	
United States	305 (34.5)
Latin America	217 (24.6)
Europe	184 (20.8)
Israel	66 (7.5)
Asia Pacific	43 (4.9)
Middle East	44 (5.0)
Canada	25 (2.8)
Ethnicity, n (% of all registry patients)	
White, non-Jewish	285 (32.2)
Jewish, Ashkenazi	151 (17.1)
Black/Caribbean	91 (10.3)
Hispanic	86 (9.7)
Other	25 (2.8)
Unknown	246 (27.8)
Genotype (N = 595), n (% of those tested)	
N370S/rare allele	184 (20.8)
N370S/L444P	131 (14.8)
N370S/N370S	70 (7.9)
Other	51 (5.8)
L444P/rare allele	50 (5.7)
N370S/84GG	63 (7.1)
L444P/L444P	28 (3.2)
N370S/IVS+1	18 (2.0)

Percentages may not add to 100 because of rounding.

TABLE 2 Height z Score, Normalized Hemoglobin Level, Platelet Count, Liver Volume, Spleen Volume, BMD z Score, and Bone Crisis Responses to ERT for Pediatric Patients With GD1

ERT Response Variable (in Follow-up Period)	No. of Patients (No. of Observations)	Percentile at Baseline	Measurement		
			At First Infusion	After 8 y of Follow-up Monitoring	
1 Height z score ^a	702 (5602)	5th	-3.4	-1.5	
			25th	-2.5	-1.0
			50th	-1.4	-0.3
			75th	-0.4	0.3
			95th	0.5	1.0
2 Normalized hemoglobin level, g/dL ^a	771 (8022)	5th	-1.8	1.1	
			25th	-1.1	1.4
			50th	-0.3	1.7
			75th	0.4	1.9
			95th	1.1	2.1
3 Platelet count, 10 ³ platelets per mm ^{3a}	768 (7991)	5th	57	111	
			25th	73	137
			50th	98	171
			75th	130	209
			95th	168	247
4 Liver volume, MN ^a	420 (1524)	5th	1.5	0.7	
			25th	1.7	0.8
			50th	2.0	1.1
			75th	2.3	1.1
			95th	2.7	1.3
5 Spleen volume, MN ^a	458 (1593)	5th	12	2.5	
			25th	17	3.4
			50th	23	4.8
			75th	33	6.9
			95th	45	9.3
6 BMD z score ^b	127 (244)	5th	-1.93	-1.51	
			25th	-1.19	-0.77
			50th	-0.35	0.07
			75th	0.49	0.91
			95th	1.22	1.65
7 Bone crisis ^c	532				

Conclusion

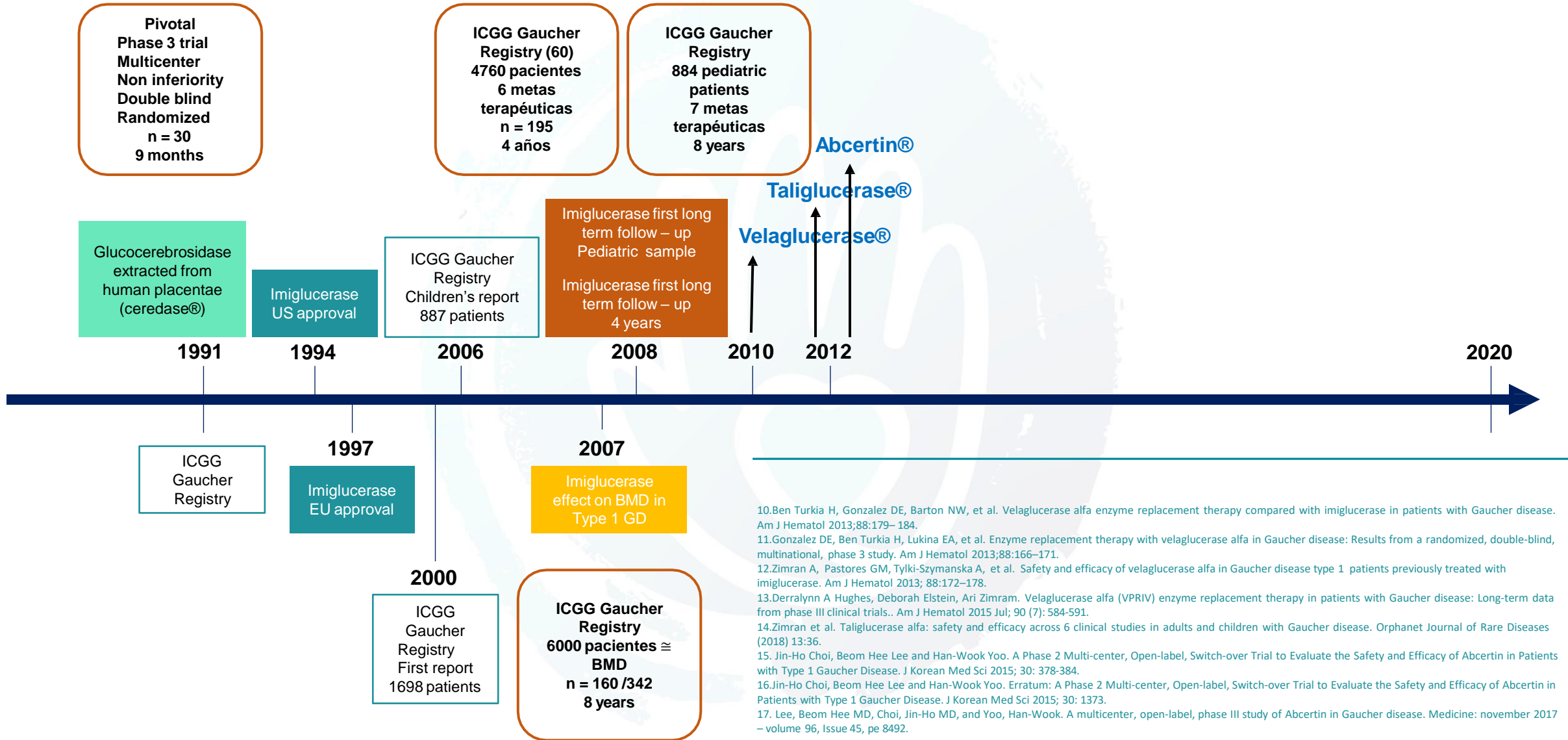
This study clearly delineates the range of **expected improvement** for pediatric patients with GD1 treated with ERT with alglucerase and/or imiglucerase for up to **8 years** and offers the first data on long-term outcomes for a **large, worldwide, pediatric cohort**.

Pediatricians can use these data to gauge their patients' responses to ERT and to give the patients some expectations of treatment response.

The study also shows the **ongoing benefit** of ERT with imiglucerase for pediatric patients over many years, justifying the need for continuous long-term treatment

9. Hans Andersson, Paige Kaplan, Katherine Kacena and John Yee. Eight-Year Clinical Outcomes of Long-Term Enzyme Replacement Therapy for 884 Children With Gaucher Disease Type 1. *Pediatrics* 2008;122;1182

Safety and Efficacy in Gaucher Disease



10. Ben Turkia H, Gonzalez DE, Barton NW, et al. Velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease. *Am J Hematol* 2013;88:179–184.

11. Gonzalez DE, Ben Turkia H, Lukina EA, et al. Enzyme replacement therapy with velaglucerase alfa in Gaucher disease: Results from a randomized, double-blind, multinational, phase 3 study. *Am J Hematol* 2013;88:166–171.

12. Zimran A, Pastores GM, Tylki-Szymanska A, et al. Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase. *Am J Hematol* 2013; 88:172–178.

13. Derrallynn A Hughes, Deborah Elstein, Ari Zimran. Velaglucerase alfa (VPRIV) enzyme replacement therapy in patients with Gaucher disease: Long-term data from phase III clinical trials. *Am J Hematol* 2015 Jul; 90 (7): 584-591.

14. Zimran et al. Taliglucerase alfa: safety and efficacy across 6 clinical studies in adults and children with Gaucher disease. *Orphanet Journal of Rare Diseases* (2018) 13:36.

15. Jin-Ho Choi, Beom Hee Lee and Han-Wook Yoo. A Phase 2 Multi-center, Open-label, Switch-over Trial to Evaluate the Safety and Efficacy of Abcertin in Patients with Type 1 Gaucher Disease. *J Korean Med Sci* 2015; 30: 378-384.

16. Jin-Ho Choi, Beom Hee Lee and Han-Wook Yoo. Erratum: A Phase 2 Multi-center, Open-label, Switch-over Trial to Evaluate the Safety and Efficacy of Abcertin in Patients with Type 1 Gaucher Disease. *J Korean Med Sci* 2015; 30: 1373.

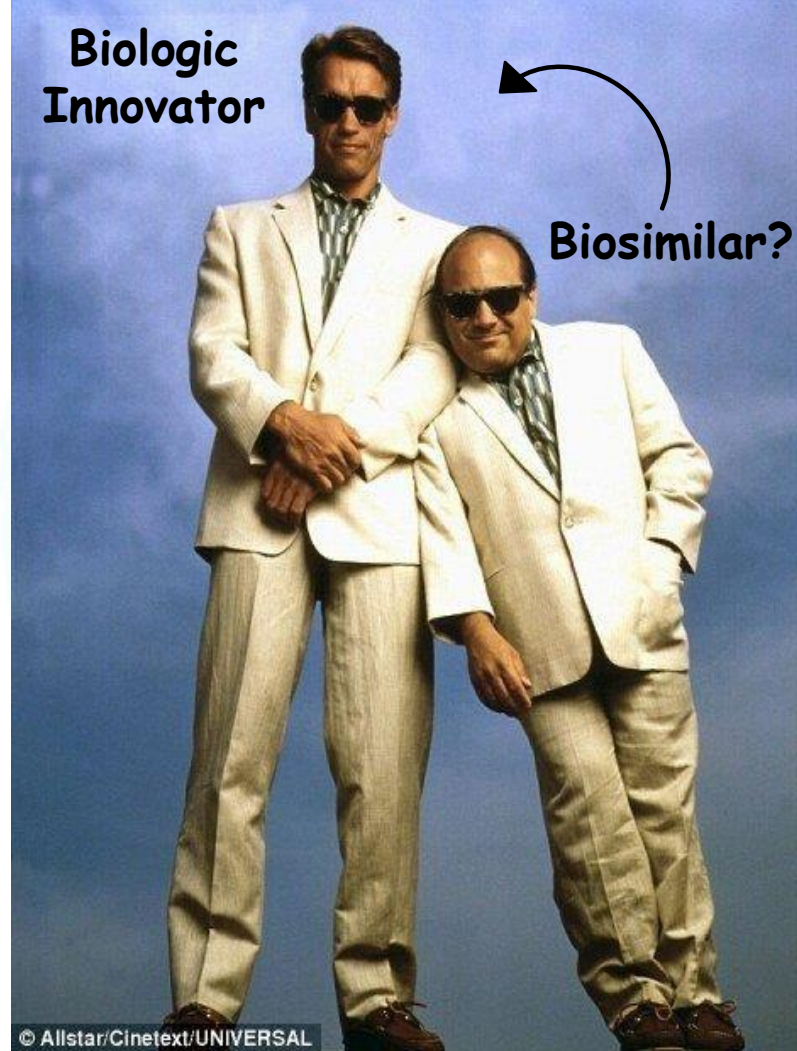
17. Lee, Beom Hee MD, Choi, Jin-Ho MD, and Yoo, Han-Wook. A multicenter, open-label, phase III study of Abcertin in Gaucher disease. *Medicine*: november 2017 – volume 96, Issue 45, pe 8492.

Biologic Innovator



What is a Biologic?
What does it mean to be a biological
innovator or reference product?

Biologic Innovator



What is a Biosimilar?

Biologic Innovator

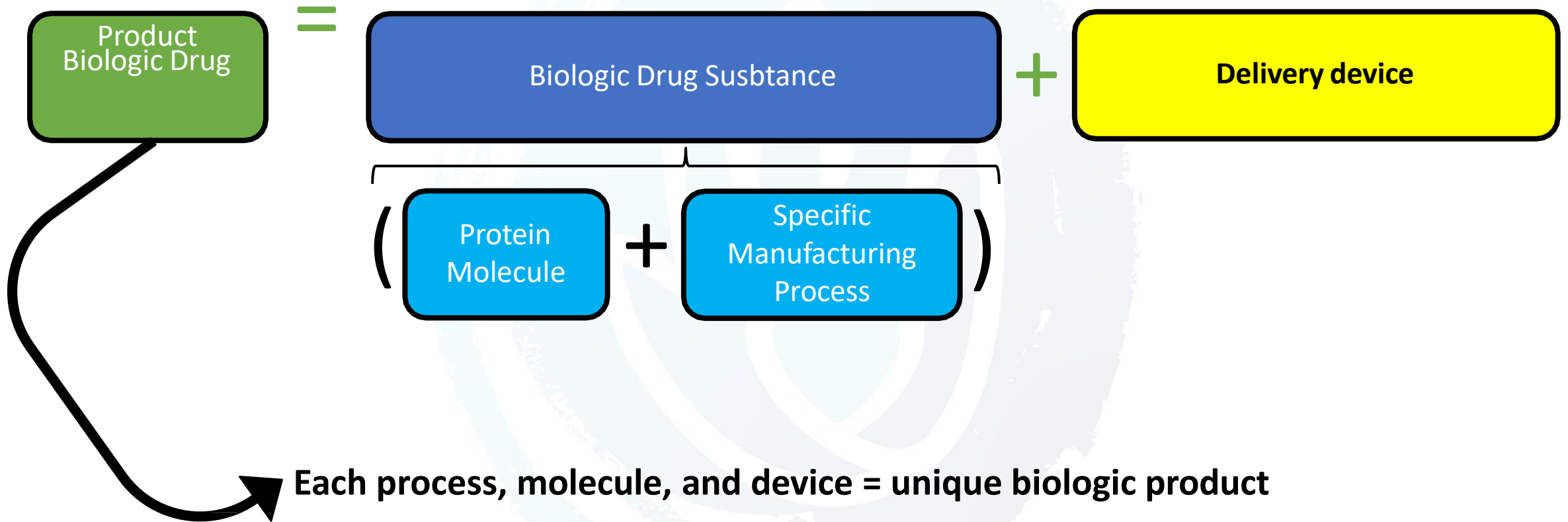


What is a Non
Compatible (NCBT)
or intended copy?

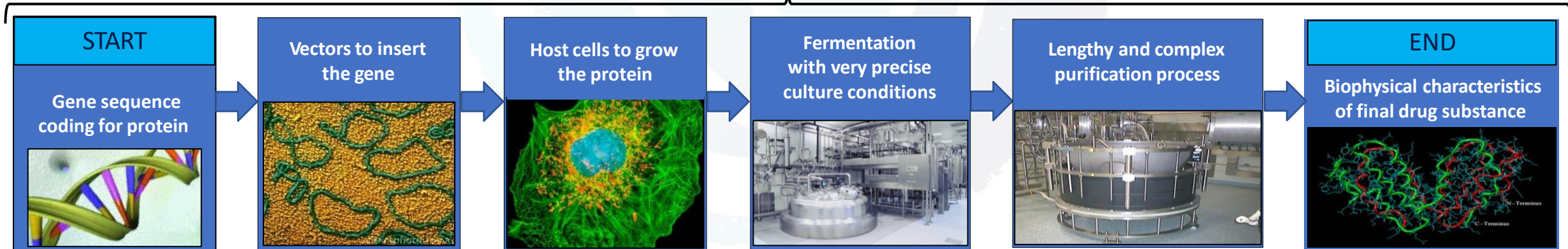
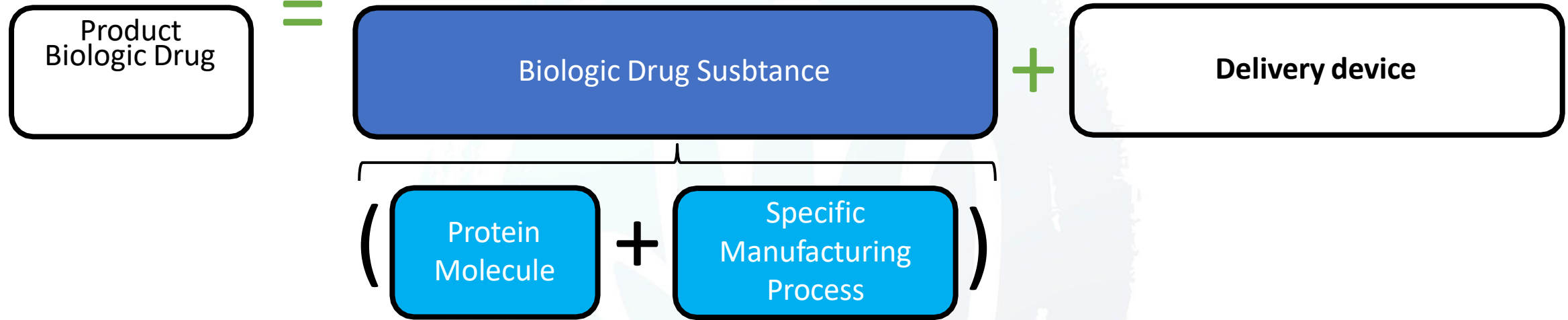
Biologic Innovator



What is a Biologic Drug Product?



What is a Biologic Drug Product?



What Is a Biosimilar?



EMA guidance: Biosimilar sponsor is to “generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorized in the Community.”



US FDA definition: a follow-on biologic means

The biological product is **highly similar to the reference product**, notwithstanding minor differences in clinically inactive components; **and**

No clinically meaningful differences exist between the biological product and the reference product in terms of the safety, purity, and potency.



WHO definition: “Similar Biotherapeutic Products” is a biotherapeutic product that is **similar** in terms of **quality, safety and efficacy** to an already licensed biotherapeutic product

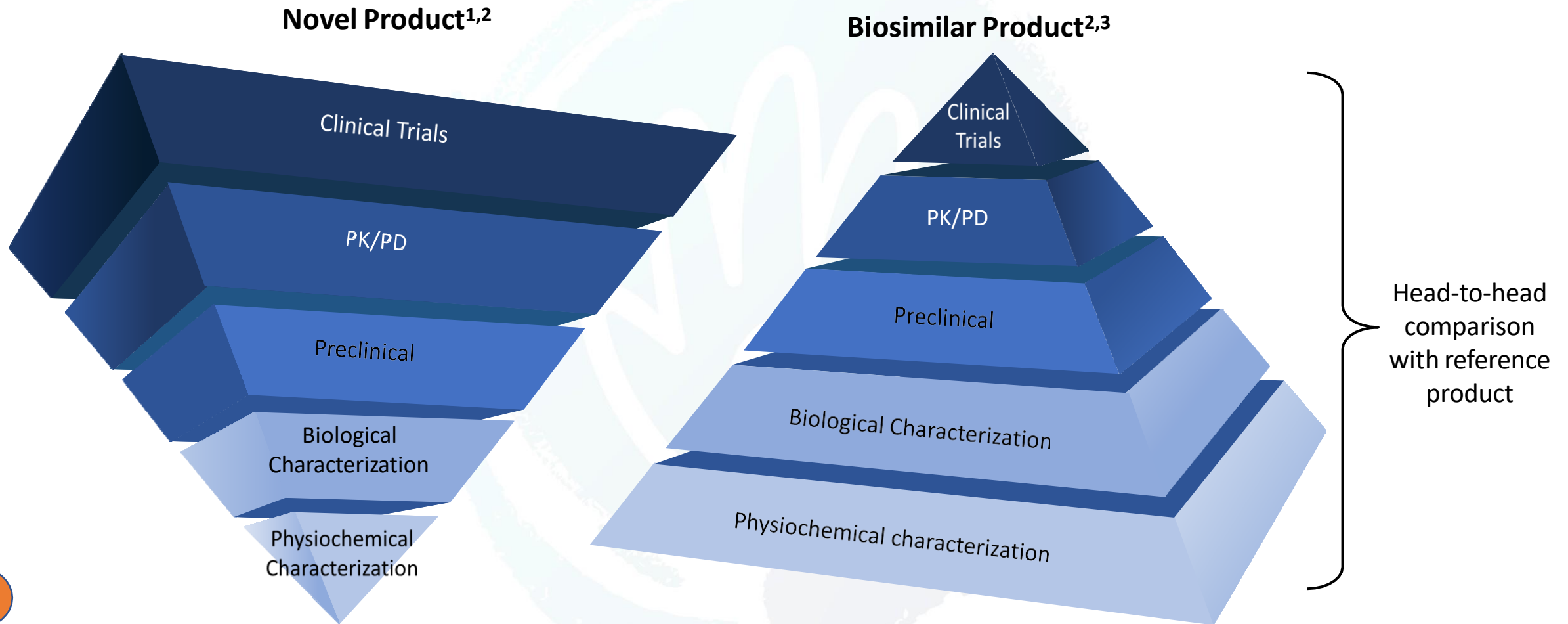
Biosimilars are those products that are “highly similar” to the reference biologic product based on submission of quality, safety and efficacy data

1. FDA Draft Guidances – Quality and Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance)

2 http://www.who.int/biologicals/areas/biological_therapeutics/BIOOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

3. EMA: CHMP Guideline on Similar Biological Medicinal Products (October 2005)

Approval Processes for Novel and Biosimilar Products



- Development of a biosimilar involves greater emphasis on non-clinical (physicochemical) development²

PD, pharmacodynamic; PK, pharmacokinetic.

Image adapted from: Alten R, et al. Semin Arthritis Rheum 2015;44:S2–S8

1. Lipsky MS and Sharp LK. J Am Board Fam Pract 2001;14:362–7; 2. Alten R, et al. Semin Arthritis Rheum 2015;44:S2–S8; 3. McCamish M and Woolton G. mAbs 2011;3:209–17

Clinical Data Requirements for Biosimilar Products

Phase II trials are not required¹⁻³

Dosing schedule and route of administration have been defined by the reference product³

Phase III data requirements influenced by:

Patient population and disease to be treated^{1,2}

Extent of knowledge about reference product

- Mechanism(s) of action¹⁻³
- Clinical experience and risk/benefit profile¹
- Established sensitive clinical endpoints¹⁻³

Outcomes of CMC, pre-clinical, PK/PD biosimilarity exercise¹⁻³

CMC, chemistry, manufacturing, and controls; PD, pharmacodynamic; PK, pharmacokinetic.

1. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015;

2. EMA CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Dec 2014;

3. WHO Guidelines on Evaluation of Similar Biotherapeutic Products. Geneva, 19–23 Oct, 2009

Definitions

Switching

- An action taken by a physician to replace a patient's medication with another
- May be driven by medical or non-medical reasons

Automatic Substitution

- A policy that allows a pharmacist to dispense an equivalent product in place of the prescribed product
- Does not involve consultation with prescribing physician

Interchangeability: FDA¹

- A designation that it is safe to substitute 2 products but individual states will legislate own policies on automatic substitution:
 - Granted to drugs on a case by case basis
 - Will allow 1 product to be substituted for the other
 - Evidentiary standards required to gain designation are currently being determined

Interchangeability: EMA²

- The EMA has no remit to formally designate 2 products as interchangeable
- Each member state must decide on policies related to switching and automatic substitution

EMA, European Medicines Agency; FDA, US Food and Drug Administration

1. FDA Draft Guidance for Industry. Considerations in Demonstrating Interchangeability With a Reference Product. Jan 2017

2. EMA and European Commission. Biosimilars in the EU. Information guide for healthcare professionals. May 2017

Glycosylation Can Impact Critical Protein Functions^{1,2,3}

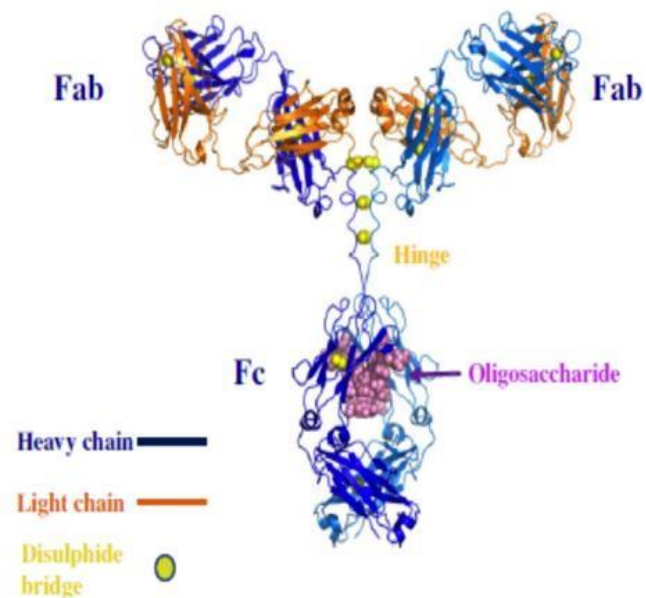
1. Glycosylation of many biologics (addition of sugars) is a crucial step in the production of a functional protein

2. Glycosylation of a biologic is particularly affected by:

- Cell type, cell line
- Raw materials
- Cell culture conditions
- Purification

3. Several critical glycosylation effects may only be detected in the human body

- Mechanism of Action
- Clearance from the body
- **Immunogenicity**



Immunogenicity

The capacity of a molecule to elicit an immune response, such as the production of specific antibodies¹

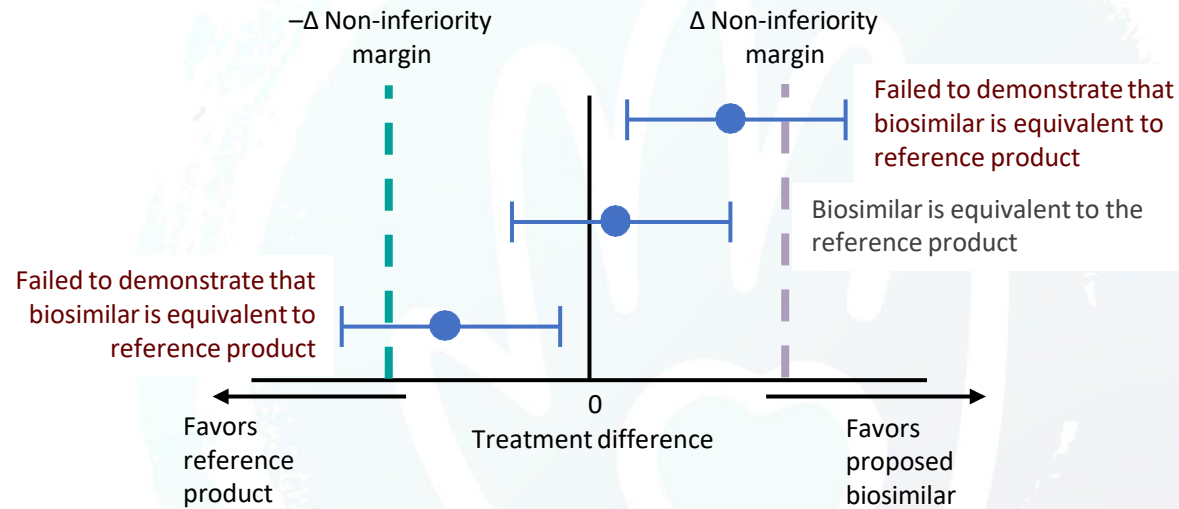
- Most commonly seen with proteins due to their:²
 - Large size
 - Ability to supply both T- and B-cell epitopes
- Therapeutic protein generates an immune response to itself and related proteins³
 - Can occur with any protein drug⁴
 - May be associated with adverse events (AEs) including loss of efficacy³

1. Schellekens H. Nat Rev Drug Discov 2002;1:457–62; 2. Baker MP, et al. Self Nonself 2010;1:314–22; 3. FDA Guidance for Industry. Immunogenicity Assessment for Therapeutic Protein Products. HHS FDA/CDER/CBER, Aug 2014; 4. Bendtzen K. Arthritis Rheum 2011;63:867–70

Clinical Trial Design: General Principles

- **Study type:**
 - **Comparative** (head-to-head), **double-blind**, randomized trials recommended¹⁻³
 - Other design(s) must be scientifically/statistically justified by the biosimilar sponsor^{1,2}
- **Population:** Patients with **the most sensitive disease condition** and the most sensitive subset within the chosen disease condition, if pertinent¹⁻⁴
- **Size, duration, and endpoints:**
 - Should allow **sufficient exposure**¹⁻³
 - Should enable detection of clinically relevant **differences in efficacy**¹⁻³
- **Totality of evidence:**
 - Should include evidence on comparative safety and efficacy, including **immunogenicity**¹
- **Clinical endpoint(s):**
 - Different from, and **more sensitive** than, those used in the efficacy trials of the reference product may be used if scientifically justified^{1,4}

Clinical Trial Design: Equivalence Trial



- **The preferred design** for comparison of efficacy and safety in biosimilarity exercises¹⁻⁴
- Requires **upper and lower comparability margins** for reference product¹⁻⁴
- Proposed biosimilar is considered equivalent if the 95% CI of the difference between the two products sits between the equivalence margins⁵

Image adapted from: Alten R and Cronstein BN. Semin Arthritis Rheum. 2015;44:S2-S8;

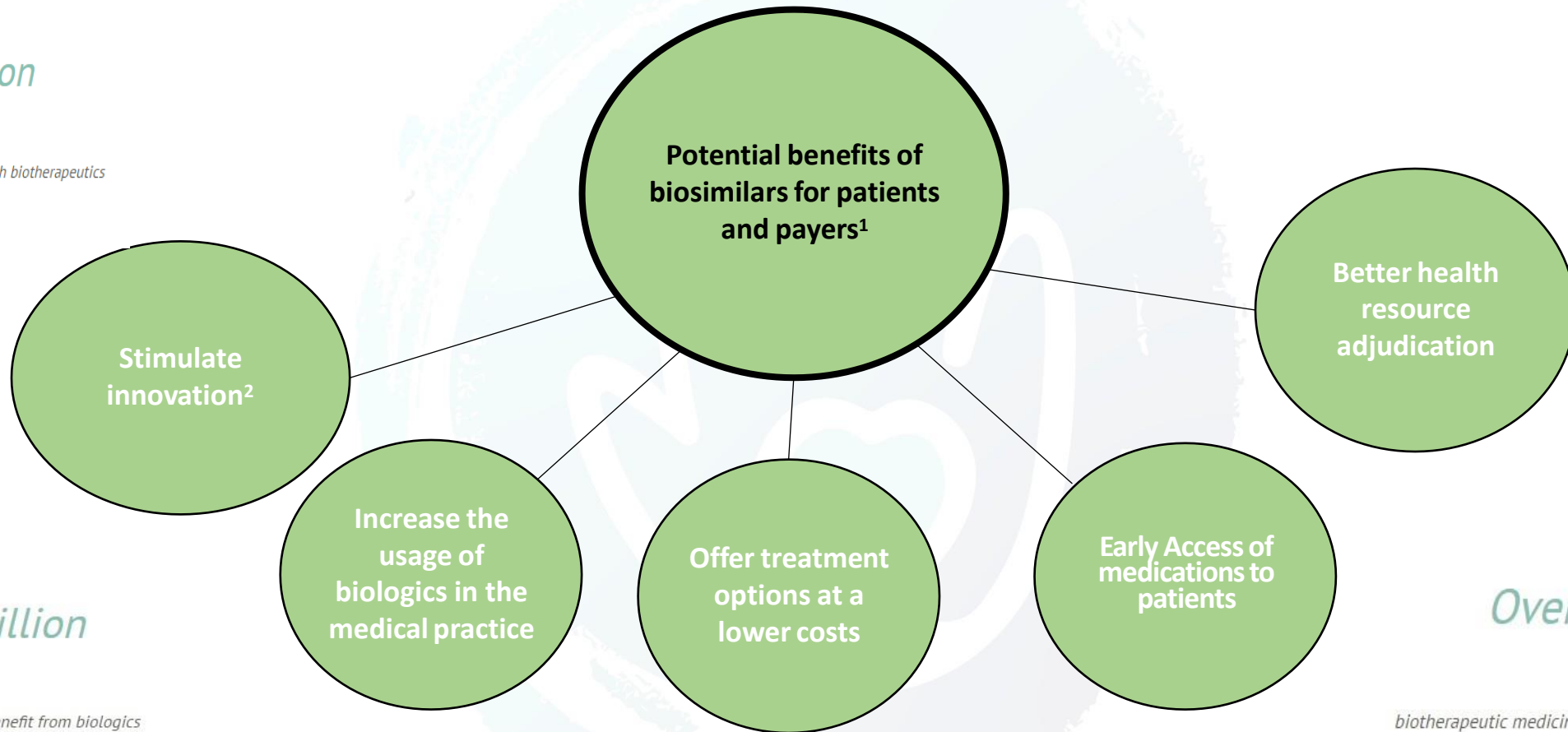
1. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015; 2. EMA CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues, Dec 2014; 3. WHO Guidelines on Evaluation of Similar Biotherapeutic Products. Geneva, 19-23 Oct, 2009; 4. EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May 2012;

5. Castañeda-Hernández G, et al. RMD Open 2015;1:e000010

Biosimilars are changing the medical practice

350 million

patients worldwide are treated with biotherapeutics



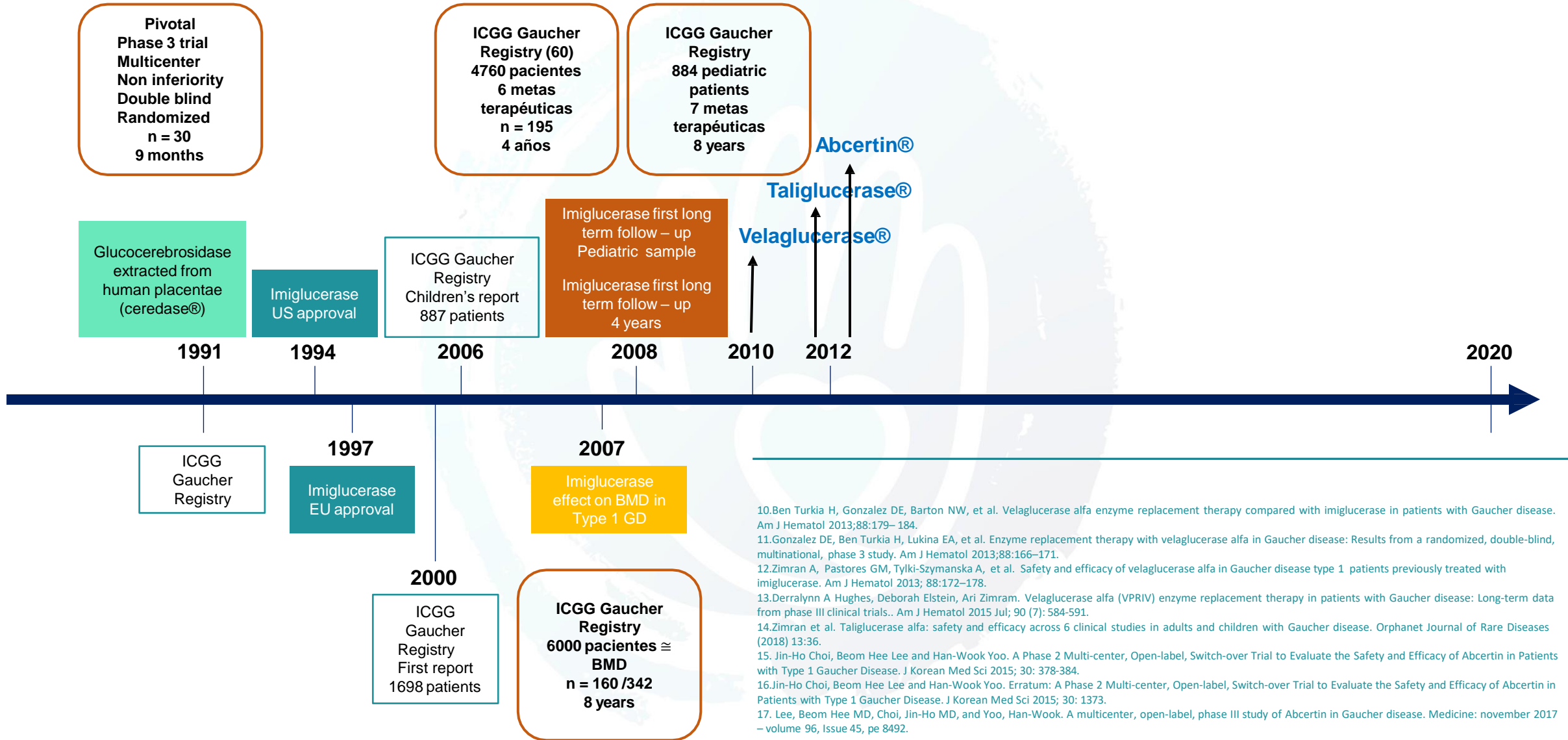
20-30 million

patients with rare diseases benefit from biologics worldwide

Over 1'000

biotherapeutic medicines are in the global pipeline

Safety and Efficacy in Gaucher Disease



Safety and Efficacy in Gaucher Disease

Abcertin® trials

Phase 1 Study

- Randomized, double-blind, placebo-controlled, single ascending dose
- Evaluate the tolerability, safety, and pharmacokinetic
- Five day study in healthy volunteers
- No serious AEs or antibody formation observed.
- Unpublished data

Phase 2 Study

- Multicenter, open-label, switch-over trial to evaluate the safety and efficacy of ISU302 in patients with Type 1 GD previously treated with Imiglucerase (cerezyme®)
- Prospective study of 5 patients followed for 24 weeks
- No statistically significant changes in any endpoints after 24 weeks
 - Hemoglobin
 - platelet count
 - liver and spleen volumes
 - biomarker levels
 - bone mineral density



Table 1. Baseline clinical characteristics of patients with Gaucher disease

No.	Age at diagnosis (yr)	Age at enrollment (yr)	Sex	Height SDS	Weight SDS	Dose of imiglucerase treatment before enrollment (units/kg)	Spleen volume (mL)	Liver volume (mL)	Genotype	Enzyme activity (6-10 nM/hr/mg)
1	20.1	29.9	Male	-0.03	-0.05	30	433	1,518	L444P/D409H	1.07
2	1.4	16.7	Female	0.01	0.15	37.2	596	1,317	L444P/L444P	0.71
3	12.9	18.6	Male	-0.88	0.27	55	297	1,555	G46E/F213I	0.53
4	1.9	8.2	Male	-0.17	-0.2	46	185	898	G46E/F213I	0.95
5	4.5	10	Female	-0.38	-0.92	43	149	647	G46E/R257Q	0.74
Mean ± SD (range)		16.2 ± 8.26		-0.29 ± 0.36	-0.15 ± 0.47	42.24 ± 9.39				

ND, not determined; SD, standard deviation; SDS, standard deviation score.

Table 2. Efficacy parameters in a phase 2 study of five patients with Gaucher disease

Parameters	Baseline	24 weeks	Percentage change at 24 weeks	P value
Hemoglobin (g/dL)	13.76 ± 1.89	13.86 ± 2.61	0.30 ± 7.63	0.625
Platelets (× 10 ³ /μL)	154.40 ± 34.62	162.60 ± 47.04	6.86 ± 28.73	1.000
Liver volume (mL)	US	1,100.8 ± 380.11	-5.86 ± 16.90	0.438
Spleen volume (mL)	US	330.0 ± 142.26	14.67 ± 69.07	0.625
AST (IU/L)	23.40 ± 4.67	41.60 ± 44.14	68.95 ± 163.63	1.000
ALT (IU/L)	16.80 ± 12.15	38.80 ± 42.48	212.16 ± 446.38	0.313
ACE (U/L)	79.42 ± 31.77	81.50 ± 41.84	-2.59 ± 20.61	1.000
ACP (IU/L)	18.68 ± 8.71	17.10 ± 4.77	-0.92 ± 22.97	1.000
Chitotriosidase (nM/mL/hr)	1,279.82 ± 1,041.47	1,103.76 ± 884.36	-9.11 ± 15.53	0.438
L-spine BMD Z-score	-1.27 ± 0.40	-0.80 ± 0.53	24.56 ± 50.60	0.625
Femur neck BMD Z-score	-0.43 ± 1.37	-0.20 ± 1.35	-147.33 ± 441.79	0.875
Osteosclerosis*	XRay	0.0 ± 0.0	No change	
Osteonecrosis*	XRay	0.2 ± 0.45	-100.0	1.000

*None, 0 points; Mild, 1 point; Moderate, 2 points; Severe, 3 points. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACP, acid phosphatase; ACE, angiotensin converting enzyme; BMD, bone mineral density.

15. Jin-Ho Choi, Beom Hee Lee and Han-Wook Yoo. A Phase 2 Multi-center, Open-label, Switch-over Trial to Evaluate the Safety and Efficacy of Abcertin in Patients with Type 1 Gaucher Disease. J Korean Med Sci 2015; 30: 378-384.
 16. Jin-Ho Choi, Beom Hee Lee and Han-Wook Yoo. Erratum: A Phase 2 Multi-center, Open-label, Switch-over Trial to Evaluate the Safety and Efficacy of Abcertin in Patients with Type 1 Gaucher Disease. J Korean Med Sci 2015; 30: 1373.

Safety and Efficacy in Gaucher Disease

Abcertin® trials

17. Lee, Beom Hee MD, Choi, Jin-Ho MD, and Yoo, Han-Wook. A multicenter, open-label, phase III study of Abcertin in Gaucher disease. *Medicine*: november 2017 – volume 96, Issue 45, pe 8492.

NCT02770625

Phase 3 Study

- Multicenter, Open-Label
- Evaluate the Safety and Efficacy of ISU302 (Imiglucerase for Injection) in Patients with Type 1 Gaucher Disease
- Prospective study of 8 treatment-naïve patients with Type 1 Gaucher disease for 24 weeks
- Primary efficacy endpoint was change in hemoglobin concentration
- Secondary efficacy variables were: platelets counts, liver and spleen volumes (by US), skeletal status (by Xrays) and BMD.
- Safety was assessed by serious drug-related adverse events only

Table 4

Anti-Abcertin antibodies.

Parameter	Visit	Result	Abcertin (60U/kg) (N=7) n (%)
Anti-Abcertin	Baseline	Negative	7 (100.0%)
		Positive	0 (0.0%)
	Week 24	Negative	6 (85.7%)
		Positive	1* (14.3%)

* Antibody without neutralizing activity.

Table 1

Demographics and baseline clinical characteristics of the per protocol population.

No.	Sex	Ethnicity	Age at enrollment, y	Height, cm	Weight, kg	Hemoglobin, g/dL	Platelet, ×10 ³ /μL	Spleen volume, MN	Liver volume, MN	Genotype	Enzyme activity (1–5 μmol/g /h)
1	Male	Egyptian	15	137 (<3 rd P)	31 (<3 rd P)	8.9	129	56.32	1.23	NA	0.34*
2	Male	Egyptian	9	122 (3 rd P)	25 (<3 rd P)	10.1	120	12.24	0.69	NA	0.42*
3	Male	Egyptian	6	108 (10 th P)	17 (5 th P)	8.9	44	43.18	2.08	NA	0.2*
4	Male	Egyptian	8	114.2 (<3 rd P)	23 (25 th P)	10.3	193	17.26	1.03	NA	0.5*
5	Male	Egyptian	2	79 (<3 rd P)	10 (<3 rd P)	9.8	258	7.2	1.34	L444P/L444P	0.49*
6	Male	Egyptian	2	82 (5 th P)	11 (3 rd P)	10.3	110	22.09	2.25	L444P/N370S	0.49*
7	Male	Egyptian	2	83 (25 th P)	14 (50 th –75 th P)	8.1	74	45.04	2.09	L444P/N370S	1.6†
Mean ± SD (range)	Male	Egyptian	6.3±4.86 (2–15)	103.6±03.61 (79–137)	18.7±8.7 (10–31)	9.5±0.5 (8.1–10.3)	132.6±32.6 (44–258)	29.0±9.0 (7.2–56.32)	1.5±.52 (0.69–2.25)		

Table 2

Efficacy of the per protocol population.

	Baseline	24 wks	Percentage change at 24 wks	P
Hemoglobin, g/dL	9.5±0.86	11.4±0.87	20.6	.001
Platelets, ×10 ³ /μL	132.6±72.27	180.3±47.10	36	.037
Liver volume, MN	1.5±0.61	1.5±0.51	0.5	.949
Spleen volume, MN	29.0±18.91	15.2±9.47	−47.6	.019
ACE, U/L	195.7±109.0	159.3±58.25	−18.6	.372
ACP, IU/L	25.4±7.52	15.4±4.31	−39.3	.003
Chitotriosidase*, nmol/mL/h	15529.48±8644.95	4770.0±2519.23	−69.3	.078
CCL-18, ng/mL	927.1±595.46	577.3±310.05	−37.7	.037
L-spine BMD Z-score	−1.0±1.60	−0.1±2.46	−89.1	.377

Unfortunately, the high cost and global shortage of imiglucerase has been problematic for patients and health care providers (11, 12). However, a biosimilar of imiglucerase, Abcertin® (ISU302, ISU Abxis, Seoul, Korea), has recently been developed. Therefore, this study was performed to evaluate the short-term efficacy and safety of Abcertin® in patients with type 1 Gaucher disease who were previously treated with imiglucerase.

Therefore, a new biosimilar to imiglucerase, Abcertin®, was recently developed to potentially reduce medical costs, particularly in underprivileged countries, and to ease supply shortages

<http://dx.doi.org/10.3346/jkms.2015.30.4.378>

5. Conclusions

In conclusion, our Abcertin phase III study demonstrated that Abcertin achieved the clinical endpoints, including improvements in the hemoglobin concentration and other efficacy endpoints (eg, platelet count, spleen volume, and biomarkers). In addition, we did not observe any adverse events related to Abcertin. Therefore, we suggest that although the dose equivalence with other ERTs has not been established. Abcertin is effective and safe for patients with type 1 GD and should be considered as an alternative ERT option for patients with non-neuropathic GD.



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CORRESPONDENCE

<http://dx.doi.org/10.3346/jkms.2015.30.9.1373> • *J Korean Med Sci* 2015; 30: 1373

JKMS

Erratum: A Phase 2 Multi-center, Open-label, Switch-over Trial to Evaluate the Safety and Efficacy of Abcertin® in Patients with Type 1 Gaucher Disease

Jin-Ho Choi, Beom Hee Lee, Jung Min Ko, Young Bae Sohn, Jin-Sung Lee, Gu-Hwan Kim, Sun Hee Heo, June-Young Park, Yoo-Mi Kim, Ja-Hye Kim, and Han-Wook Yoo

To the Editor:

The authors want to clarify the definition of “biosimilar” based on “Regulatory expectations and risk assessment for biotherapeutic products. World Health Organization 2014. available from http://www.who.int/biologicals/WHO_Risk_Assessment_for_Biotherapeutics_1st_PC_24_Jan_2014.pdf”

In this article (*J Korean Med Sci* 2015;30:378-384), as Abcertin® does not meet the exact definition of biosimilar, the authors would like to delete the phrases “a biosimilar of imiglucerase” in Page 379 and “a new biosimilar to imiglucerase” in Page 382.

Thank you.

WHO Definition of biosimilar: a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

Biosimilares

Qué deberíamos saber como prescriptores?

Definiciones

INN

(International
Nonproprietary Name)

Fue establecido en 1950 por la WHO con el objetivo de proveer a los HCP de un nombre único para una sustancia farmacológica

Fortalezas

Clara identificación de una droga

Prescripción segura de una droga

Dispensación segura de una droga

Comunicación entre HCP y otras entidades alrededor del mundo

Ej: Cerezyme recibe el INN de Imiglucerasa en 1994 por la WHO

Debilidades

A pesar de ser una práctica estandarizada aplicar al INN a través del programa de la WHO, esta no es una condición obligatoria, por lo que cada país puede dar el INN en ese país según sus reglas, sin seguir las guías de biosimilaridad de la WHO

Ej: Abcertin en Corea del Sur en 2012 recibe el INN de Imiglucerasa

Ej: Asboder en México en 2015 recibe el INN de Imiglucerasa

The road to biosimilars in rare diseases - ongoing lessons from Gaucher disease

Guillermo Drelichman¹ | Gilberto Castañeda-Hernández²  | Muhlis Cem Ar³ | Marta Dragosky⁴ | Ricardo Garcia⁵ | Howard Lee⁶ | Sergey Moiseev⁷  | Majid Naderi⁸ | Hanna Rosenbaum⁹ | Irena Žnidar¹⁰  | Andrés Felipe Zuluaga¹¹ | Selena Freisens¹² | Pramod K. Mistry¹³ 

There is an **urgent need** for improved **education and awareness** among HCPs, and patients involved in rare diseases, on the differences between RPs, biosimilars and NCBTs, **including regulatory requirements, terminology and requirements for long-term monitoring.**

Responsibility for this lies with industry, medical societies/institutions and patient advocacy groups.

Physicians should be vigilant of product information sources and ensure that the therapies their patients receive meet global standards. All stakeholders, including healthcare providers, patients, regulatory authorities and industry, should provide input on the establishment and revision of public policies relating to biosimilars.

TABLE 1 Key differences between WHO, FDA and EMA biosimilar guidelines

TABLE 2 Considerations for the development of biosimilars for rare diseases: lessons learned from Gaucher disease





Use of Identical INN “Imiglucerase” for Different Drug Products: Impact Analysis of Adverse Events in a Proprietary Global Safety Database

So-Fai Tsang¹ · Shirali Pandya¹ · Kristina Barakov¹ · Joan Keutzer¹ · Grace Lewis¹ · Leorah Ross¹ · Selena Freisens¹

Accepted: 21 September 2021
© The Author(s) 2022



Sanofi Global
Safety
Database
(GSD)

Fuentes: estudios clínicos, reviews de la literatura, reportes de HCP, etc

Los datos son reportados con el INN de la droga

En este paper publicado en 2021 utilizando Imiglucerasa como INN

Primer análisis: desde enero 2012 a marzo 2018. Los casos donde en la narrativa se incluye la palabra asbroder o abcertin.

Segundo análisis: casos reportados en México, antes y después de la aprobación de Asbroder (11 de octubre de 2015).

Pre – aprobación (aprox 872 días) desde 21/05/2013 a 10/10/2015

Post – aprobación (aprox 872 días) desde 10/10/2015 a 01/03/2018.

Se considera que la muestra es homogénea dado que la exposición de cerezyme es constante desde 2011.

Primer análisis: desde enero 2012 a marzo 2018. Los casos donde en la narrativa se incluye la palabra Asbroder o Abcertin.

Primer análisis

56 casos

Con el nombre
Asbroder

0 casos con el
nombre Abcertin

Todos los casos posteriores a la aprobación de Asbroder en octubre 2015 en México

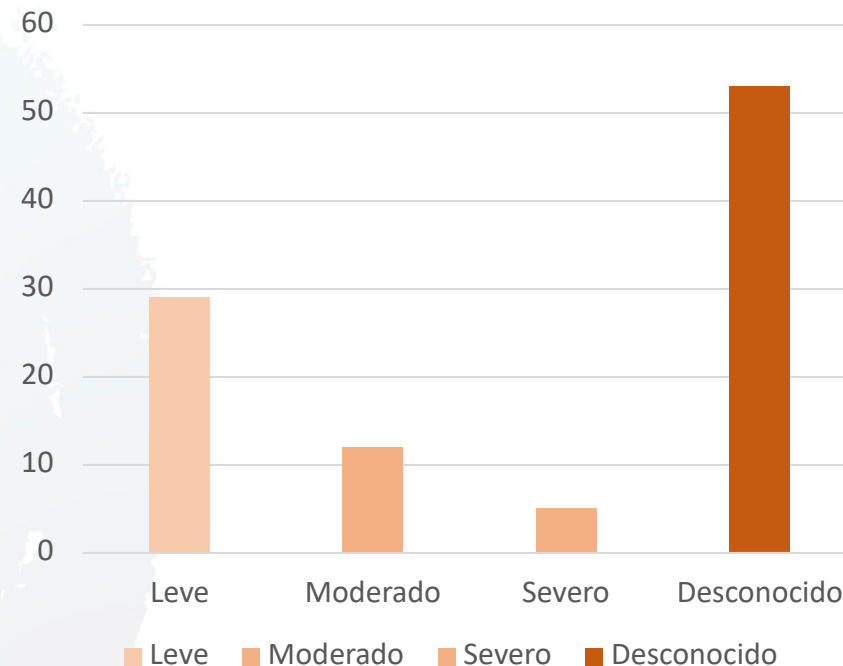
Se reportaron 151 eventos adversos serios en los 56 casos.

- Leves: 44 (29.1%)
- Moderados: 19 (12.6%)
- Severos: 7 (4.6%)
- Desconocida la severidad o inespecífica: 81 (53.6%)

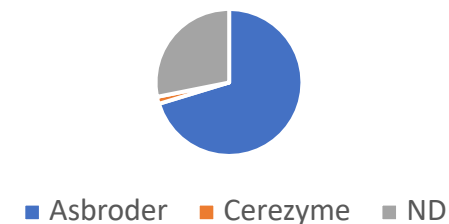
De los 56 casos la droga recibida que ocasiono el EAs fue:

- Asbroder: 45 (80.4%)
- Cerezyme: 1 (1.8%)
- Imposible de determinar: 10 (17.9%)

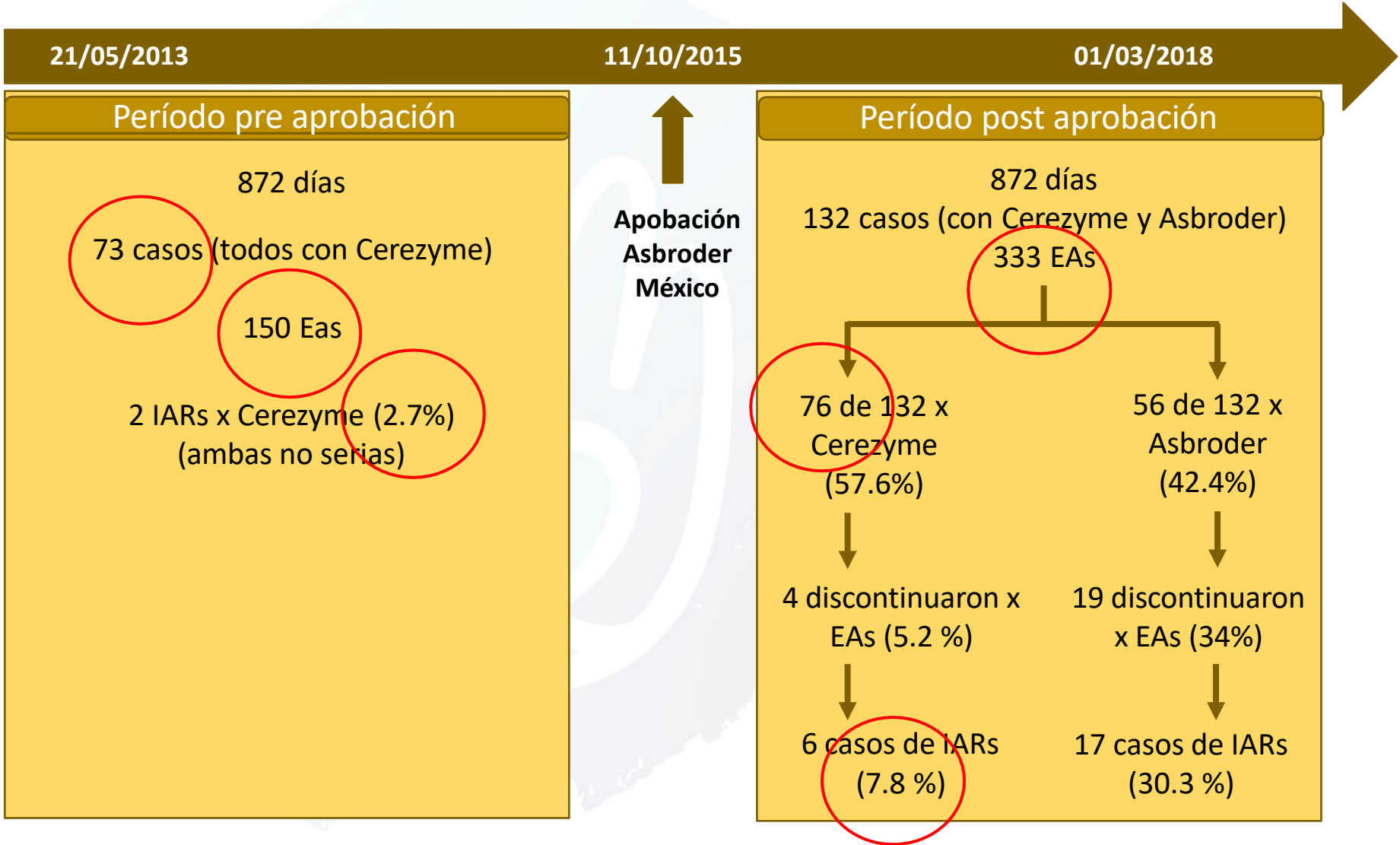
Severidad de los EAs



Droga identificada en el EAs



Segundo análisis Pre y Post
Aprobación de Asbroder



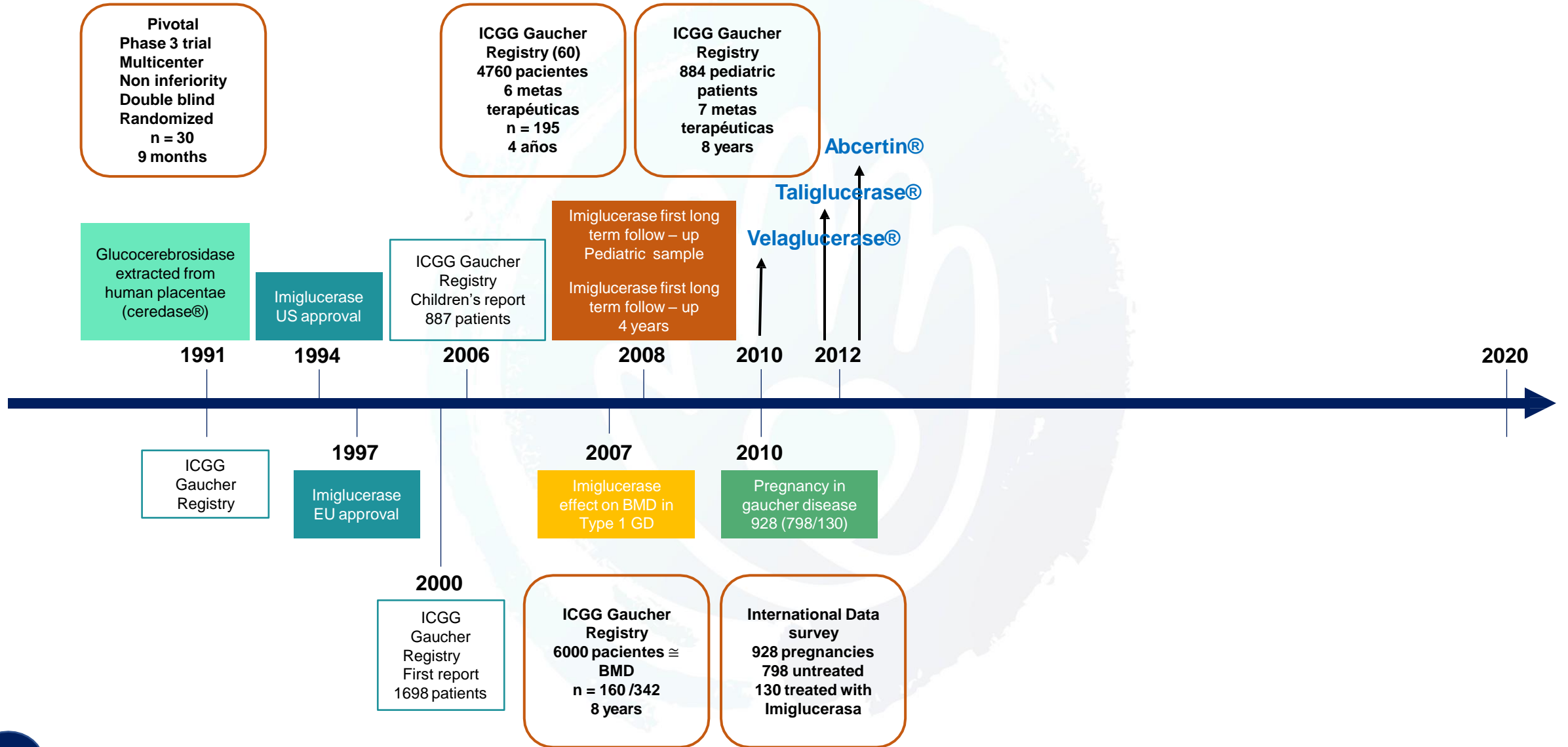
5 Conclusions

This analysis demonstrates that reporting AEs under the same INN imiglucerase could lead to (1) misreporting of AEs as being associated with potential safety signals or inaccurate pooling of AE data of products originated from ISU Abxis (such as Asbroder or Abcertin) with the Sanofi Genzyme product Cerezyme and (2) intercalated or concomitant treatment with both drugs, which could possibly be due to a misunderstanding of the interchangeability of the products with the same INN. The evidence from this analysis is consistent with the view that Asbroder may have a different safety profile from its reference product and should not necessarily be considered interchangeable with it. Most significantly, the findings highlight the challenges and confusion in AE reporting at both the HCP and marketing authorization holder level for products that use the INN imiglucerase (i.e., Cerezyme, Asbroder, and Abcertin). The use of the identical INN imiglucerase by three marketed and distinct products may potentially cause confusion for regulators, patients, and HCPs (including prescribers, pharmacists, and those administering the drug), with inadvertent switching, substitution, and potential misconceived interchangeability based on formulary availability. While the WHO INN naming guidance recommends that “for groups of glycoproteins/glycopeptides identified with a stem ... differences in glycosylation pattern are indicated by a Greek letter spelt in full and added as a second word to the name” [15], this convention is not

strictly or consistently implemented by regulatory bodies worldwide. The continued labeling of products such as Asbroder and Abcertin with the same INN as Cerezyme compromises the accuracy of pharmacovigilance data, and ultimately, could impact patient safety. A prudent step to mitigate confusion and inaccurate safety reporting due to a common INN, as well as to protect patient health and safety, is the enforcement of WHO INN guidelines for requiring a different INN or INN identifier for different products, especially those that do not comply with international standards for biosimilarity.

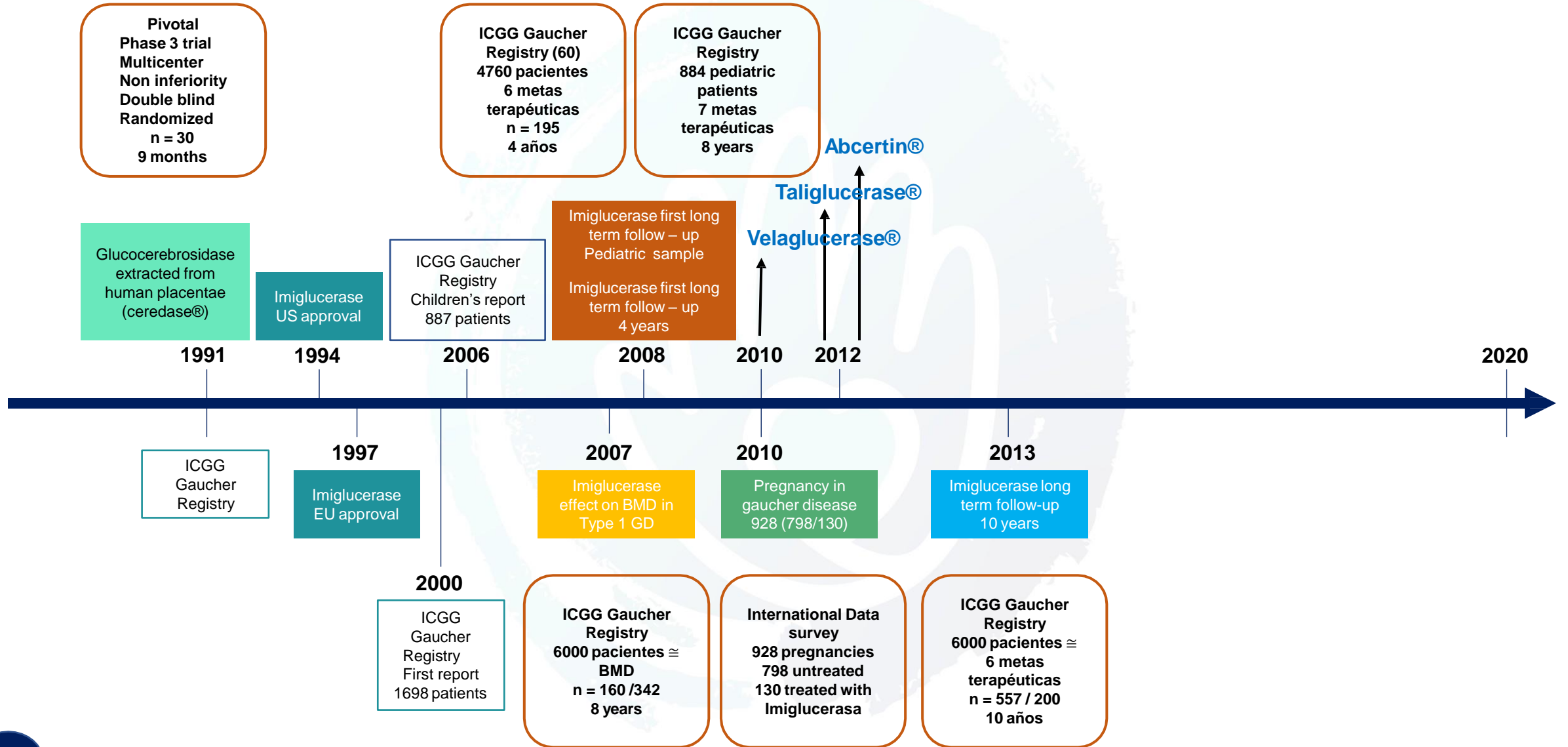
To our knowledge, this is one of the first reports on real-world safety experience with biologics sharing the same INN name. As such, it points to the necessity of creating an adequate reporting system.

Safety and Efficacy in Gaucher Disease



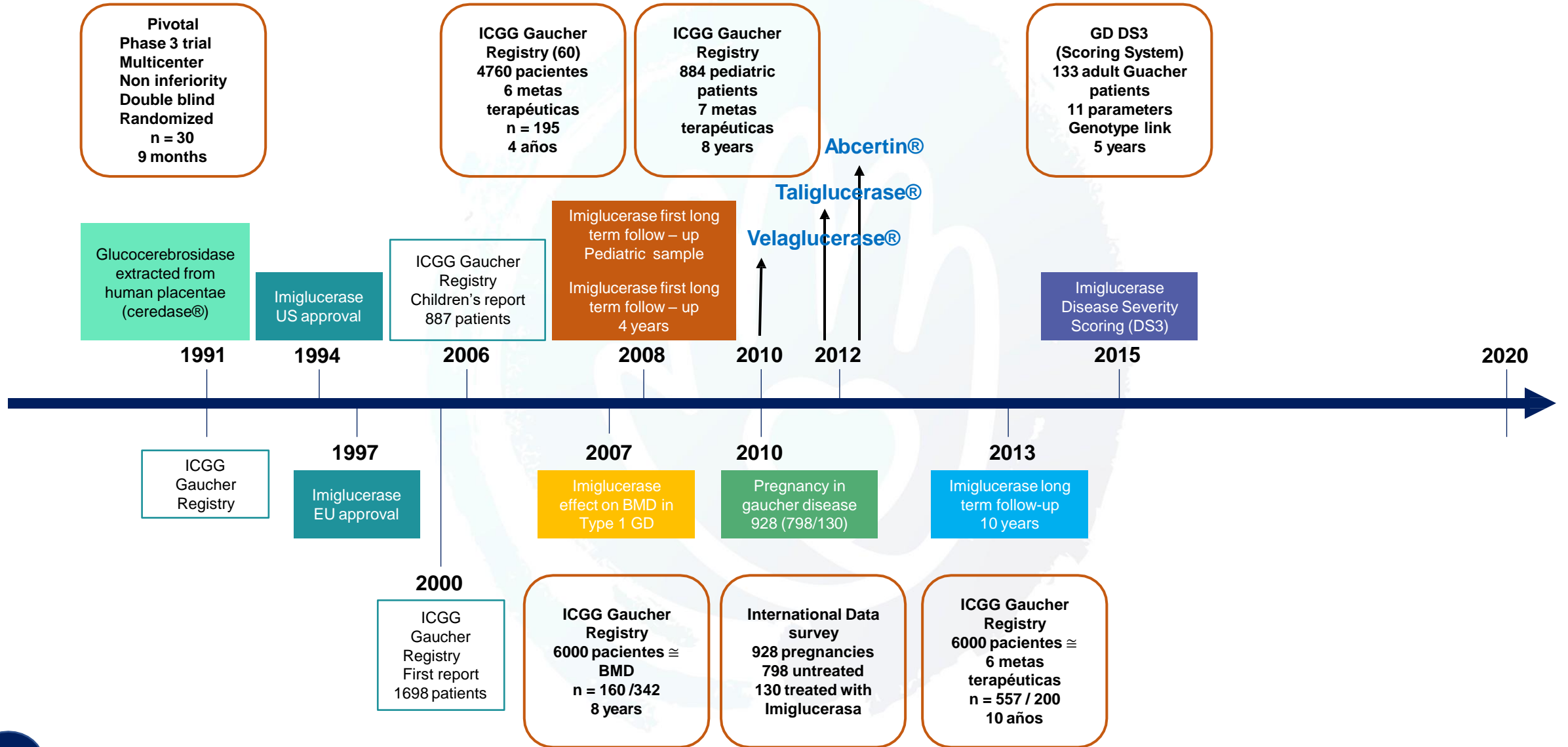
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Safety and Efficacy in Gaucher Disease



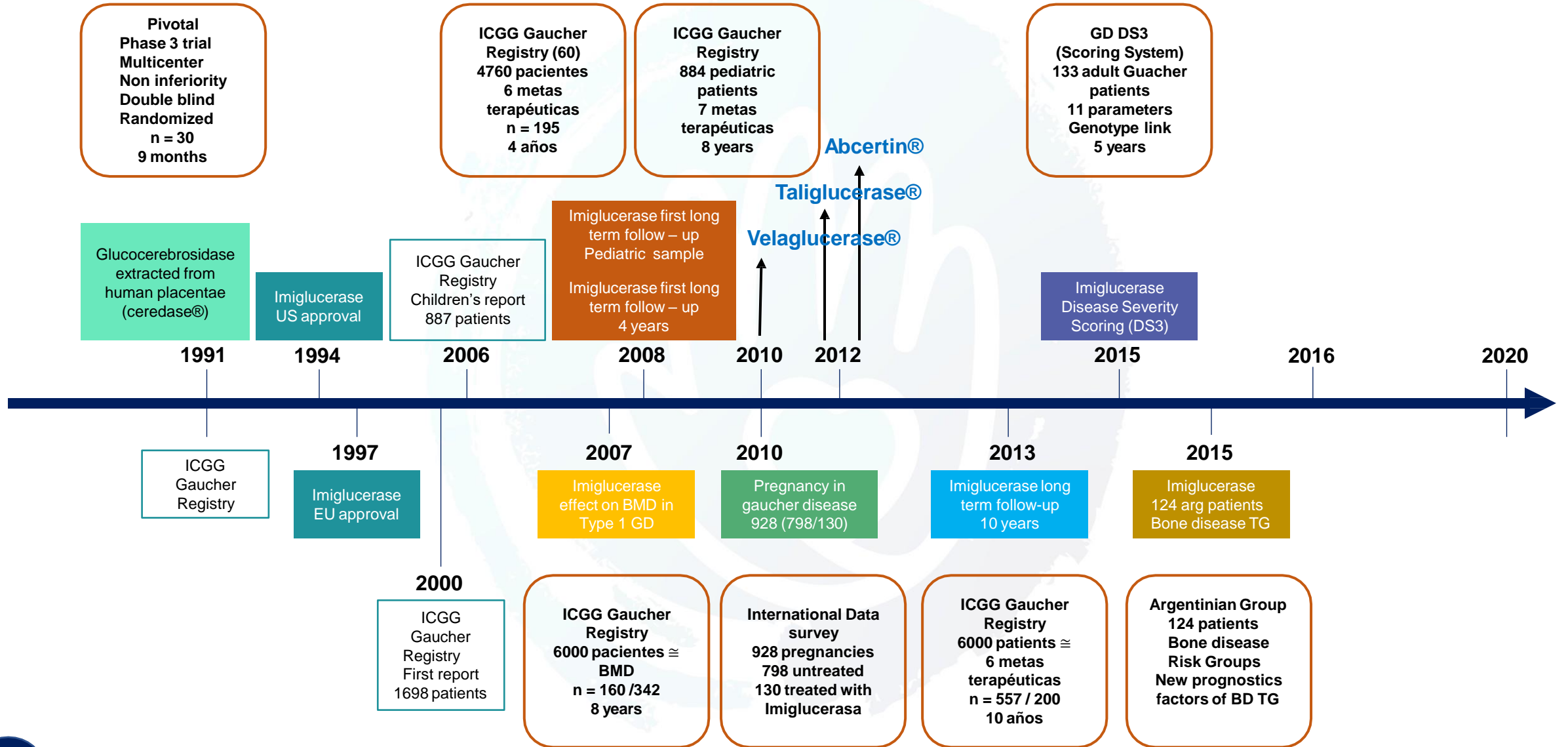
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Safety and Efficacy in Gaucher Disease



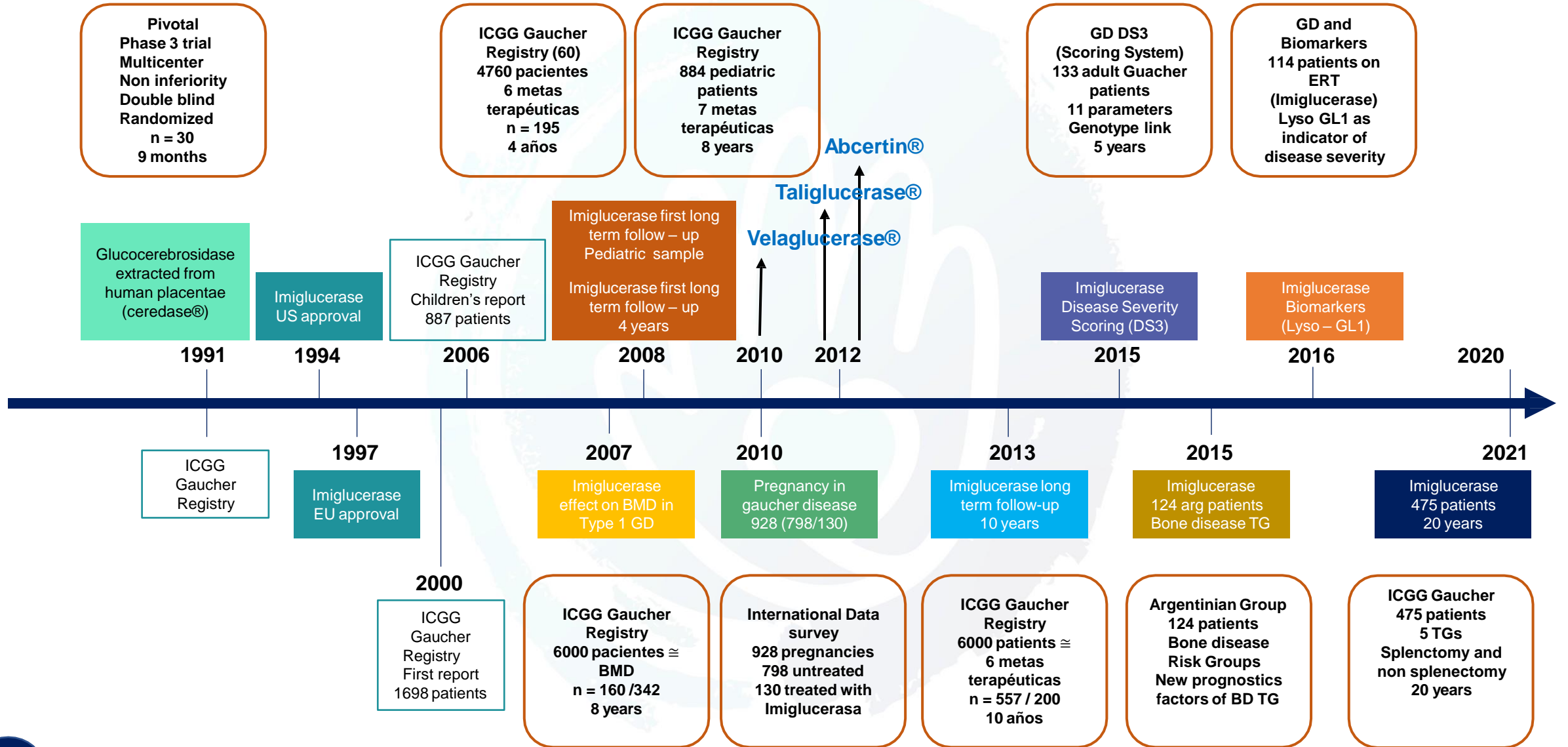
20. Neal J. Weinreb and Dominick Amato. Evaluation of disease burden and response to treatment in adults with type 1 Gaucher Disease using a validated disease severity scoring system (DS3). Orphanet Journal of Rare Diseases (2015) 10:64.

Safety and Efficacy in Gaucher Disease

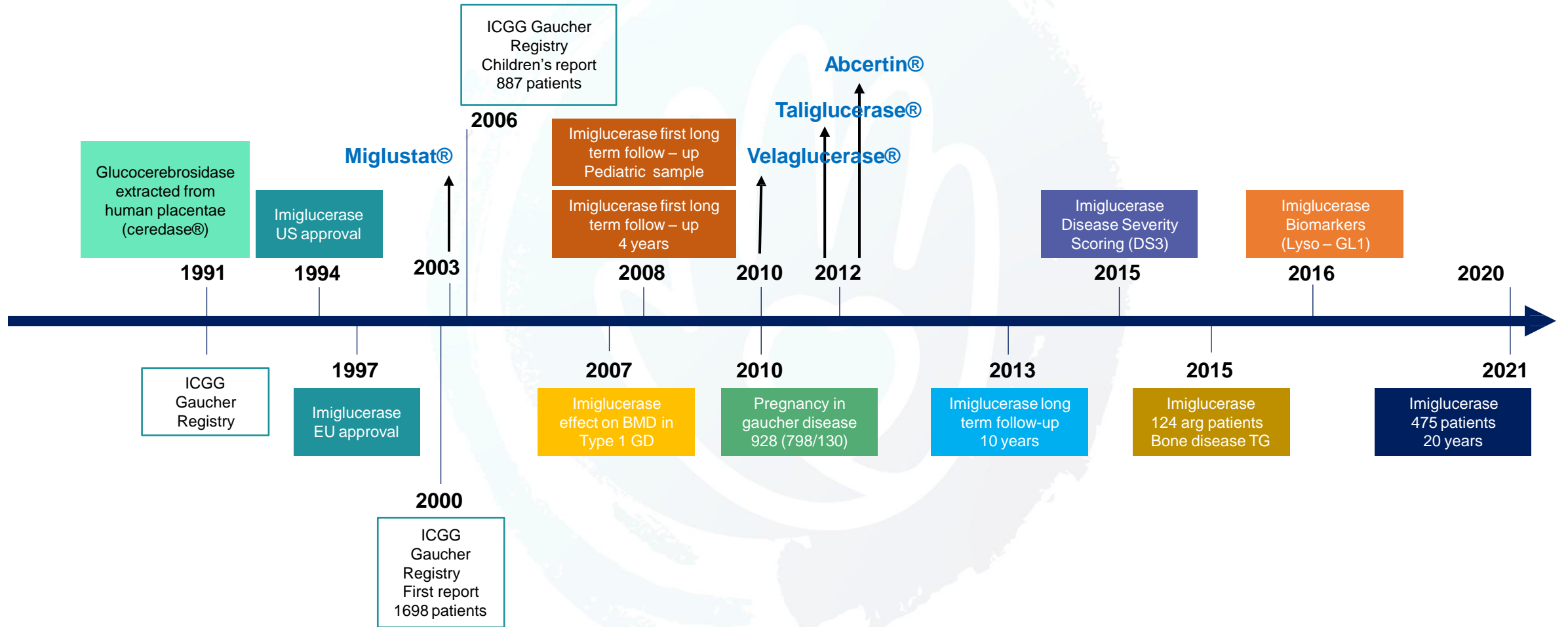


21. Guillermo Drelichman, Nicolas Fernandez Escobar et al. Skeletal involvement in Gaucher disease: An observational multicenter study of prognostic factors in the Argentine Gaucher disease patients. American Journal of Hematology, Vol. 91, No. 10, October 2016.

Safety and Efficacy in Gaucher Disease



Safety and Efficacy in GD (ERT – SRT)



What do you think
about the actual
scenario?



Challenges of pharmacovigilance



Physicians have limited time and high patient numbers¹⁻³



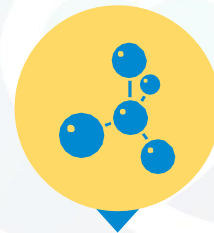
Not all stakeholders are aware of the importance¹⁻³



Infrastructure and support needed to implement good pharmacovigilance¹⁻³



Rates of reporting are generally low⁴⁻⁶



Traceability³
(which product caused the reaction?)



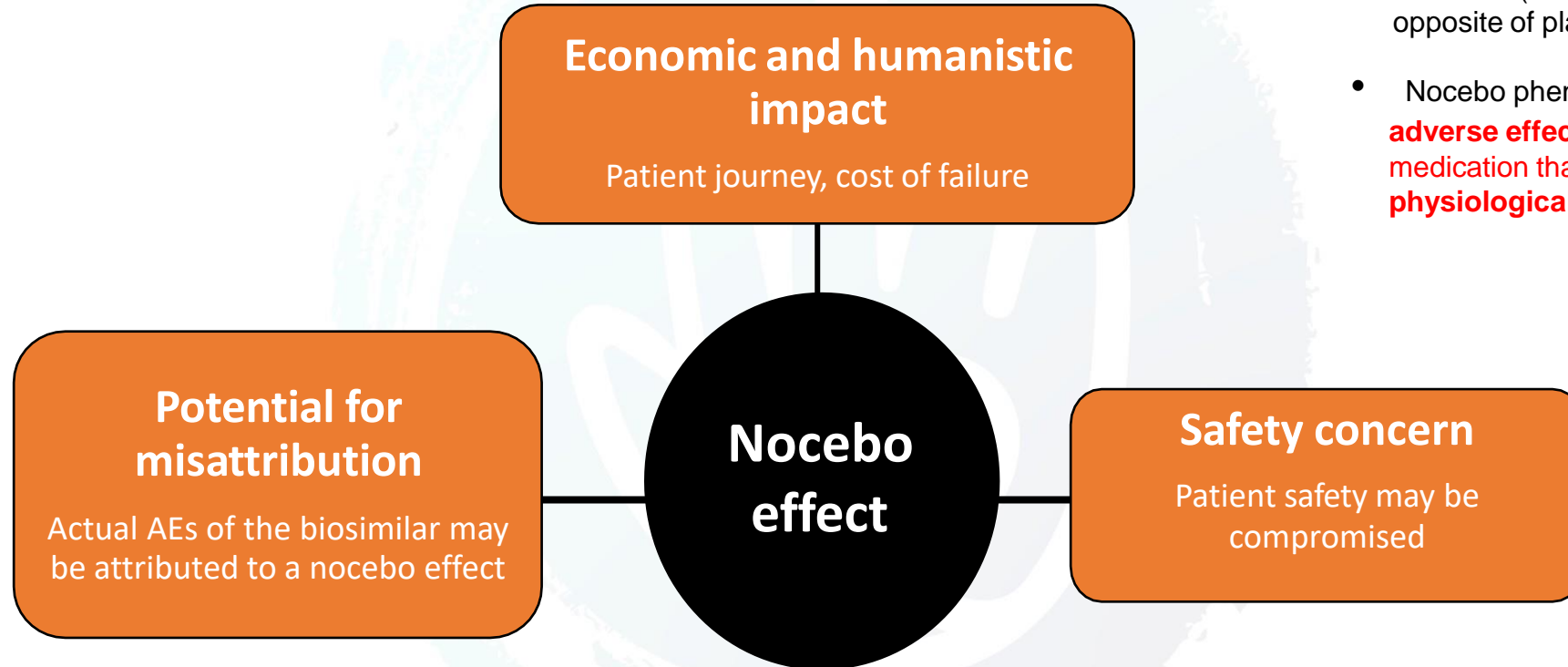
Can be expensive⁶

What can be done by
us to do it better?



AZ

Why is the Nocebo Effect Important?



- “Nocebo” (meaning “I shall harm”) is the opposite of placebo (“I shall please”)¹
- Nocebo phenomenon is defined as an **adverse effect** attributable to taking a medication that is **not specific to the physiological action** of the medication¹

Biosimilars in Latinoamérica

En LA han ido en aumento tanto los estándares sanitarios para la aprobación de biosimilares mAbs como el número de aprobaciones



- **Remsima (infiximab)** – Hospira / Celltrion
- Rigetuxer (*rituximab*) - PISA
- Infnitam (*etanercept*) – Probiomed
- Ogviri (*trastuzumab*) – Mylan / Biocon



- Reditux/Tidecron (*rituximab*) - Western Pharm
- **Truxima (rituximab)** - N/A
- **Remsima (infiximab)** - Oxialfarm
- Bevax (*bevacizumab*) - Grünenthal
- Etanar (*etanercept*) - Lafrancol/Abbott



- **Flixeli (infiximab)** - ACFARMA
- Reditux/Tidecron (*rituximab*) – Farmaindustria



- Usmal (*rituximab*) – MegaPharma



- Reditux/Tidecron (*rituximab*) - Abbot
- **Remsima (infiximab)** – Saval
- **Bsisintex (trastuzumab)** – Mylan / Biocon
- Hertraz (*trastuzumab*) – Mylan / Biocon



- Etanar (*etanercept*) - La Santé
- **Remsima (infiximab)** - Celltrion
- Ogviri (*trastuzumab*) – Mylan



- **Remsima (infiximab)** – Hospira
- Bio manguinhos infiximabe (infiximab) – Janssen / Bionovis com. by Bio Manguinhos
- **Brenzys TM (etanercept)** - Samsung B./MSD
- Zedora (*trastuzumab*) – Libbs
- **Kanjinti (trastuzumab)** – Amgen
- **Ontruzant (trastuzumab)** – Samsung B./MSD
- **Herzuma (trastuzumab)** - Celltrion



- Reditux/Tidecron (*rituximab*) - Fa.Pa.Sa.
- Bevax (*bevacizumab*) - Lab. Bioéticos
- Novex (*rituximab*) - Lab. Bioéticos



- Novex (*rituximab*) - Urufarma

- Novex (*rituximab*) - Elea
- Bevax (*bevacizumab*) - Elea
- Lumiere (*bevacizumab*) - Elea
- **Remsima (infiximab)** - Gobbi Novag
- Enerceptan (*etanercept*) - Amega Biotech



En **negrita**, también aprobados por EMA/FDA

No exhaustivo

Note: el análisis no incluye a otros biológicos como citoquinas, factores de crecimiento, interferons y hormonas. Venezuela y America Central no incluidos en el análisis

Sources: INVIMA, COFEPRIS, ANVISA

El único país de LA donde la mayoría de las aprobaciones de mAbs es de origen local



Regulations for biosimilars in Latin America



Table 1
Regulations for biosimilars in Latin America

Country	Status	Notes
<i>Latin America</i>		
Argentina	Regulation enacted	Approval pathway is similar to the World Health Organization (WHO) system (comparative data needed at all stages), although extrapolation between indications is not permitted
Bolivia	No biosimilars regulation	
Brazil	Regulation enacted	Two-pathway system: comparability (similar to WHO system; comparative data needed at all stages) and individual development (requirement for some comparative data may be waived, e.g. phase I and phase II) Each regulatory authority decides on the evidence required for approval. No differentiation is made between novel biopharmaceutical agents and biosimilars Regulations do not address the question of interchangeability
Chile	Regulation enacted	Approval pathway similar to WHO system (comparative data needed at all stages), although data on manufacture/chemistry needed as for a new drug Extrapolation between indications is possible
Colombia	Regulation drafted or in development	Etanar® approved for use via processes used for small-molecule generic drugs
Cuba	Regulation enacted	Ambiguous concept of biosimilarity: upon registration, a new biosimilar does not need to be identified as a copy of the reference drug
Dominican Republic	No biosimilars regulation	
Ecuador	No biosimilars regulation	
Guyana	No biosimilars regulation	
Honduras	No biosimilars regulation	
Jamaica	No biosimilars regulation	
Mexico	Regulation enacted	Data are mostly needed as for a new drug in relation to manufacturing, preclinical studies, and phase I studies Comparability data is sufficient for phase II and phase III studies (in some cases, phase III comparability data may not be required) No extrapolation is permitted between indications
Nicaragua	No biosimilars regulation	
Paraguay	No biosimilars regulation	
Suriname	No biosimilars regulation	
Uruguay	No biosimilars regulation	
Venezuela	Regulation enacted	Data are mostly needed as for a new drug, although comparability data may suffice for phase I and phase II studies Biosimilars are considered to be biopharmaceuticals and need the same documentation as biopharmaceuticals to be registered No extrapolation is permitted between indications

Safety and Efficacy – Closing remarks

- Imiglucerase (Cerezyme) is an effective, long-term treatment for GD1. In a long-term observational setting, improvements seen during early treatment years are sustained by continuing treatment for 20 years. These results are consistent when analyzed by different patient subsets.
- There are two other ERT options, velaglucerase and taliglucerase. Both are biological innovators. Their data is less consistent in terms of number of patients, years of follow-up, and analysis of special populations.
- We have robust data from eliglustat trials and from "real life" that validate the use of this drug in a "unique" group of adults patients.
- Biosimilars clearly are a reality in this new landscape of biologic drugs and they are welcome in rare diseases. Because they are designed to have no clinically meaningful differences from the innovator product, they **do not provide any clinical advantage**. Therefore, patients on innovator biopharmaceutical agents may be switched to biosimilars for economic rather than medical reasons.
- But Biosimilars have to follow certain rules, mostly in the process of approval and pharmacovigilance. We have analyzed all the steps that built with strength the right definition of a Biosimilar and how it was possible to

Safety and Efficacy – Closing remarks

There is an urgent need for appropriate regulatory processes to be established in many developing countries, which would avoid the potential **risks of using intended copies** as opposed to biosimilars.

Long term follow up

The most sensible population

Pharmacovigilance programs

Nocebo Effect

Comparative trial with the biologic innovator

Considerations of special populations

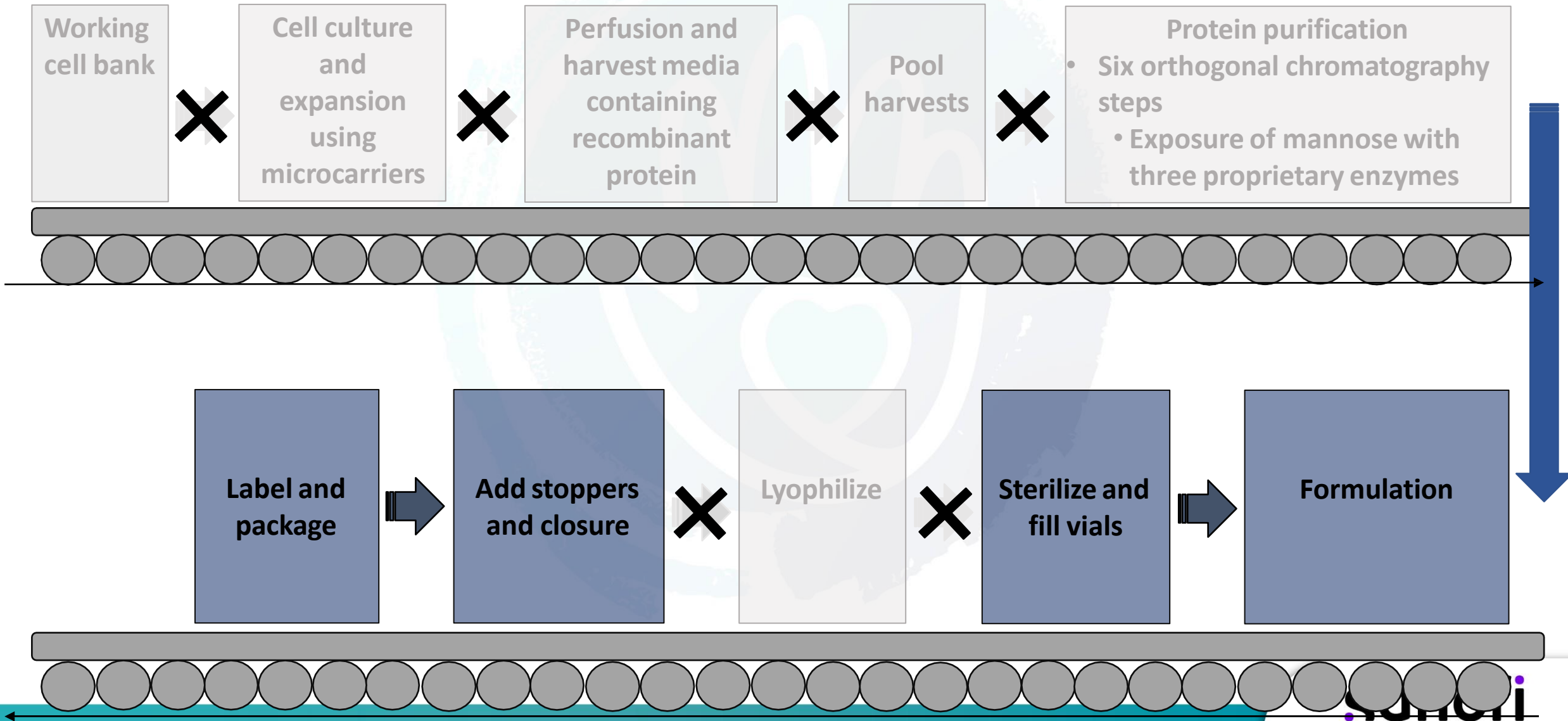


2ND SUMMIT
RARE
DISEASES
C O P A C

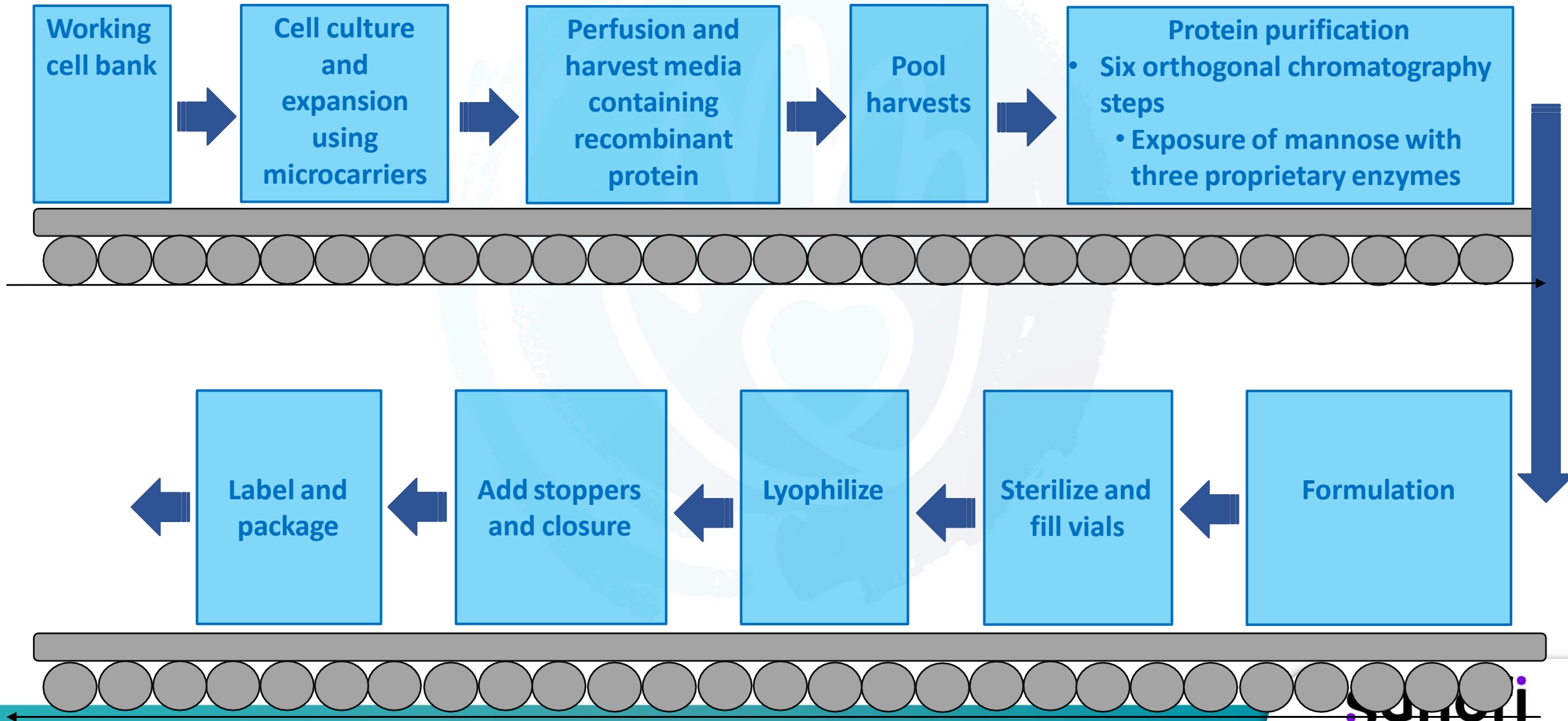
¡GRACIAS!

sanofi

Biosimilar developers do not have access to **proprietary processes** and steps



2.000 site procedures and 22.000 line items are used to make 1 vial of Cerezyme



**1. Innovator
biopharmaceutical
agents:**



Mendoza

Valle de Uco

Year 2017

Barrica de roble x 5 años



2. Biosimilars



Mendoza

Valle de Uco

Year 2022

Barrica de roble x 4 años



**3. Intended copies =
Non Comparable
Biotherapeutics (NCBT)**



Francia

Year 2021



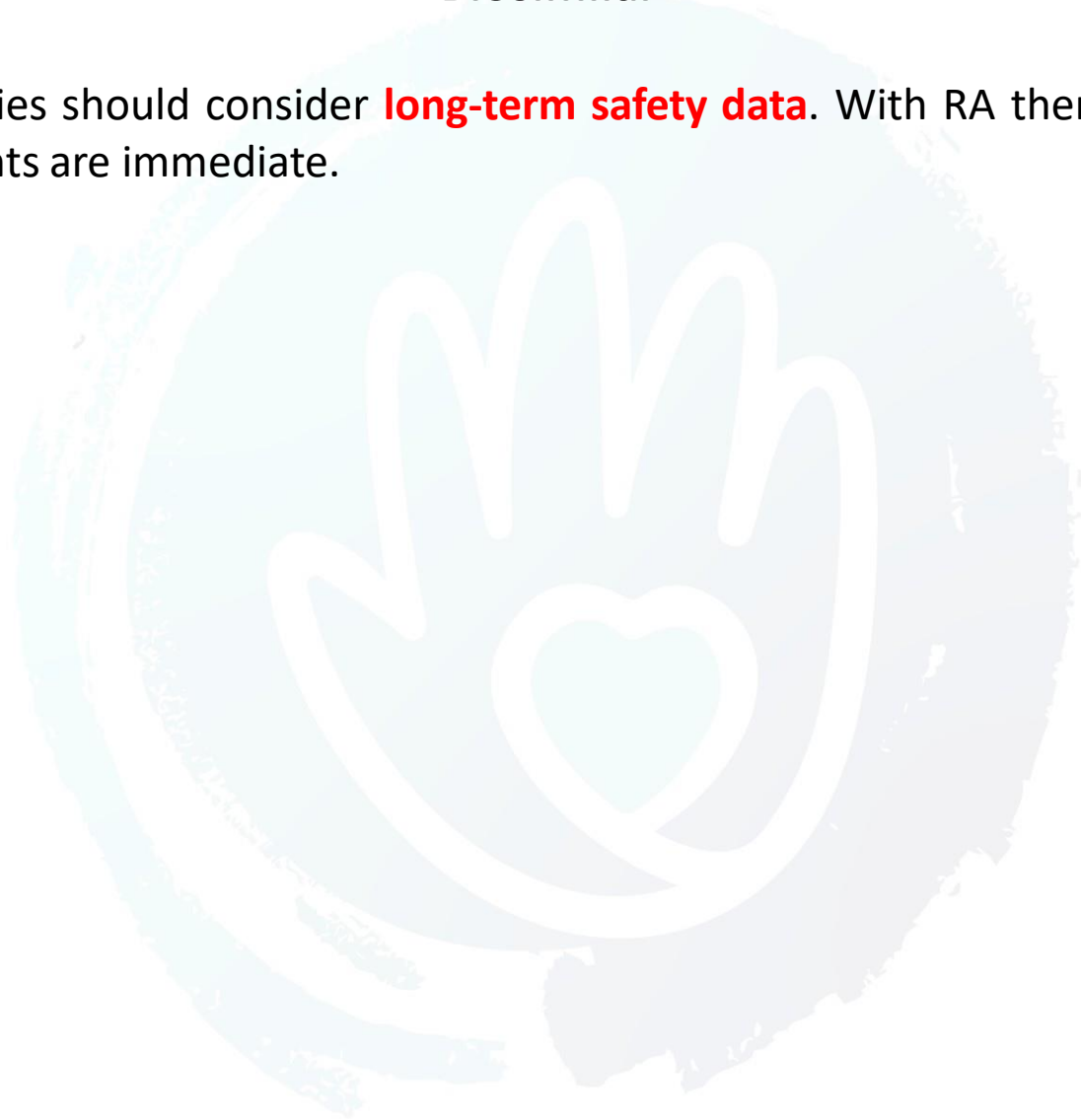
Barrica de cemento x 5 años

Safety and Efficacy in therapeutical options for Gaucher Disease

Brand name	INN (WHO INN Programme)	When/where it was approved	Randomized trials	Special populations	Years since 1 st launch	TG explored and achieved
Cerezyme® (Country of origin: US)	Imiglucerase (1994) Stand-alone biologic/ Orphan Drug	US: 1994 EU: 1997 91 other countries	Yes	Yes	26	Hemoglobin ----- AVN ----- chitotriosidase Platelet count --- Infarcts ----- CCL - 18 ---- BMB Liver volume ----- Lytic lesions – Lyso GL 1 Splenic Volume – BMD ----- Pulmonary disease Bone pain----- Height ----- Genotype Bone crisis----- Pregnancies – Alfa sinucleopathy
Abcertin® (Country of origin: South Korea) Asbroder®	Imiglucerase (do not meet the definition of biosimilar of FDA, EMA or WHO)	Not approved in US/EU (South Korea: 2012 6 other countries)	No	No	8	Hemoglobin ----- chitotriosidase Platelet count ----- CCL - 18 Liver volume (US) ---- Splenic Volume (US) BMD ----- genotype (mixed sample) Bone disease (X rays)
VPRIV® (Country of origin: US)	Velaglucerase alfa (2007) Stand-alone biologic/ Orphan Drug	US: 2010 EU: 2010 56 other countries	Yes	Yes	10	Hemoglobin ----- AVN ----- chitotriosidase Platelet count --- Infarcts ----- CCL - 18 Liver volume ----- Splenic Volume – BMD Bone pain----- Height ----- Genotype Bone crisis----- Pregnancies
Elelyso® (Country of origin: US)	Taliglucerase alfa (2009) Stand-alone biologic/ Orphan Drug	US: 2012 Not approved in EU 18 other countries	No	No	8	Hemoglobin ----- chitotriosidase Platelet count --- CCL - 18 Liver volume ----- Bone disease Splenic Volume – BMD Bone pain Bone crisis

Biosimilar

Ideally, regulatory authorities should consider **long-term safety data**. With RA therapies, for example, not all immunogenic adverse events are immediate.



Biosimilar



Biosimilar

Clarity of **product nomenclature** is especially critical for accurate post-marketing surveillance. Unclear nomenclature may lead to inaccurate reporting of adverse events, which would be particularly problematic for interchangeable biosimilars as there may be uncertainty regarding which drug the patient actually was receiving, as well as to differences in reporting to national and international drug registries. There is an urgent need for appropriate regulatory processes to be established in many developing countries, which would avoid the potential **risks of using intended copies** as opposed to biosimilars.

NOCEBO effect:

Intended copies = non-innovator biopharmaceutical products that, unlike biosimilars, do not have enough clinical evidence to demonstrate biosimilarity.



Generics:

1. Reference product



2. Copies from the reference product

