Disclosures

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Polish Lymphoma Research Group

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Uniwersytet Jagielloński Collegium Medicum

Celgene (Research Funding); Eisai (Research Funding); Gilead (Research Funding); Jansen (Research Funding); Mundipharma (Scientific Advisory Board); Pharmacyclics (Research Funding); Pfizer (Research Funding); Roche (Research Funding); Sandoz – Novartis (Research Funding, Scientific Advisory Board); Spectrum (Research Funding, Scientific Advisory Board); Takeda (Research Funding, Scientific Advisory Board); Teva (Research Funding, Scientific Advisory Board).

FL – Biosymilar Rituximab

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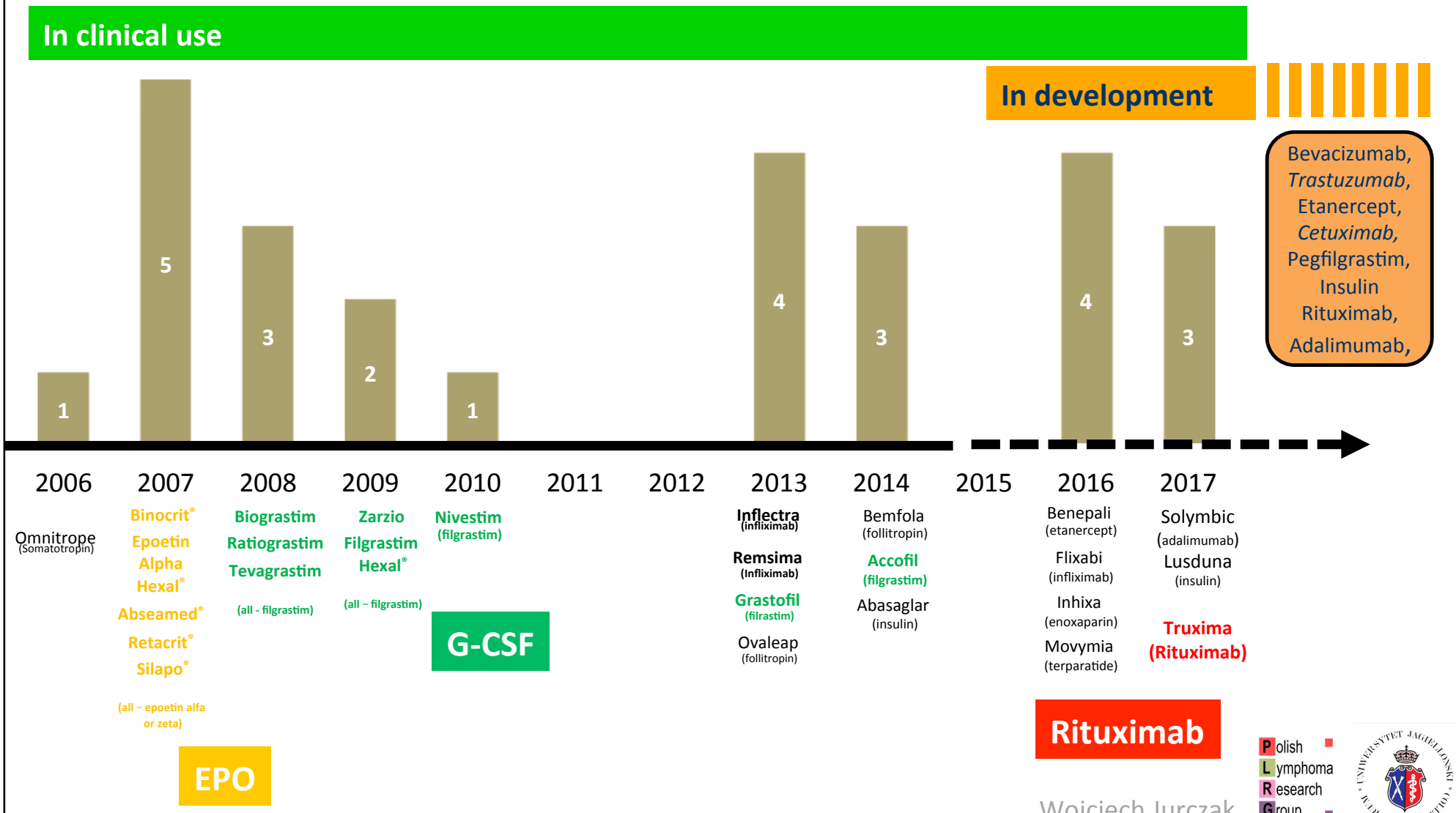
UNIWERSYTET JAGIELLOŃSKI COLLEGIUM MEDICUM

Biosimilars approved by EMA



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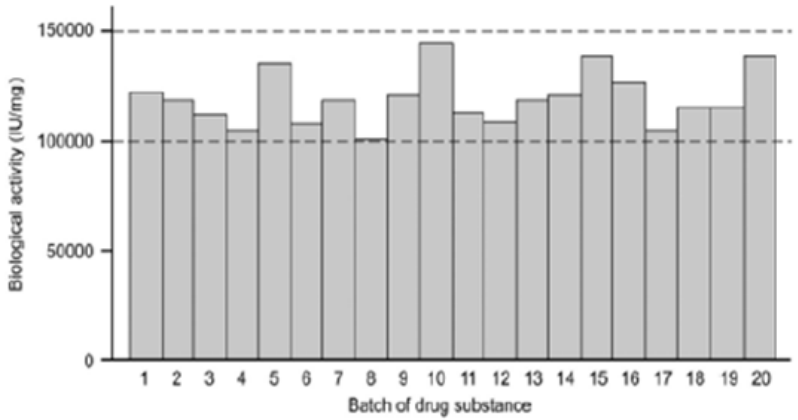
Every Biologic varies from batch to batch

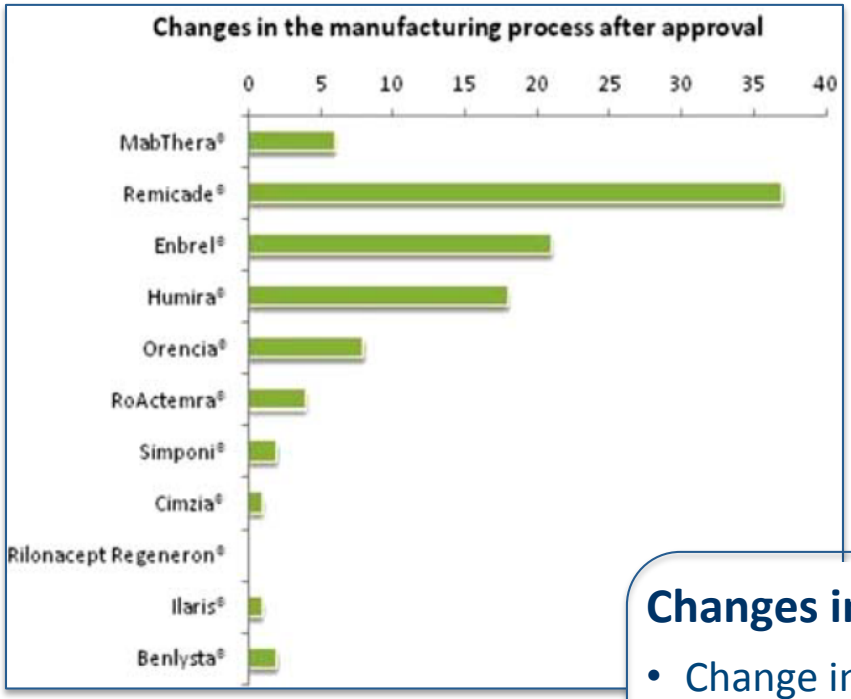
- „Non-identicality“ is a normal principle in biotechnology.
- No batch of any biological is „identical“ to the others



- The „art“ is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, within current technical and scientific limitations (inherent variability)

C Schneider, Ann Rheum Dis 2013 Vol 72 No 3

Changes in the manufacturing process after approval

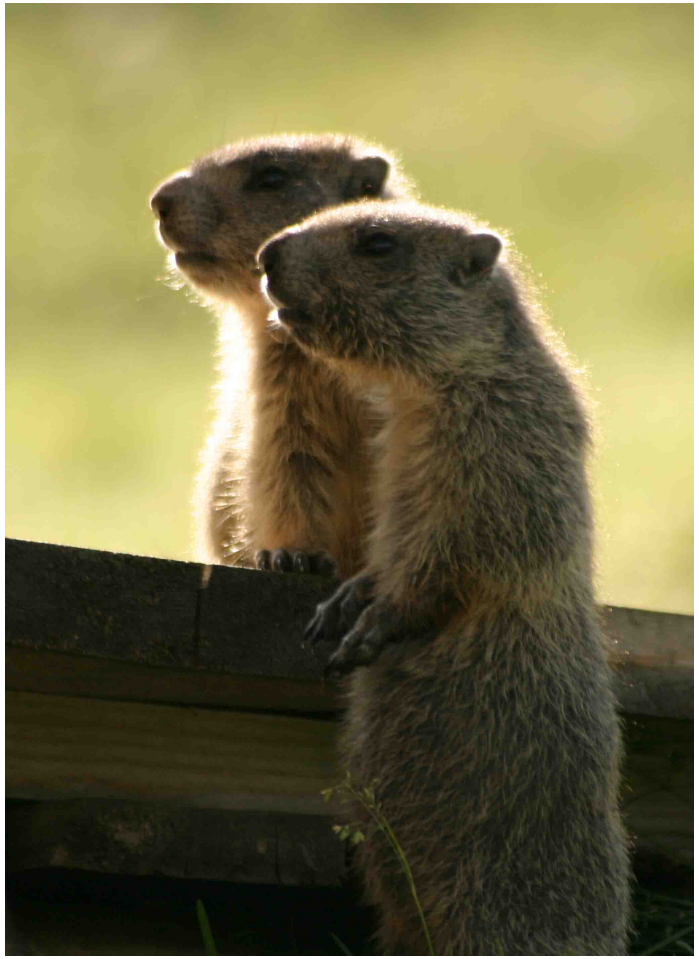


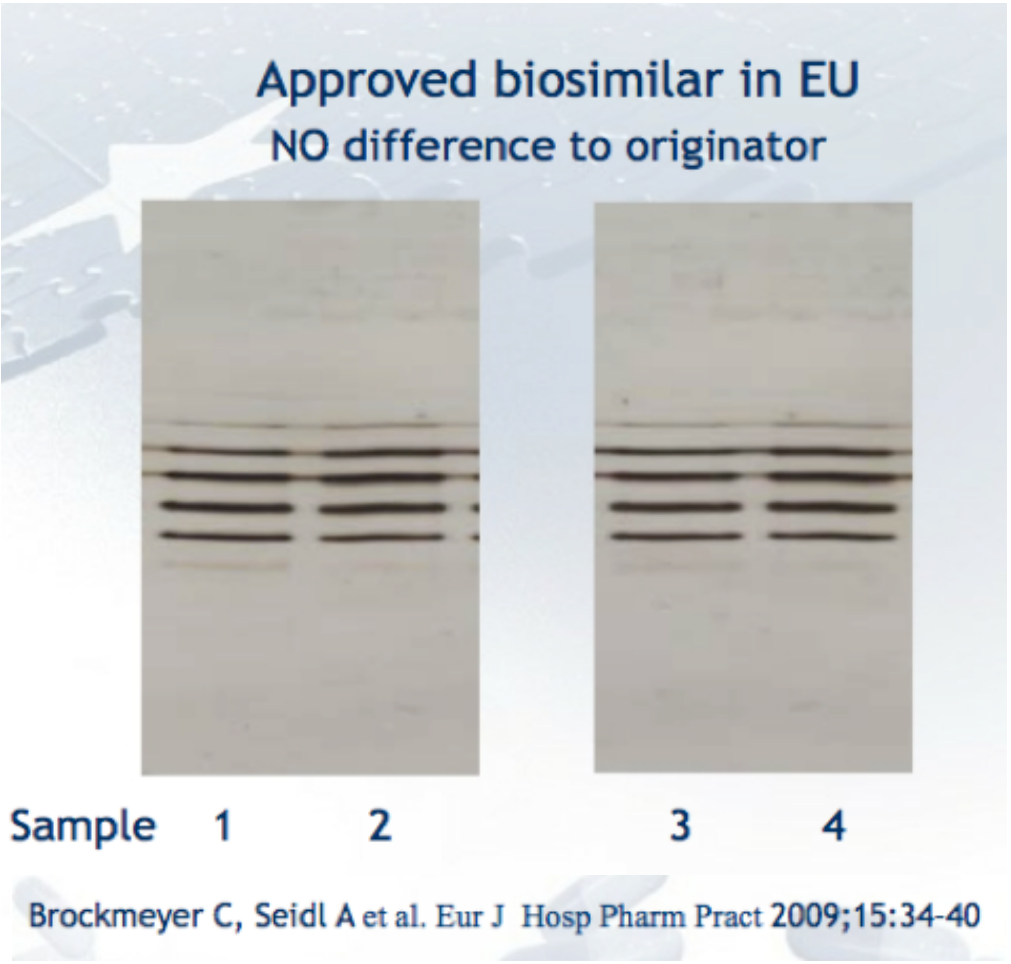
Changes include e.g.

- Change in the supplier of a cell culture media
- New purification methods
- New manufacturing sites

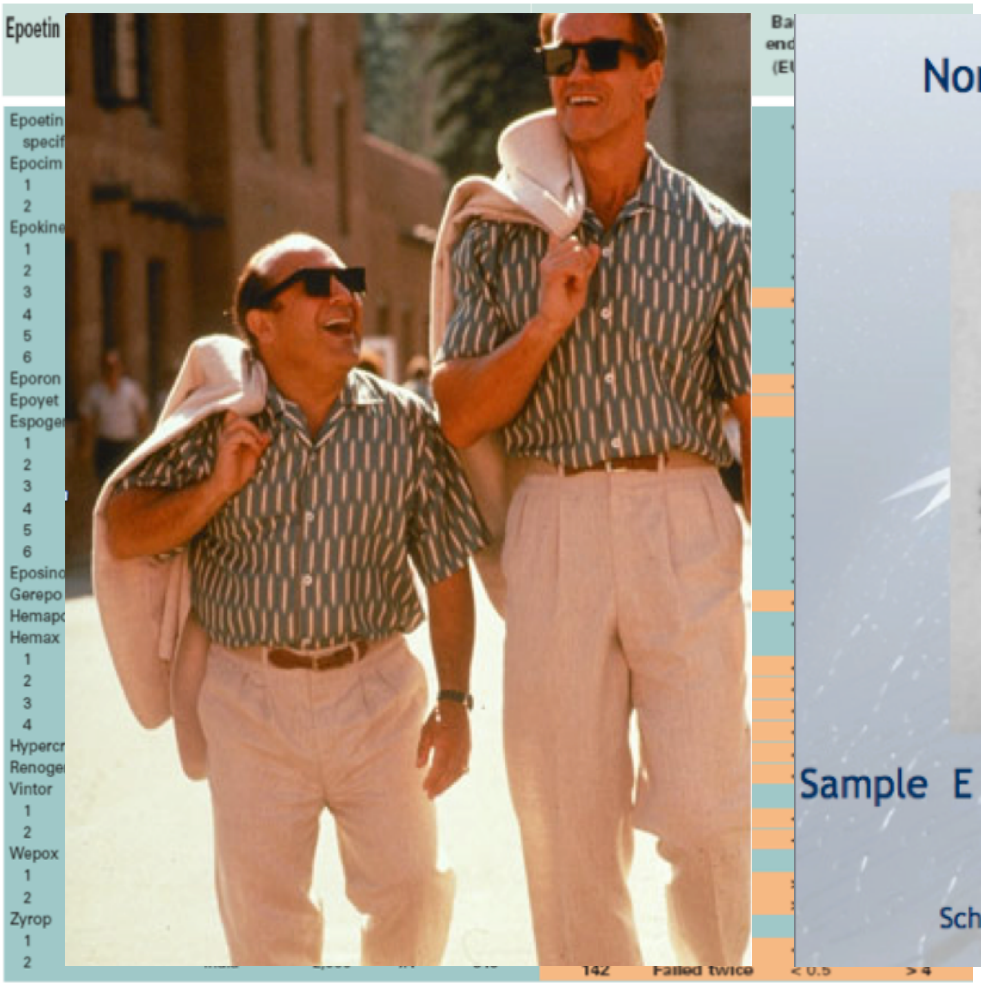
C Schneider, Ann Rheum Dis 2013 Vol 72 No 3

Biosimilars – approved by EMA / FDA



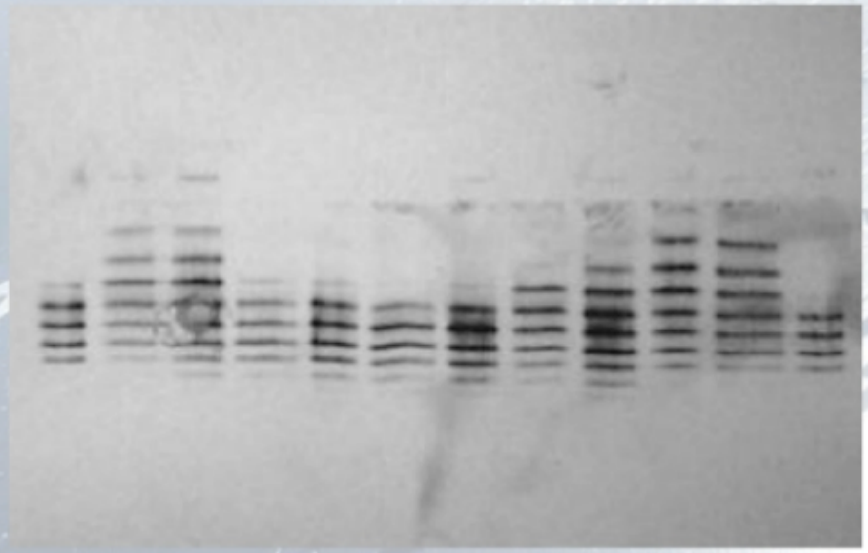


Copy-biologic



Non comparable copy biologics ≠≠ biosimilars

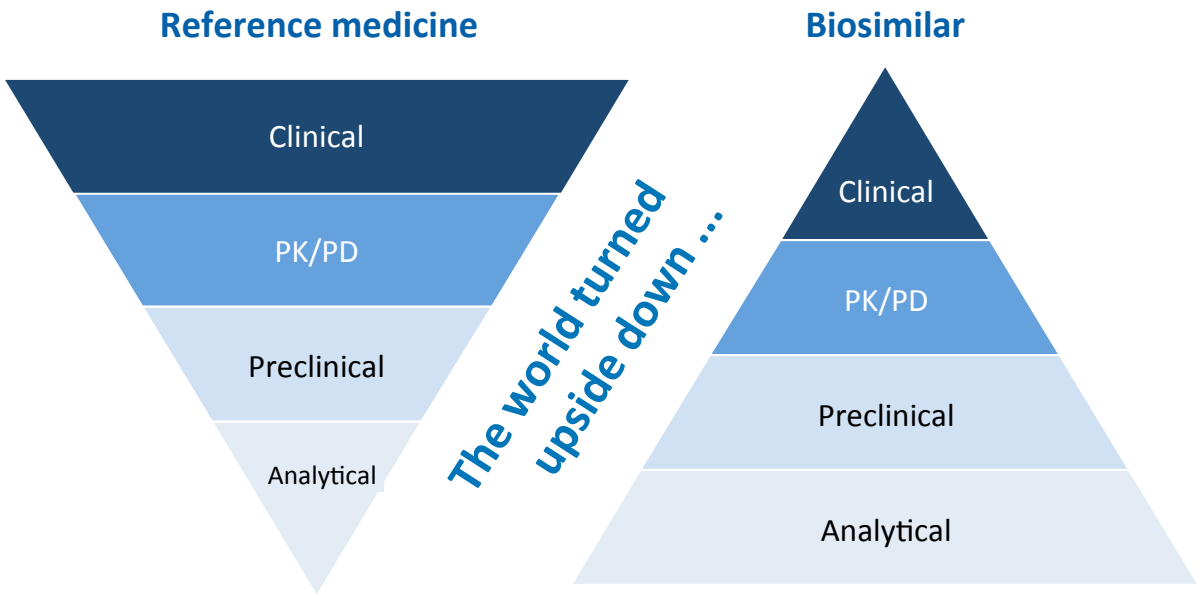
NOT similar to Reference E



Sample E IA IB IIA IIB IIIA IIIB IV V VII VIII E

Schellekens H et al. Eur J Hosp Pharm Pract 2004;3:43-7

Different focus between originator and biosimilar development



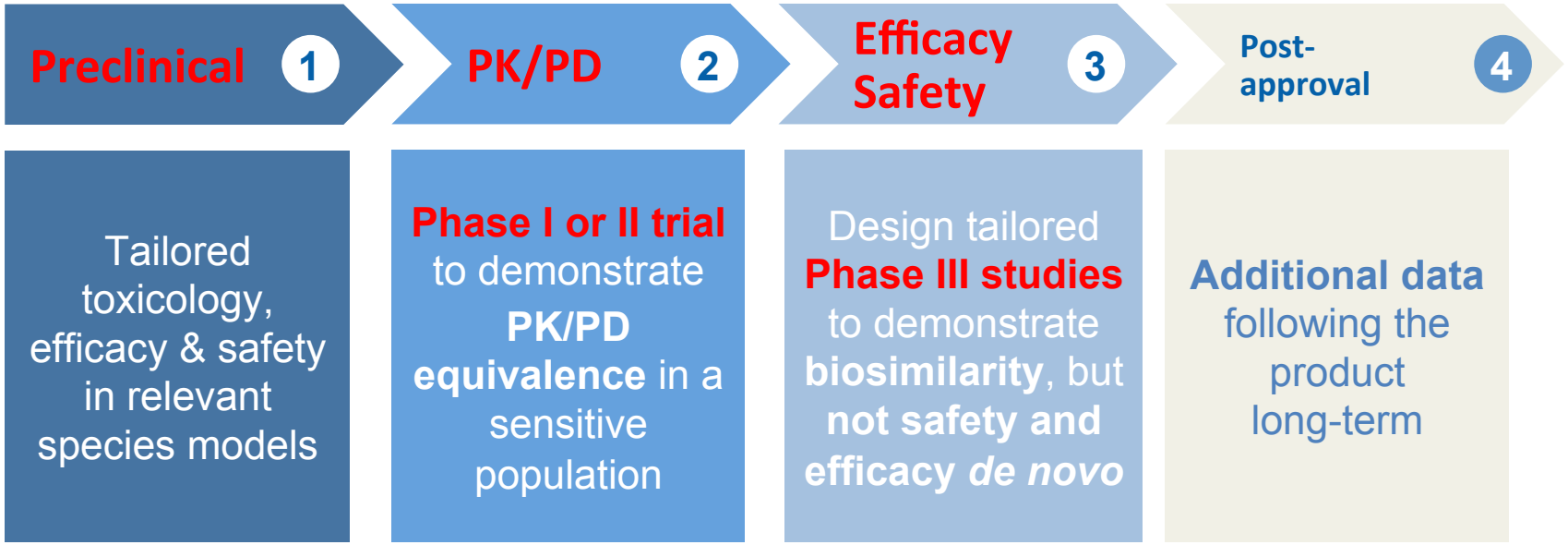
Major goal is to **determine the clinical effect**

Major goal is **to determine similarity**; establishment of the scientific bridge to the clinical experience of the originator

In the end, both approaches provide the same level of confidence with regard to safety and efficacy of the medicine

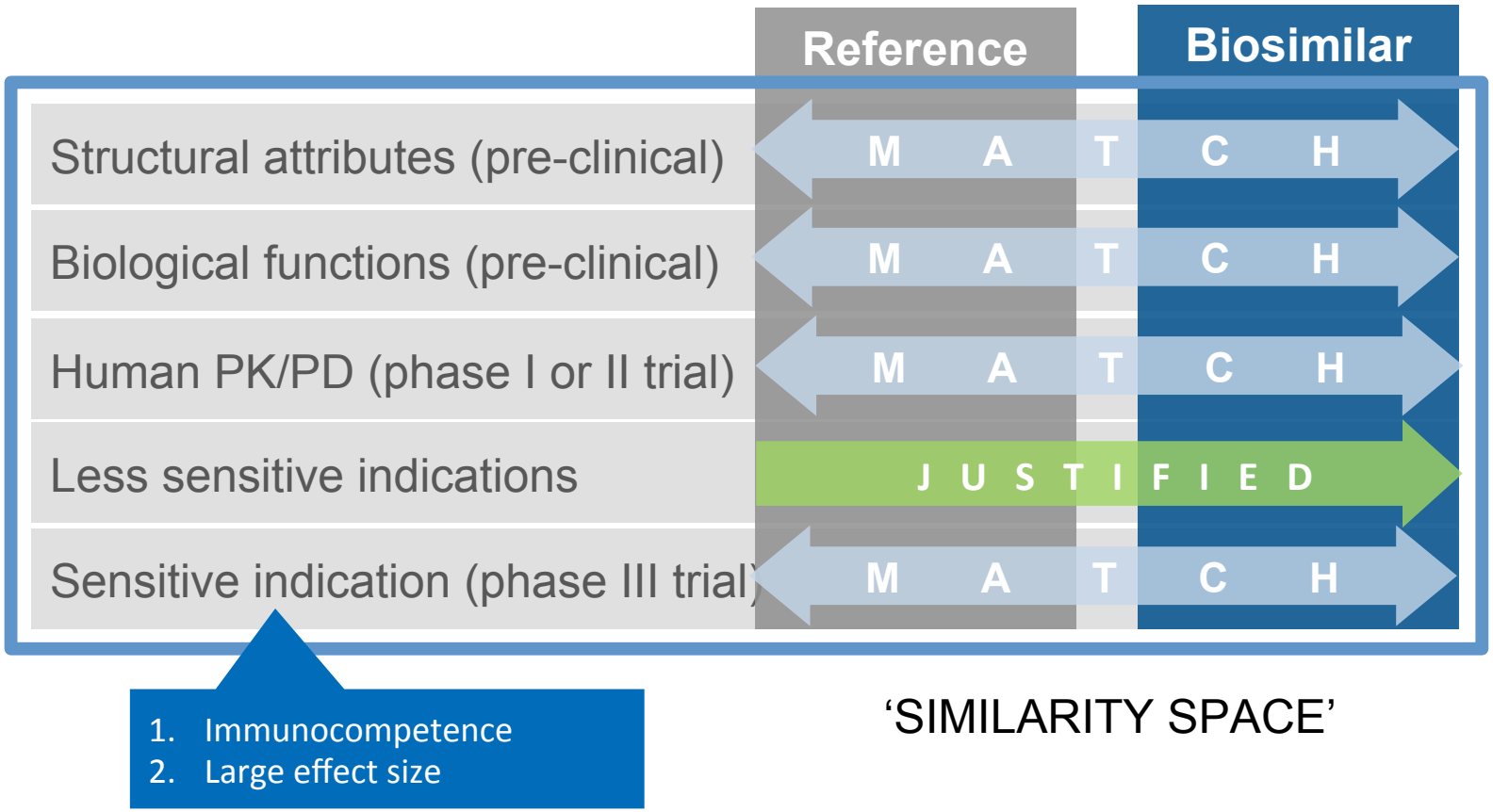
PD, pharmacodynamics; PK, pharmacokinetics

Clinical development confirms biosimilarity



European Medicines Agency (EMA). Guideline on similar biological medicinal products. CHMP/437/04 Rev 1/2014 [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf [Accessed 2016 March 18];
US Food and Drug Administration. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 2015 [online] Available from URL: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf [Accessed 2016 March 18].

Extrapolation is based on the entire similarity exercise



PD, pharmacodynamics; PK, pharmacokinetics
Kurki P, et al. J Crohns Colitis 2014;8:258; Weise M, et al. Blood 2014;124:3191–6; Weise M, et al. Blood 2012;120:5111–17; Sandoz-generated/owned figure (November 18 2014).

Rituximab Biosimilars

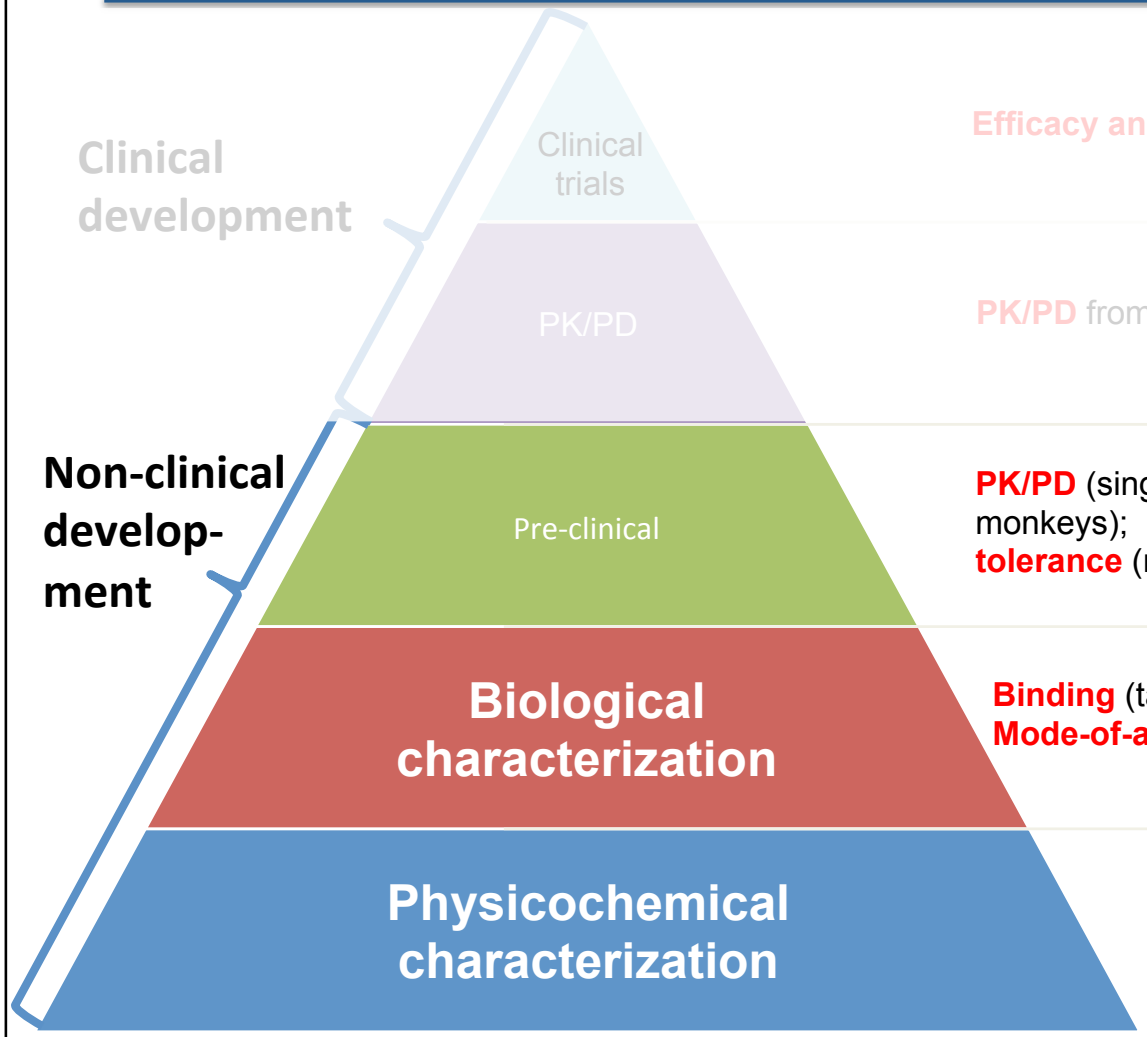
CELLTRION

CT-P10
Registered by EMA

SANDOZ
a Novartis company

GP2013
Being assessed by EMA

GP2013 development program



Efficacy and safety from two indications: RA & FL

PK/PD from two indications: RA & FL

PK/PD (single dose in monkeys); **toxicity** (repeat dose in monkeys); **Efficacy** (xenograft tumor models in SCID mice); Local **tolerance** (rabbits); **Tissue cross reactivity**, **ADCC** (in vitro)

Binding (target binding, receptor binding)
Mode-of-action (programmed cell death, CDC, ADCC)

Primary structure, higher order structure, size, **heterogeneity** (C-and N-terminal),**post-translational modifications** (variants glycosylation, glycation, oxidation, deamidation). **Purity**, **Aggregates**

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; FL, follicular lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency

Functional characterization:

Surface plasmon resonance Fc-receptor binding assays

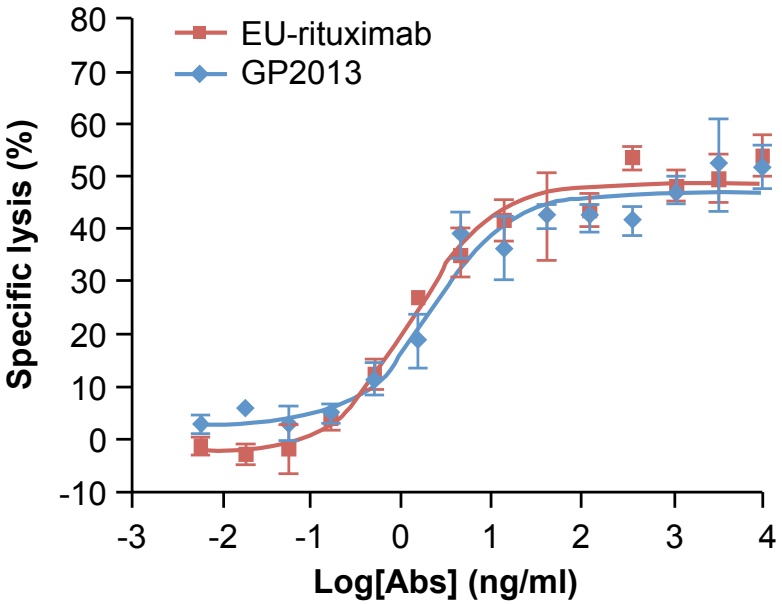
	Reference K_D	GP2013 K_D
FcRn	0.55–0.58 μM	0.54–0.58 μM
$Fc_\gamma RIa$	10.4–11.8 nM	10.9–12.4 nM
$Fc_\gamma RIIa$	2.4–2.7 μM	2.4–2.7 μM
$Fc_\gamma RIIb$	11.4–12.8 μM	11.0–12.7 μM
$Fc_\gamma RIIIa$ F158	7.4–10.3 μM	8.5–10.9 μM
$Fc_\gamma RIIIa$ V158	3.5–4.9 μM	4.2–5.0 μM
$Fc_\gamma RIIIb$	9.2–11.7 μM	9.9–12.4 μM

Rituximab biosimilar (GP2013) is functionally indistinguishable from its reference product

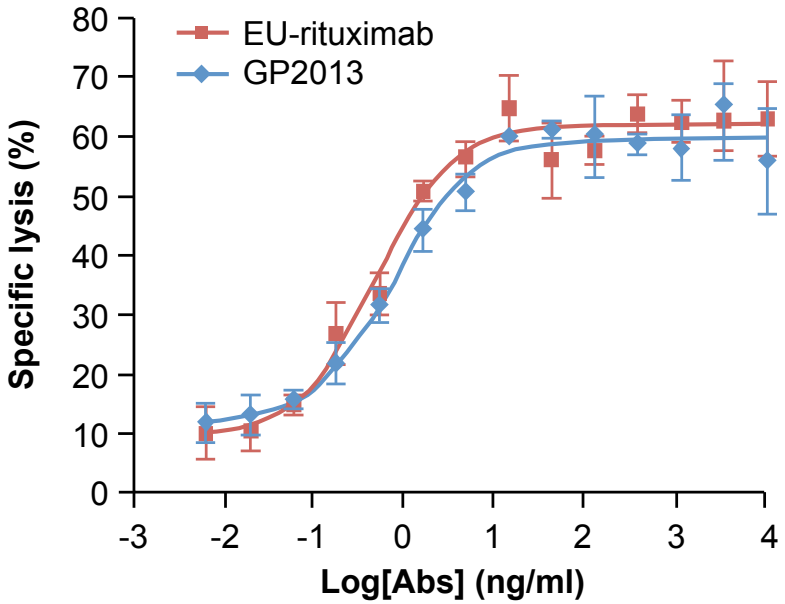
Visser et al. BioDrugs 2013;27:495–507

Pre-clinical *in vitro* comparability: ADCC assays with fresh NK cells

Daudi cell line & fresh effector cells



SU-DHL4 & fresh effector cells



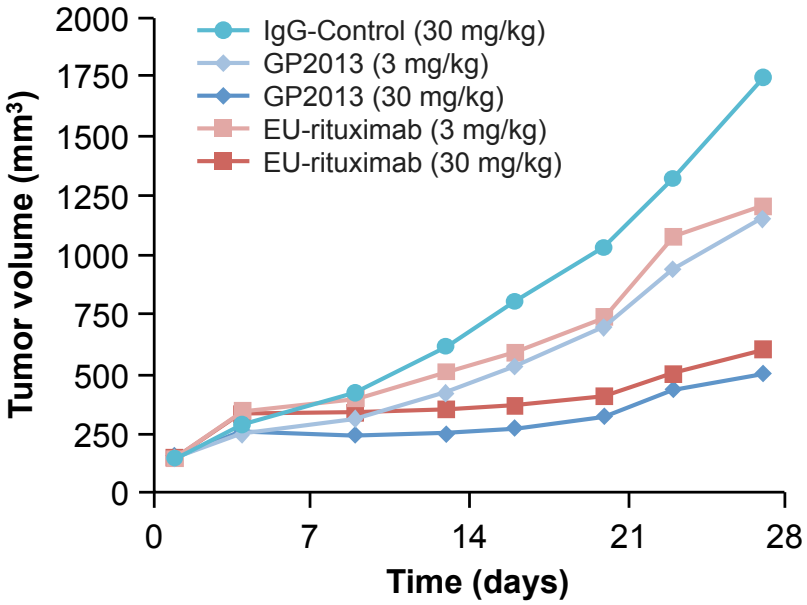
Further cell lines tested: Raji, Z138

ADCC comparable to EU-sourced reference rituximab

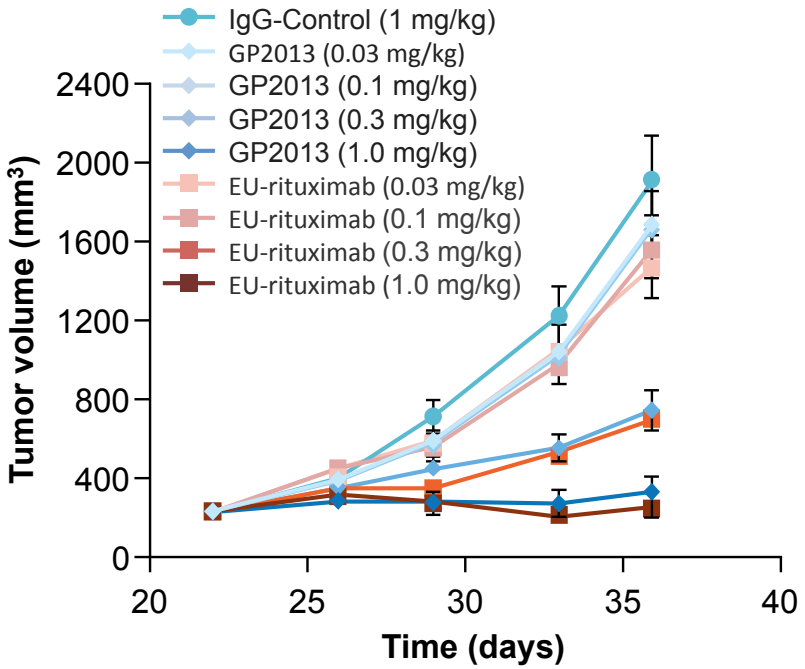
da Silva et al. Leuk Lymphoma 2014;55:1609–17.

Pre-clinical *in vivo* comparability (tumor growth): two models for NHL

SU-DHL-4 model



Jeko-1 model



Efficacy is similar

da Silva et al. Leuk Lymphoma 2014;55:1609–17.

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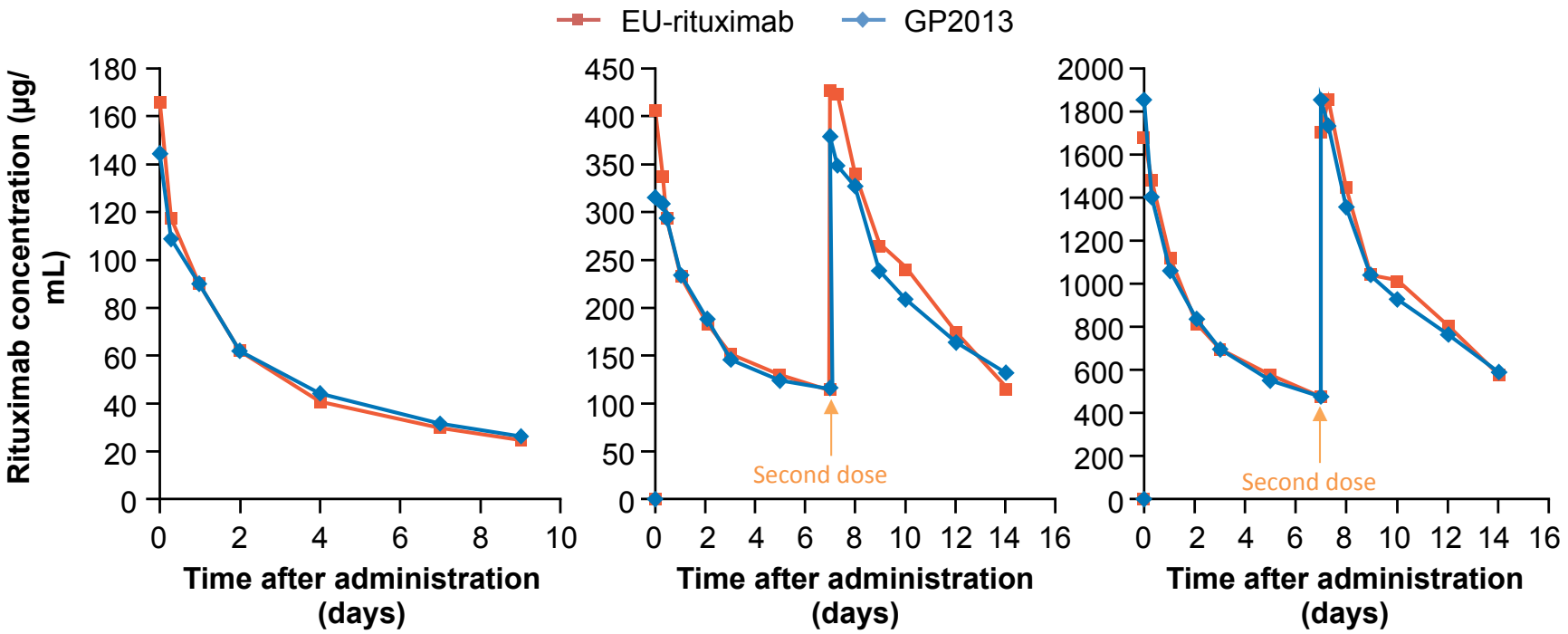
Pre-clinical *in vivo* comparability: PK following IV administration to primates

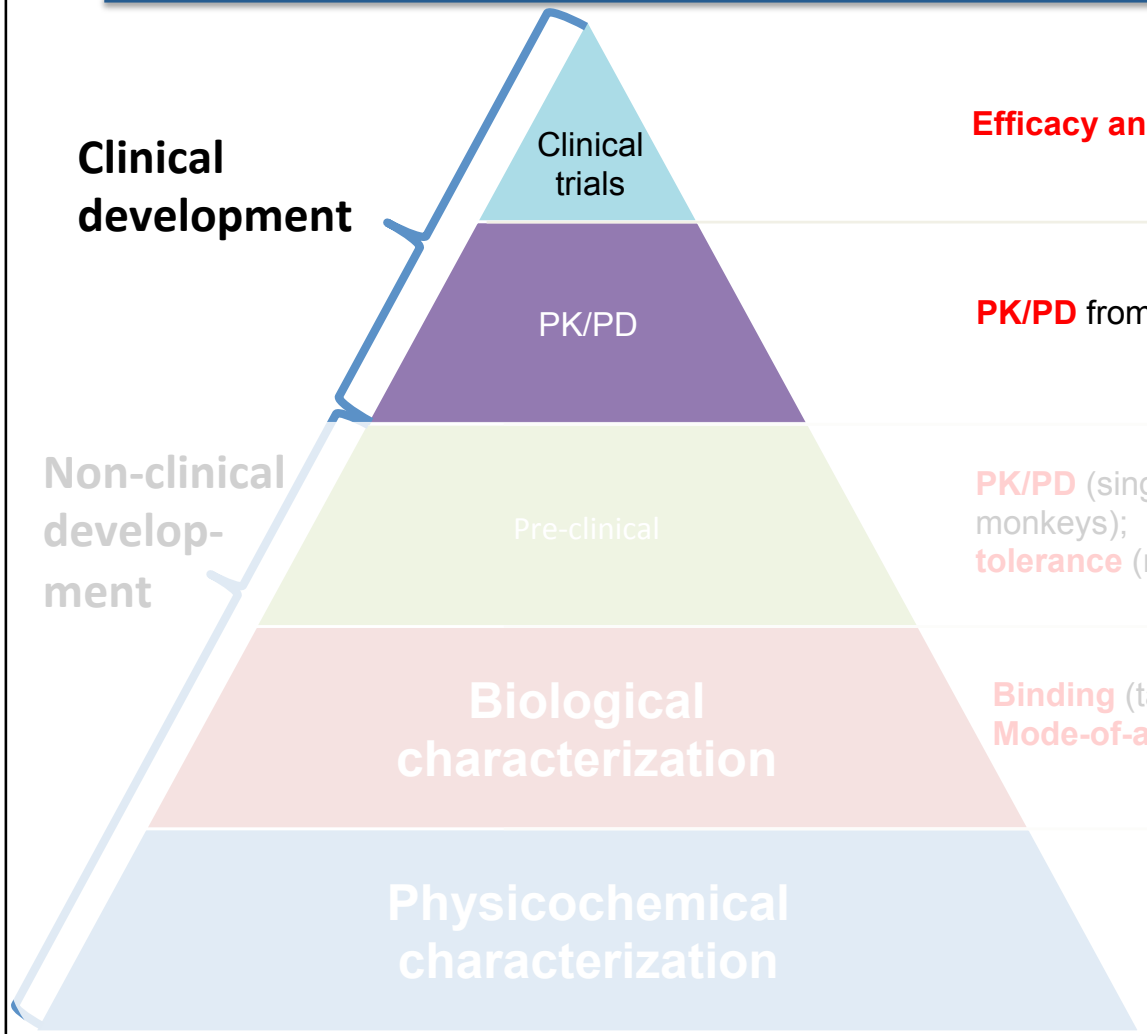
5 mg/kg	20 mg/kg, repeat dosing	100 mg/kg , repeat dosing



PK: AUC and C_{max} are similar

da Silva et al. Leuk Lymphoma 2014;55:1609–17.

GP2013 and CT-P10 development program



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ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; FL, follicular lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency

Key considerations for Phase III trial designs

	Originator	Biosimilar
Patient population	Any	Sensitive and homogeneous
Clinical design	**Superiority versus standard of care**	**Comparative versus innovator** (therapeutic equivalence studies)
Study endpoints	Clinical outcomes data (**OS & PFS**) or accepted/established surrogates	**Pharmacokinetic and Pharmacodynamic** markers; objective **response rate (RR)**
Safety	**Acceptable risk/benefit profile** versus standard of care	**Similar safety profile** to innovator
Immunogenicity	**Acceptable risk/benefit profile** versus standard of care	**Similar immunogenicity profile** to innovator
Extrapolation	**Not allowed**	**Possible** if justified

prIME Podcast Series 2013: A Focus on Biosimilar Antibodies, Reference Slidk [online]. Available at: https://www.youtube.com/watch?v=VwNWUzyuJuw [Accessed 2016 March 22].

GP2013 clinical development

SANDOZ A Novartis Division

RA refractory or intolerant of standard DMARDS and anti-TNFs

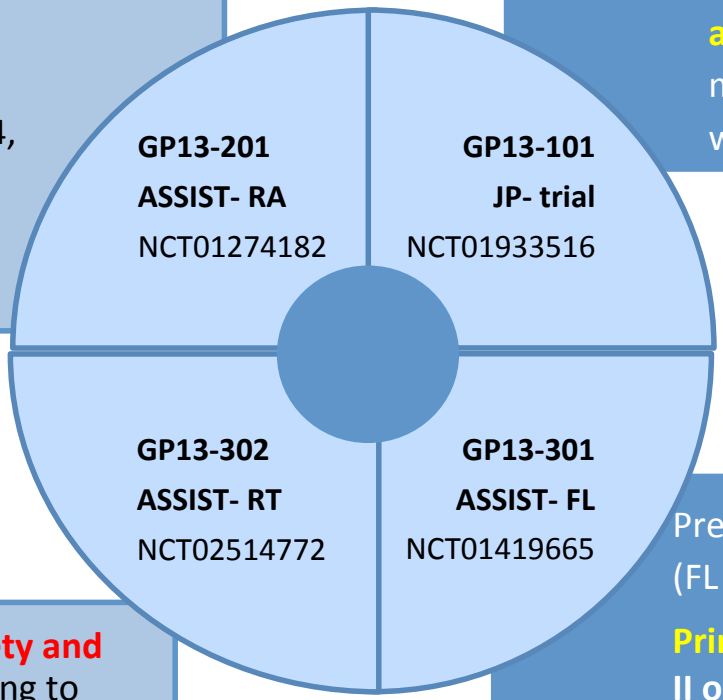
Primary objective: PK

II objectives: DAS28 at week 24, PK/PD,safety

EU-sourced rit **(N=173 pts)**
US-sourced rit **(N=139 pts)**

RA trials

Clinical trial assessing the **safety and immunogenicity** of transitioning to GP2013 treatment in patients with RA who received at least one prior dose of Rituximab[4]



Clinical trial assessing the **safety and PK of GP2013** weekly monotherapy in Japanese patients with iNHL[1] **(N=6)**

Oncology trials

Previously untreated, advanced-stage (FL 8 x RCVP + 2 years maint.)

Primary objective: ORR at week 24

II objectives: CR/PR, PFS, OS, PK/PD, safety

(N=629)

Total Safety Data: about 1000 pts (500 in GP2013), Efficacy data: 312 (RA)+ 629 (FL)

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CT-P10 Clinical Overall Program♪

Study	Indication	Primary Endpoint	Sample size♪	Status♪
1.1 **1.3** (1.1 Extension Study)	RA	**PK equivalence** Long term safety and efficacy	154 58	Completed
3.2	RA	▪ Part 1: **PK equivalence** ▪ Part 2: **Therapeutic equivalence♪**	372	Study Ongoing Week 48 results available
3.3	AFL	▪ Part 1: **PK equivalence** ▪ Part 2: **Therapeutic non-inferiority♪**	140♪	Study Ongoing Week 24 results available
3.4	LTBFL	**Therapeutic equivalence**	174**	**Recruiting**

Safety Data: 650 (325 in CT-P10), Efficacy data: 372 (RA)+ 140 (FL)

ASSIST-RA : study design

Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

PART 1:

	24 weeks	1 year	Max. 1.5 years
R → 1:1	GP2013 1000 mg IV days 1 and 15 (n=86)	Follow-up + 2nd course if needed	Follow-up of 2nd course
R → 1:1	MabThera® 1000 mg IV days 1 and 15 (n=87)	Follow-up + 2nd course if needed	Follow-up of 2nd course

Week 24 first interpretable results → report for EMA submission

24-week analysis

Part 1: final analysis

PART 2:

	24 weeks	1 year	Max. 1.5 years
R → 1:2	GP2013 1000 mg IV days 1 and 15 (n=42)	Follow-up + 2nd course if needed	Follow-up of 2nd course
R → 1:2	Rituxan® 1000 mg IV days 1 and 15 (n=82)	Follow-up + 2nd course if needed	Follow-up of 2nd course

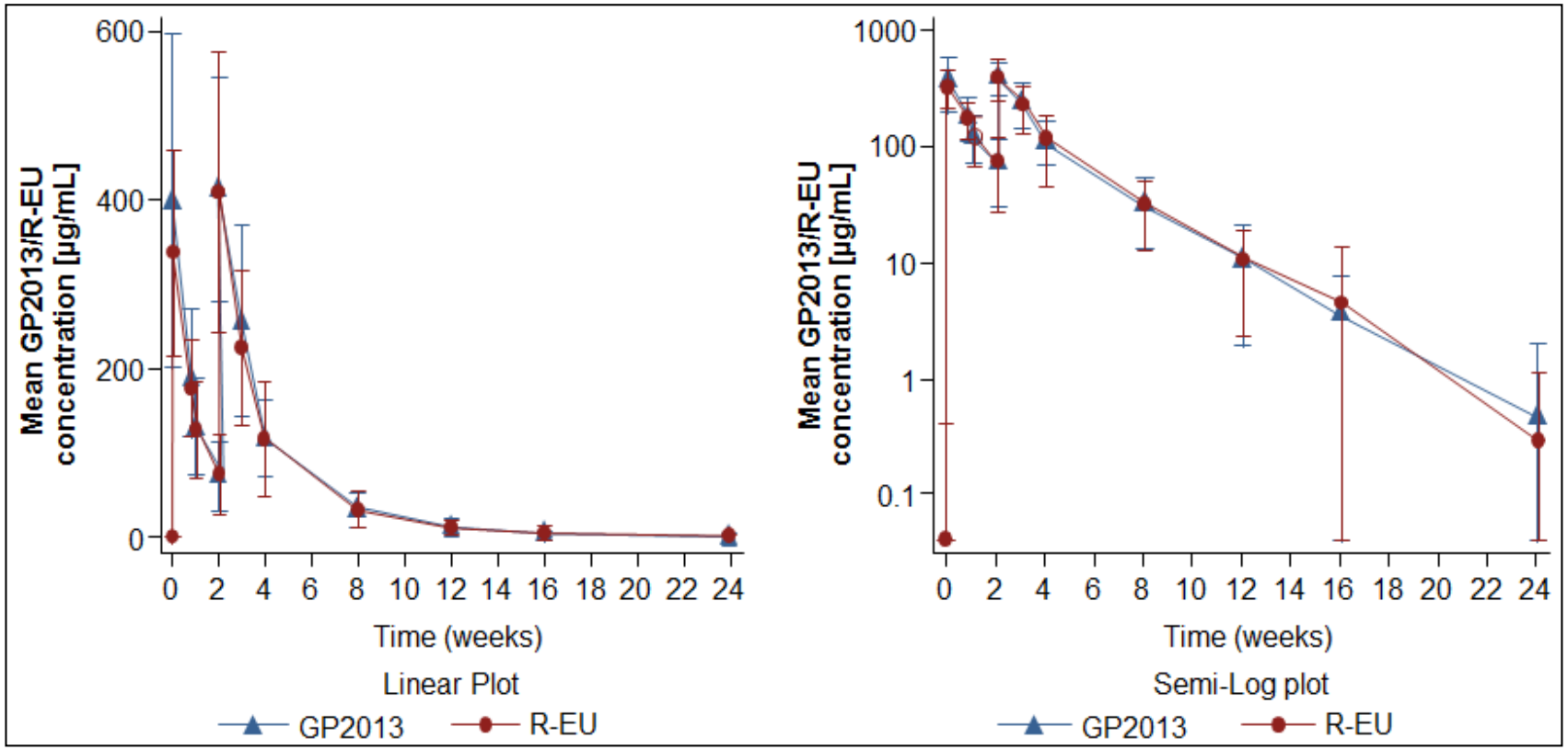
Week 24 first interpretable results → report for FDA submission

CT-P10 3.2 RA
is literally identical, in therms of study design and pts numbers

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

Pharmacokinetics - ($AUC_{(0\text{-}inf)}$)- (PAS)

Arithmetic mean (SD) serum PK concentration-time profile over 24 weeks by treatment (PK analysis set*)



Serum concentration-time profiles for the two treatments were similar up to week 24

$AUC_{(0\text{-}inf)}$, The area under the concentration-time curve from time zero to infinity; FAS, full analysis set; PK, pharmacokinetics; SD, standard deviation
*The PK analysis set was a subset of the FAS and consisted of patients who did not have any major protocol deviations

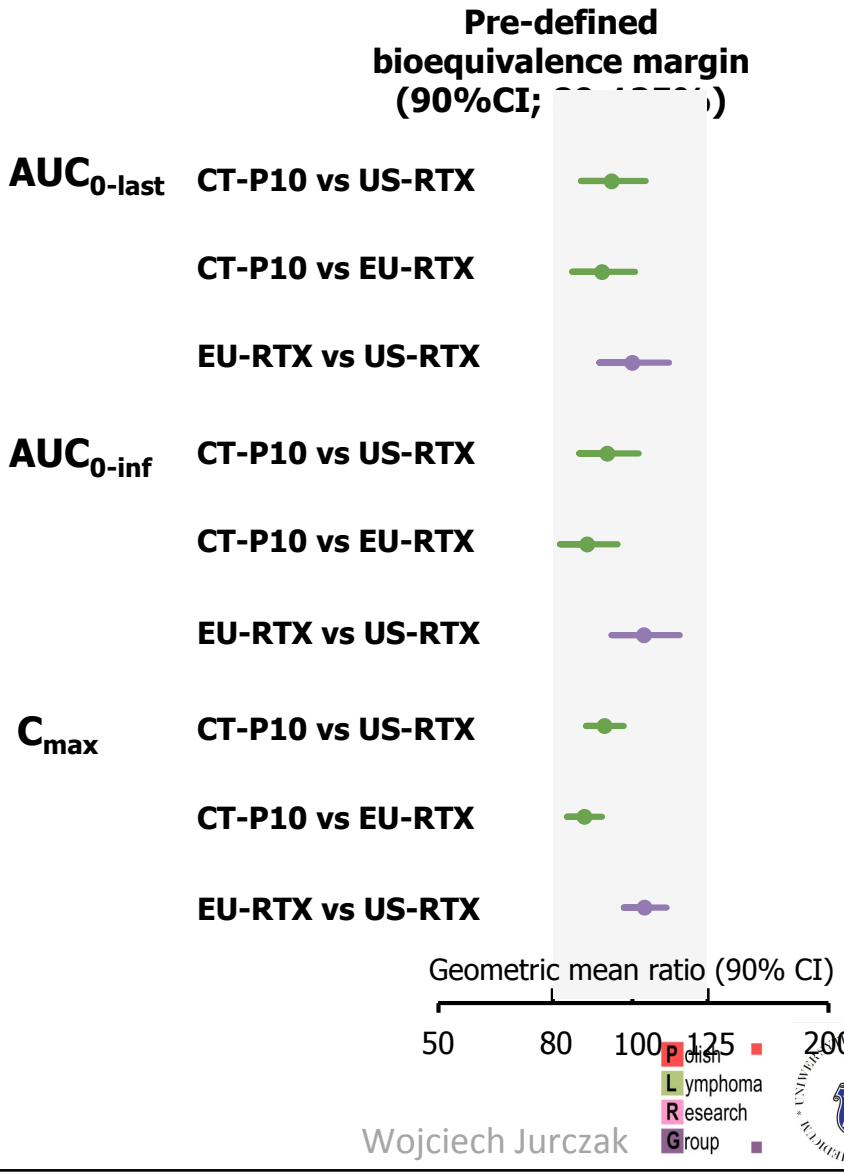
Smolen J et al., EULAR congress, 8-11 June, London UK: FRI0222

CT-P10 3.2 RA

Pharmacokinetics

Parameters (Unit)	Geometric Mean		
	CT-P10	US-RTX	EU-RTX
$AUC_{0\text{-last}}$ [1] (h*µg/mL)	162415	167309	172451
$AUC_{0\text{-inf}}$ [2] (h*µg/mL)	162377	169481	180638
C_{max} [3] (µg/mL)	367	387	412

[1] CT-P10 (n=62), US-RTX (n=60), EU-RTX (n=59)
[2] CT-P10 (n=59), US-RTX (n=60), EU-RTX (n=56)
[3] CT-P10 (n=62), US-RTX (n=59), EU-RTX (n=59)

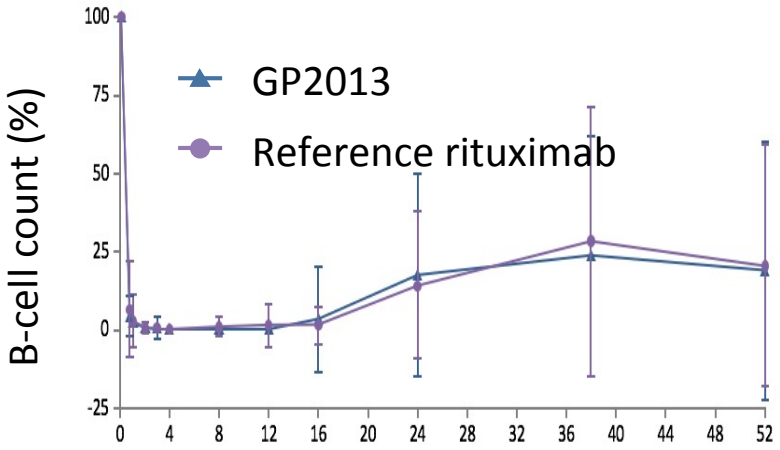


Pharmacodynamics - periph. B cell depletion

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

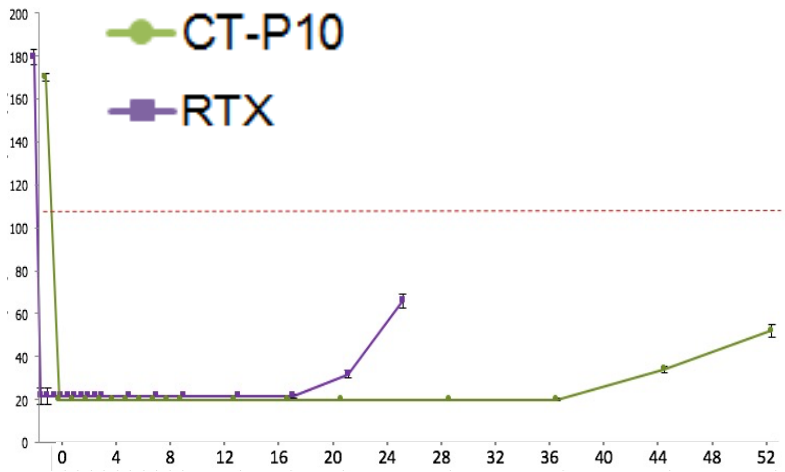
CT-P10 3.2 RA

Geometric mean ratio in $AUEC_{0-14d}$
1.019 (95% CI: 0.997, 1.042)



Time (weeks) GP2013

Median (±SE) B-cell Kinetics (cells/µL)

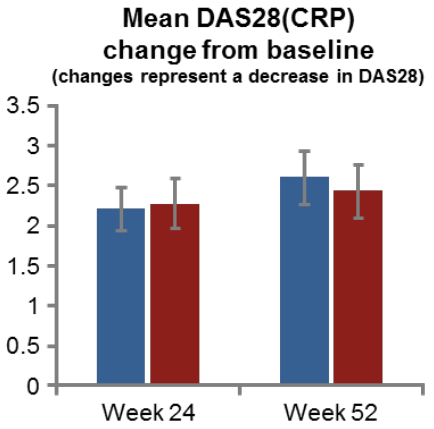


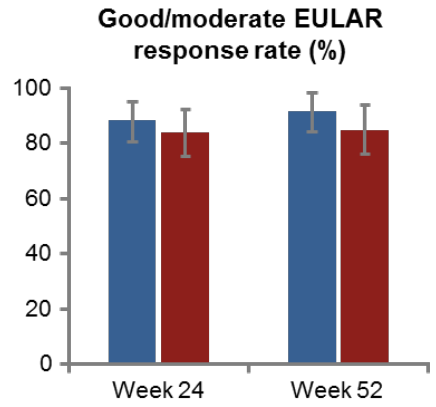
Time (weeks) CT-P10

Efficacy DAS (Disease Activity Score)

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

CT-P10 3.2 RA





GP2013

Reference rituximab

Parameters TreMedian (±SE) B-cell Kinetics (cells/µL)	n	Adjusted Mean (SE)	Estimate of Treatment Difference (95% CI)
DAS28 (CRP) – Efficacy Primary endpoint			
CT-P10	139	-2.14 (0.177)	
US/EU-RTX	196	-2.09 (0.176)	-0.29 -0.05 0.20
DAS28 (ESR)			
CT-P10	140	-2.41 (0.182)	
US/EU-RTX	196	-2.35 (0.182)	-0.31 -0.06 0.19

-0.6 -0.3 0 0.3 0.6

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

Safety profiles of GP2013 and reference rituximab

n (%)	GP2013 (n=86)	Rituximab reference (n=87)
Deaths	1 (1.16)	0 (0.0)
Other non-fatal SAEs	10 (11.63)	14 (16.09)
Leading to discontinuation	2 (2.33)	4 (4.60)
Any AE	56 (65.1)	57 (65.5)
Leading to study drug discontinuation	2 (2.33)	3 (3.45)
AEs by most frequent SOCs		
Infections and infestations	27 (31.4)	31 (35.6)
Musculoskeletal	16 (18.6)	14 (16.1)
Gastrointestinal disorders	13 (15.1)	15 (17.2)
General disorders	12 (14.0)	9 (10.3)
Skin and subcut. tissue	9 (10.5)	11 (12.6)
Injury and poisoning	9 (10.5)	11 (12.6)
Resp., thoracic, mediastinal	7 (8.1)	12 (13.8)
Vascular disorders	7 (8.1)	10 (11.5)
Nervous system disorders	7 (8.1)	10 (11.5)
Potential infusion related reaction	32 (37.2)	37 (42.5)

CT-P10 3.2 RA Safety profiles of CTP-10 and reference rituximab

Events, n (%)	CT-P10 (N=161)	US-RTX (N=151)	EU-RTX (N=60)	RTX (N=211)
AE	122 (75.8)	96 (63.6)	37 (61.7)	133 (63.0)
- Related	73 (45.3)	47 (31.1)	25 (41.7)	72 (34.1)
SAE	13 (8.1)	14 (9.3)	2 (3.3)	16 (7.6)
- Related	0	5 (3.3)	1 (1.7)	6 (2.8)
Infection	61 (37.9)	53 (35.1)	17 (28.3)	70 (33.2)
- Related	27 (16.8)	25 (16.6)	6 (10.0)	31 (14.7)
IRR	33 (20.5)	12 (7.9)	13 (21.7)	25 (11.8)
Malignancy	0	2 (1.3)	1 (1.7)	3 (1.4)
Discontinuation due to AEs	3 (1.9)	7 (4.6)	2 (3.3)	9 (4.3)
- Related	2 (1.2)	5 (3.3)	1 (1.7)	6 (2.8)

ASSIST-FL
Clinical Trial Assessing the Efficacy and Safety of a Rituximab Biosimilar Treatment

CT-P10 3.3 AFL

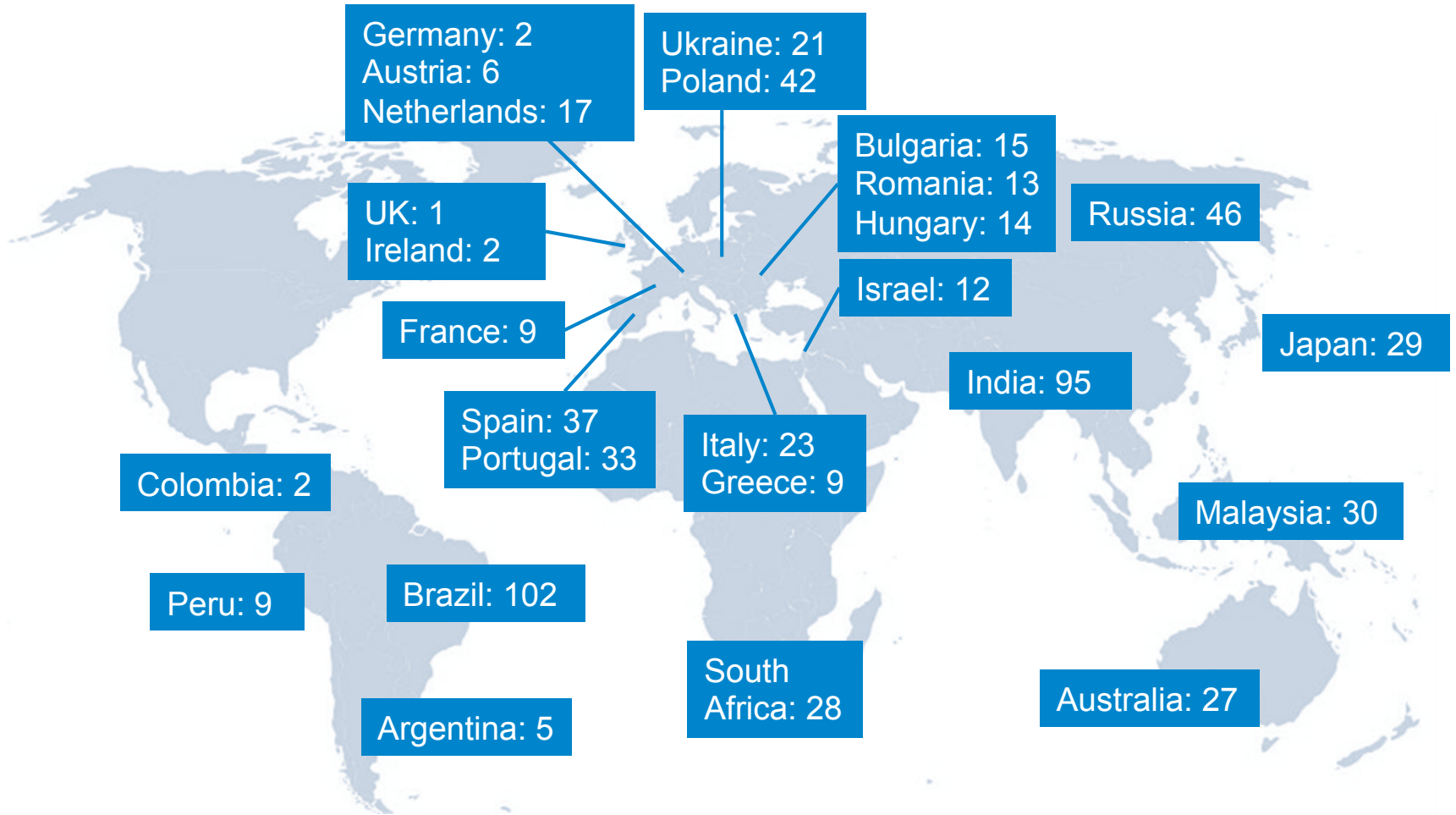
: study rationale

- **Designed to confirm non-inferior clinical effectiveness**
- **Follicular lymphoma** was chosen as the most appropriate indication as the disease **has a more homogeneous nature** amongst the approved oncology indications of rituximab
- Further, the combination **R-CVP was considered the most sensitive treatment option**, as rituximab had shown the largest additive treatment effect to a chemotherapy backbone treatment in the combination with CVP

Jurczak W, et al. Abstract 1809 presented at the 58th ASH San Diego, USA, 3–6 December 2016.
Coiffier B ,et al Abstract 1807presented at the 58th ASH, San Diego, USA, 3–6 December 2016.

ASSIST-FL (GP13-301): 629 randomized pts in 22 countries

Clinical Trial Assessing the Efficacy and Safety of a Rituximab Biosimilar Treatment



Jurczak W, et al. Abstract 1809 presented at the 58th ASH San Diego, USA, 3–6 December 2016.

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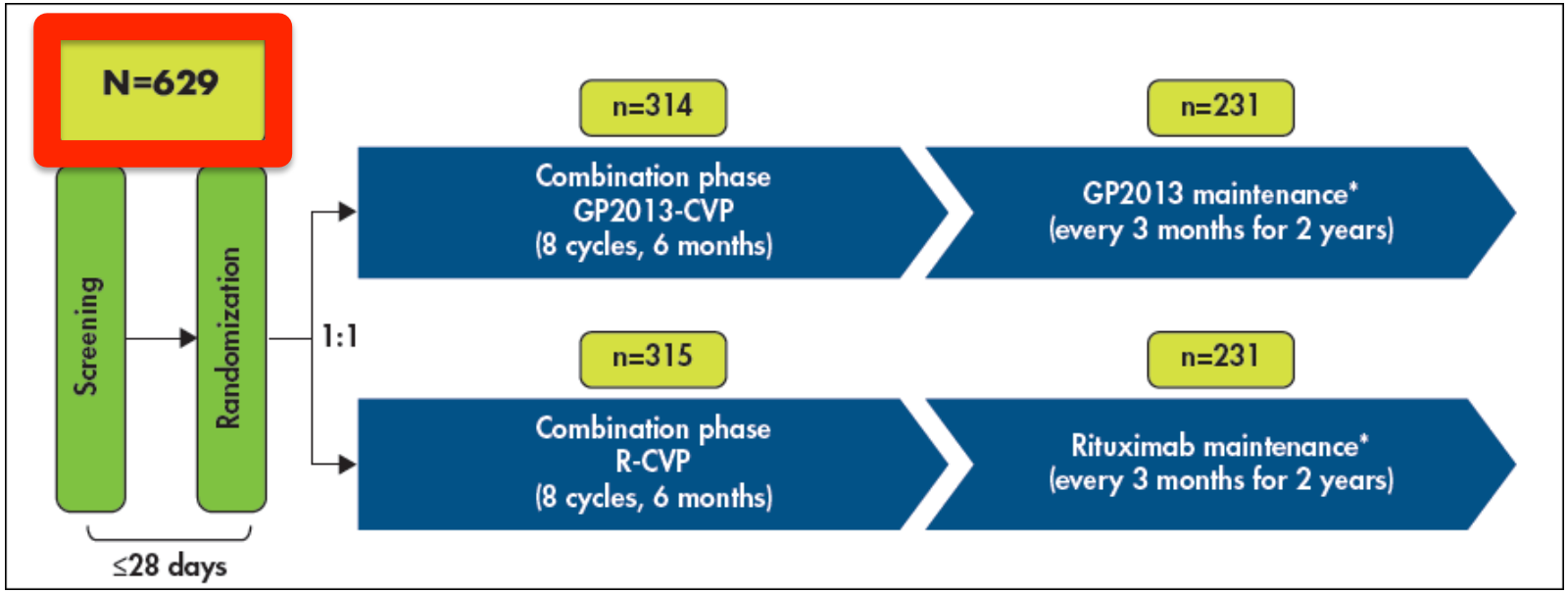
ASSIST-FL Study design

Clinical Trial Assessing the Efficacy and Safety of a Rituximab Biosimilar Treatment

- The study consisted of a combination treatment phase over 6 months and a maintenance treatment phase over 2 years



GP-2013 (375 mg/m^2) + cyclophosphamide (750 mg/m^2 IV D1) + vincristine (1.4 mg/m^2 D1) + prednisone (100 mg p.o. D1–D5)
Rituximab (375 mg/m^2) + cyclophosphamide (750 mg/m^2 IV D1) + vincristine (1.4 mg/m^2 D1) + prednisone (100 mg p.o. D1–D5)

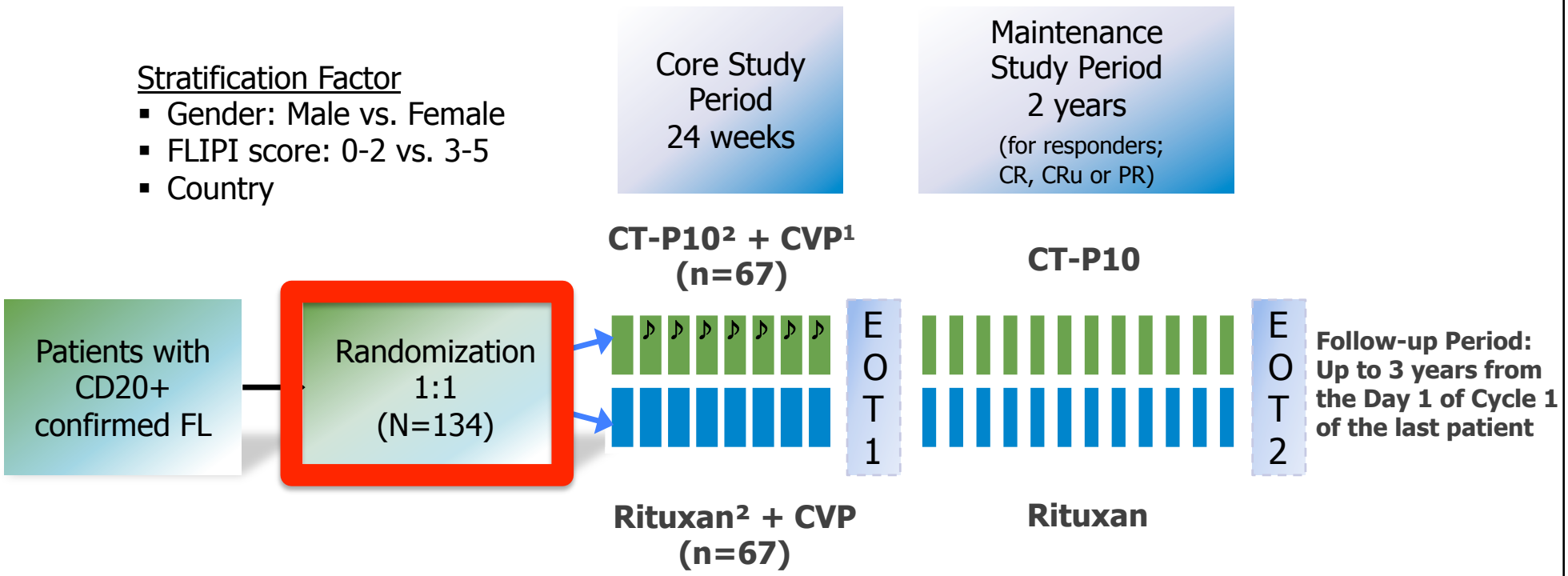
**For responders (partial or complete response) treated with GP2013-CVP or Rituximab-CVP, according to the original treatment assignment*

Jurczak W, et al. Abstract 1809 presented at the 58th ASH San Diego, USA, 3–6 December 2016.

CT-P10 3.2 RA

Study design

Stratification Factor
- Gender: Male vs. Female
- FLIPI score: 0-2 vs. 3-5
- Country



1. CVP: Cyclophosphamide 750 mg/m², Vincristine 1.4 mg/m² [max 2mg], Prednisone or prednisolone 40 mg/m²
2. Rituximab: 375 mg/m² (Core study: 3-weekly, Maintenance study: every 2 months)

Abbreviations: FL, Follicular Lymphoma; EOT, End of Treatment; FLIPI, Follicular Lymphoma International Prognostic Index

Coiffier B ,et al Abstract 1807presented at the 58th ASH, San Diego, USA, 3–6 December 2016.

ASSIST-FL
Clinical Trial Assessing the Efficacy and Safety of a Rituximab Biosimilar Treatment

Study assessments

Efficacy	Safety (secondary endpoints)	PK/PD (secondary endpoints)

• **Efficacy assessments:**
  • **primary endpoint:**
  • **Overall response rate (ORR)**
  • **Secondary endpoints:**
  • Complete response (CR)
  • Partial response (PR)
  • Progression free survival (PFS)
  • Overall survival (OS)
	• **Safety assessments:** AEs, SAEs, with their severity and relationship to study drug, pregnancies, monitoring of hematology, blood chemistry and urine, vital signs, performance status, ECG, and body weight
	• **Immunogenicity:** ADA formation
		• **PK:** C_{max}, C_{trough}, $AUC_{(0-t)}$, and AUC_{all}
		• **PD:** peripheral CD19+ B cell counts (absolute and relative to baseline) and $AUEC_{(0-21d)}$ in Cycle 1

CT-P10 3.3 AFL
PK being the primary target, ORR the secondary target

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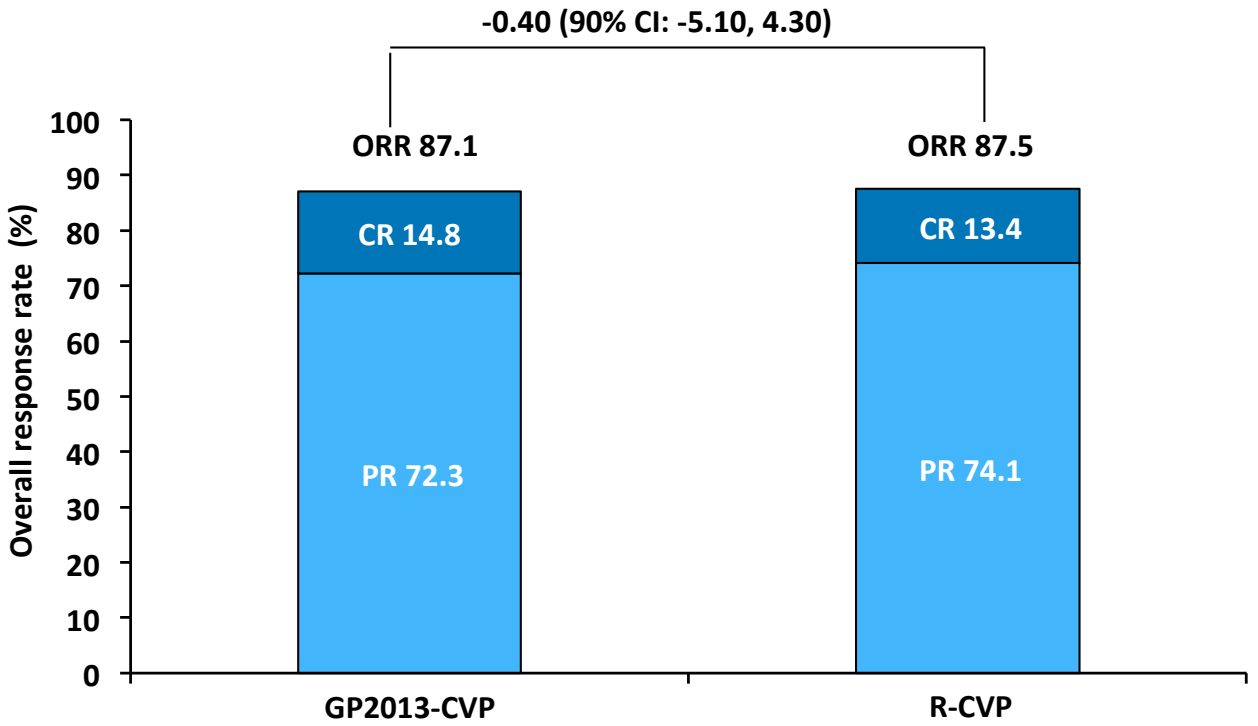
Efficacy results (ORR) – primary endpoint



The study met its primary objective showing equivalence of ORR between GP2013 and Rituximab in the PPS* and FAS# population

Jurczak W, et al. Abstract 1809 presented at the 58th ASH San Diego, USA, 3–6 December 2016.

Polish Lymphoma Research Group

CT-P10 3.2 RA

Efficacy results (ORR) – secondary endpoint

ITT Population		
Response	**CT-P10 (N=70)**	**Rituxan (N=70)**
ORR[1]	**67 (95.7%)**	**63 (90.0%)**
CR	21 (30.0%)	15 (21.4%)
CRu	6 (8.6%)	8 (11.4%)
PR	40 (57.1%)	40 (57.1%)

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Pharmakocinetics

ASSIST-FL
Clinical Trial Assessing the Efficacy and Safety of a Rituximab Biosimilar Treatment

CT-P10 3.2 RA

Sampling time Point	PK parameter	GP2013-CVP N=119	Rituximab-CVP N=120
Cohort 1 Cycle 4 assessment Day 1	C_{max} (mcg/mL) mean (SD)	356.03 (121.61)	350.99 (116.79)
	Geometric mean ratio (90% CI)	1.00 (0.925; 1.09)	
	C_{trough} (mcg/mL) mean (SD)	66.42 (47.59)	82.13 (61.52)
Sampling time Point	**PK parameter**	**GP2013-CVP N=27**	**Rituximab-CVP N=22**
Cohort 2 Cycle 4 assessment	$AUC_{(0\text{-}21d)}$ (mcg*day/mL) mean (SD)	3320 (872)	3500 (1020)
	Geometric mean	3210	3340
	AUC_{all} (mcg*day/mL) mean (SD)	2820 (1250)	2950 (1510)
	Geometric mean	2510	2310

Para-meter	Treat-ment	N	Geometric LS Mean	Ratio (%) of Geometric LS Means (90 % CI)
AUC_{tau} (h*µg/mL)	CT-P10	50	41002	102 (94 - 111)
	Rituxan	56	40099	
$C_{max, ss}$ (µg/mL)	CT-P10	53	256	101 (94 - 108)
	Rituxan	56	254	

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Immunogenicity: ADA (anti drug antibodies)

ASSIST-FL Clinical Trial Assessing the Efficacy and Safety of a Rituximab Biosimilar Treatment	ADA frequency Combination phase n (%)	ADA frequency Maintenance phase n (%)	Overall n (%)
All Patients* (N=551)	7 (1.3)	1 (0.2)	8 (1.5)
GP2013 (N=268)	4 (1.5)	1 (0.4)	5 (1.9)
Rituximab (N=283)	3 (1.1)	0	3 (1.1)

CT-P10 3.2 RA	ADA frequency Combination phase n (%)	NAb
CT-P10 (N=70)	**3/70 (4.3)**	**2/70 (2.9)**
Rituximab (N=70)	**2/70 (2.9)**	**2/70 (2.9)**

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ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

Safety profiles of GP2013 and reference rituximab

Deccription	GP2013-CVP	R-CVP arm
AEs were reported in:	92.6%	91.4%
Discontinuation due to AE:	23 (7.4%)	22 (7.0%)
Serious AEs were reported in : **febrile neutropaenia:**	22.8% 4.8%	20.0% 2.9%
Deaths during comb. phase:	4 (1.3%)	7 (2.2%)
Deaths (data cutoff in July 2015): **deaths due to lymphoma:**	18 (5.8%) 8 (2.6%)	17 (5.4%) 6 (1.9%)

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CT-P10 3.2 RA Safety profiles of CT-P10 and reference rituximab

n (%)	CT-P10 (N=70)		Rituxan (N=70)	
	Total	Related[1]	Total	Related[1]
AE	58 (82.9)	37 (52.9)	56 (80.0)	34 (48.6)
SAE	16 (22.9)	6 (8.6)	9 (12.9)	4 (5.7)
Infection	22 (31.4)	6 (8.6)	26 (37.1)	9 (12.9)
IRR	16 (22.9)	15[2] (21.4)	17 (24.3)	17 (24.3)
Malignancy	0	0	1 (1.4)[3]	0
Discontinuation due to AEs	5 (7.1)	3 (4.3)	1 (1.4)	0
Death[4]	1 (1.4)	0	0	0

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ASSIST-FL
Clinical Trial Assessing the Efficacy and Safety of a Rituximab Biosimilar Treatment

CT-P10 3.2 RA

: summary

1. **ORR** with GP2013 and CT-P10 equivalent to reference rituximab
2. **PK (C_{max})** of GP2013 and CT-P10 equivalent to reference rituximab
3. Medians not yet reached for PFS and OS
4. **PD (B-cell depletion)** with GP2013 and CT-P10 equivalent to reference rituximab
5. **No clinical meaningful differences** between GP2013 and CT-P10 and reference rituximab in safety, tolerability or immunogenicity

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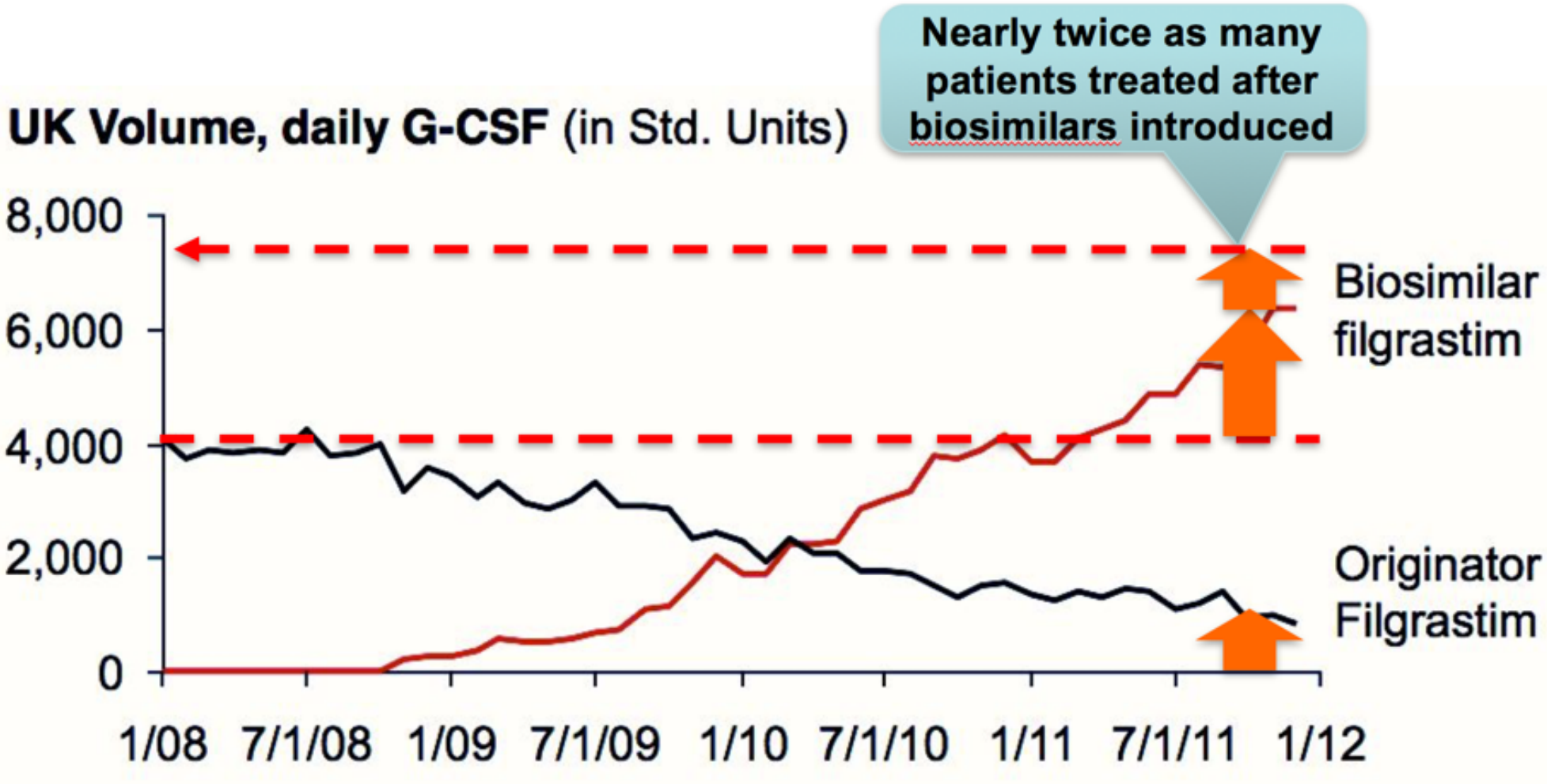
Once Biosimilar is approved it has substantial financial impact

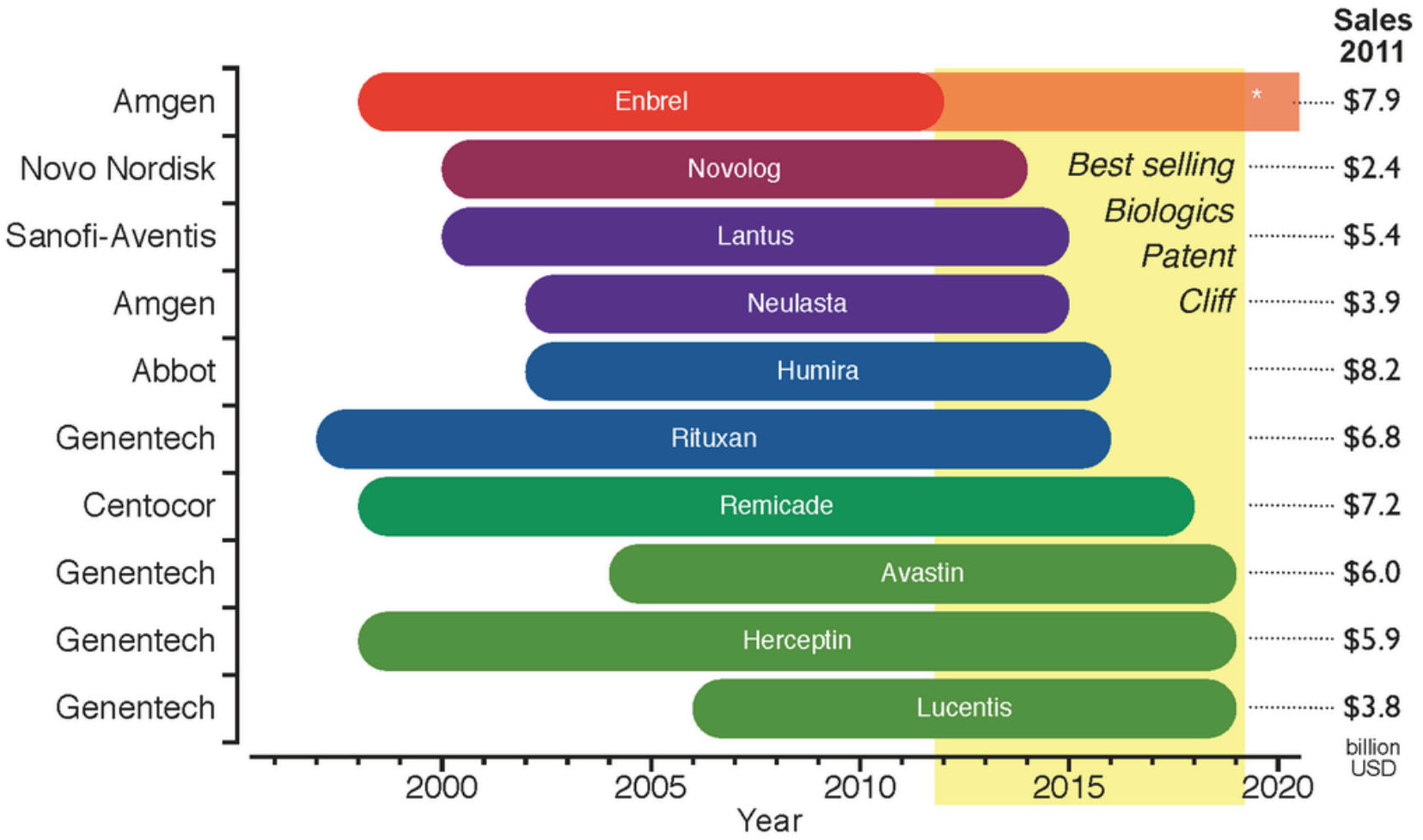
"Biosymilars – symilar but not identical"

After introducing G-CSF biosimilar it's usage doubled – UK example



Walsh K.: Biosimilar Medicines 11th EGA International Symposium, 2013

Biosimilars may be potentially developed for several inovative biologics in the next 10 years



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