Disclosures

Prof. Wojciech Jurczak, M.D., Ph.D.

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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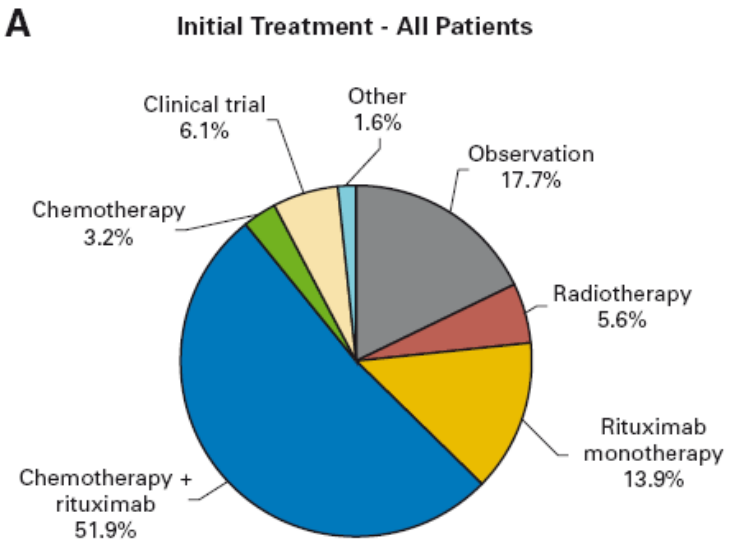
Polish Lymphoma Research Group

UNIWERSYTET JAGIELLOŃSKI COLLEGIUM MEDICUM

During the entire life, we may offer most of the patients 5-7 therapy lines ...

Chemotherapy without MoAb is not used as I line FL treatment

Clinical practice in US
FL, N= 2728, years 2004-2007



Friedberg, et al., JCO 2009

Immunochemotherapy - stadard of care in FL patients

Rituximab maintenance ?

- No OS benefit
- More AE (infections, secondary malignancies)
- Efficacy of Rituximab retreatment
- Cost effectivness

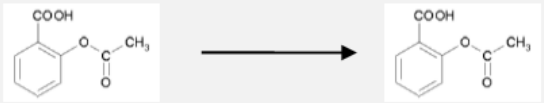
ASCO Annual '16 Meeting

Maintenance Rituximab

Small molecules vs Biologic drugs

Small molecule → **Generic**

i.e. Acetylsalicylic acid - 21 atoms



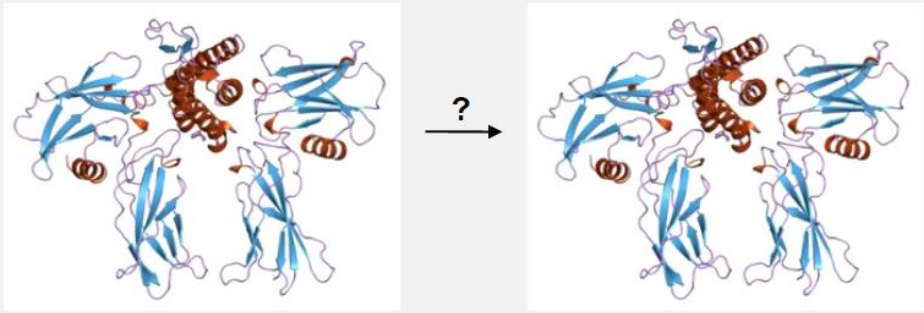
Original molecule **Generic**

- Usually manufactured using chemical synthesis
- Majority of pharmaceuticals in the market are small molecule drugs

- Has the same active ingredients and proven bio-equivalence as an original small-molecule drug

Biological drug → **Biosimilar**

i.e. IgG1 antibody > 20,000 atoms



Original protein **Biosimilar**

- Developed by genetically engineering methods
- Produced in cell lines

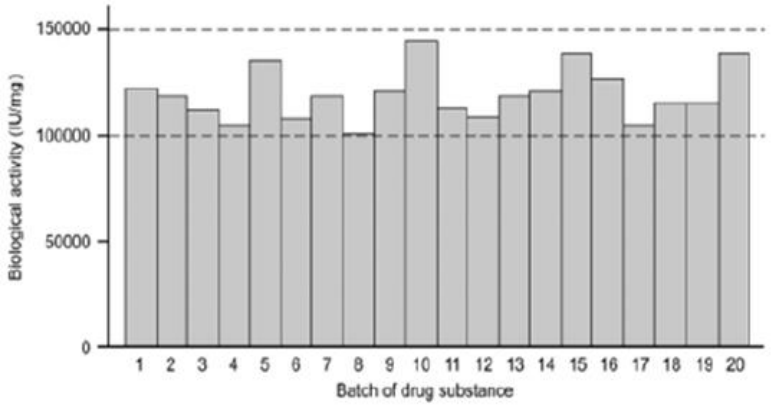
- As true replication of the existing protein drug cannot be established
- High level of similarity and comparable structure and efficacy to their branded reference product

Small molecules vs Biologic drugs

	Small molecule drugs	Biologic drugs
Drug production	• By chemical synthesis	• By genetically engineering methods, **produced in cell lines**
Product characterization	• Well characterized	• Difficult to characterize -- they tend to be produced as **diverse mixture of molecules** which are very slightly different from one another
Purification. contamination possibility	• Easy to purify • Contamination can be generally avoided, is easily detectable and often removable	• Lengthy and complex purification process • **High possibility of contamination**, detection is harder and removal is often impossible
Lab analysis	• Easily analyzed with routine lab tests	• Current physico-chemical analytical methods or bioassays **cannot detect all product variations**
Susceptibility to environmental or process changes	• Not affected by environmental changes or any changes in the steps of production process.	• **Highly susceptible to slightest changes in environment**, cell strains or the manufacturing process

Every Biologic varies from batch to batch

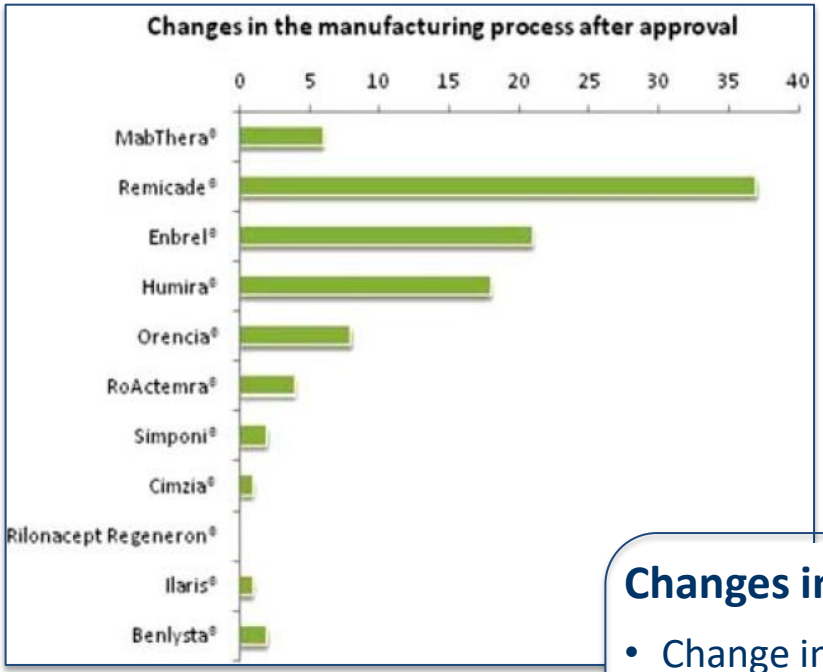
- „Non-identicality“ is a normal principle in biotechnology.
- No batch of any biological is „identical“ to the others



- 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

Bio-better / Bio-similar / Copy-biologic

Biologic drugs	Definition
Innovative biologic	**A novel biologic that has been patented**
Bio-better (biosuperior/ 2nd generation biologic)	An innovative biologic **drug that has been structurally and/or functionally altered** to achieve an improved or different clinical performance
Bio-similar	**A copy version of an already authorized innovative biological drug** with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise, and **approved through an official biosimilars pathway**
Copy-biologic	A copy of an innovative biologic that has been **approved in a country where no official biosimilar pathway exists**.

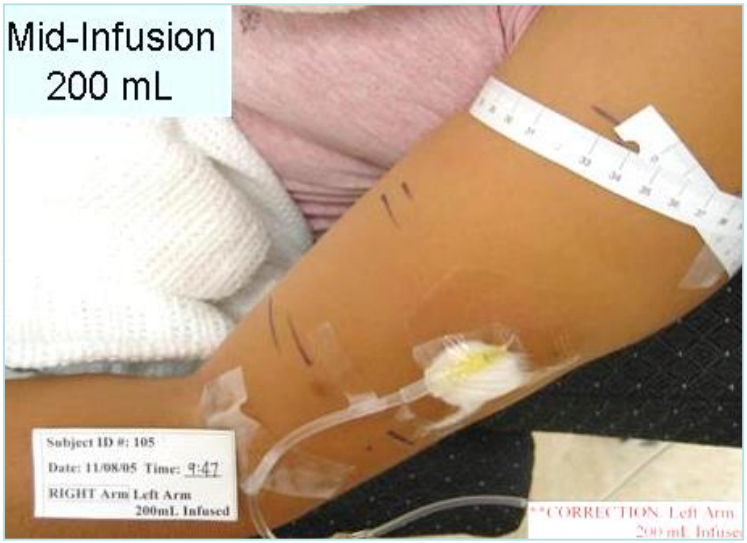
Biosimilar Medicinal Products Working Party, 2011

Bio-better (biosuperior/2nd generation biologic)

CAMPATH

MabCAMPATH

Bio-better (biosuperior/2nd generation biologic)



Rituximab i.v.

Rituximab s.c.

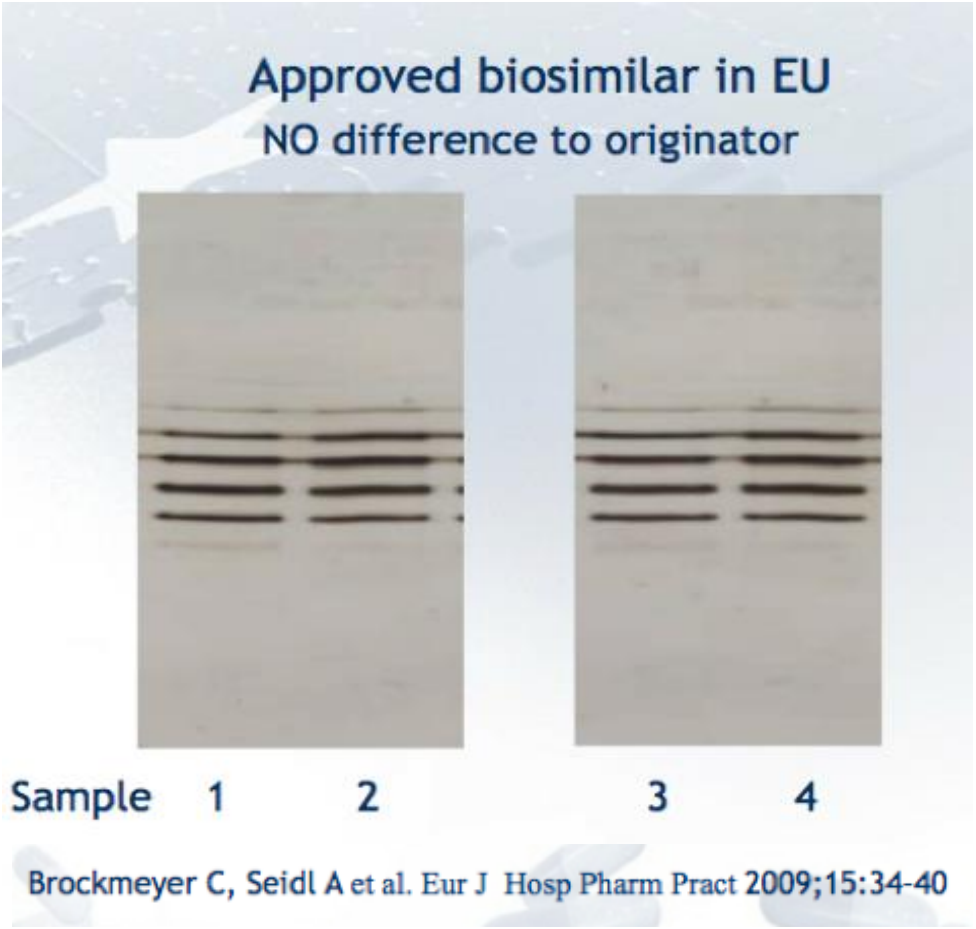
Bio-similar definitions

Source	Definition
WHO	**2 line definition**
EMA	**4 line definition**
FDA	**5 line definition**

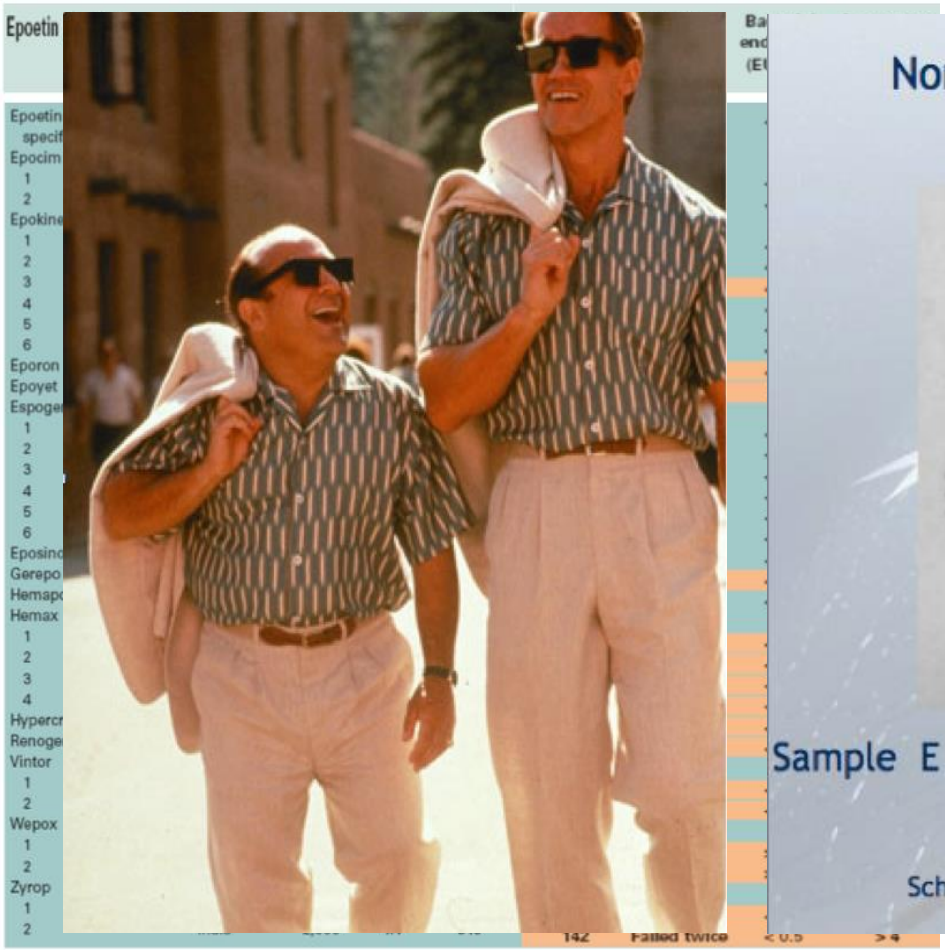
WHO - Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. [Online] October 23, 2009. [Cited: March 23, 2012.
EMA - European Medicines Agency. [Online] September 27, 2012. [Cited: October 1, 2012.] http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. . EMA/837805/2011.
FDA - Guidance for Industry: Quality considerations in demonstration biosimilarity to a reference protein product. Washington DC : U.S. Food and Drug Administration, 2012.

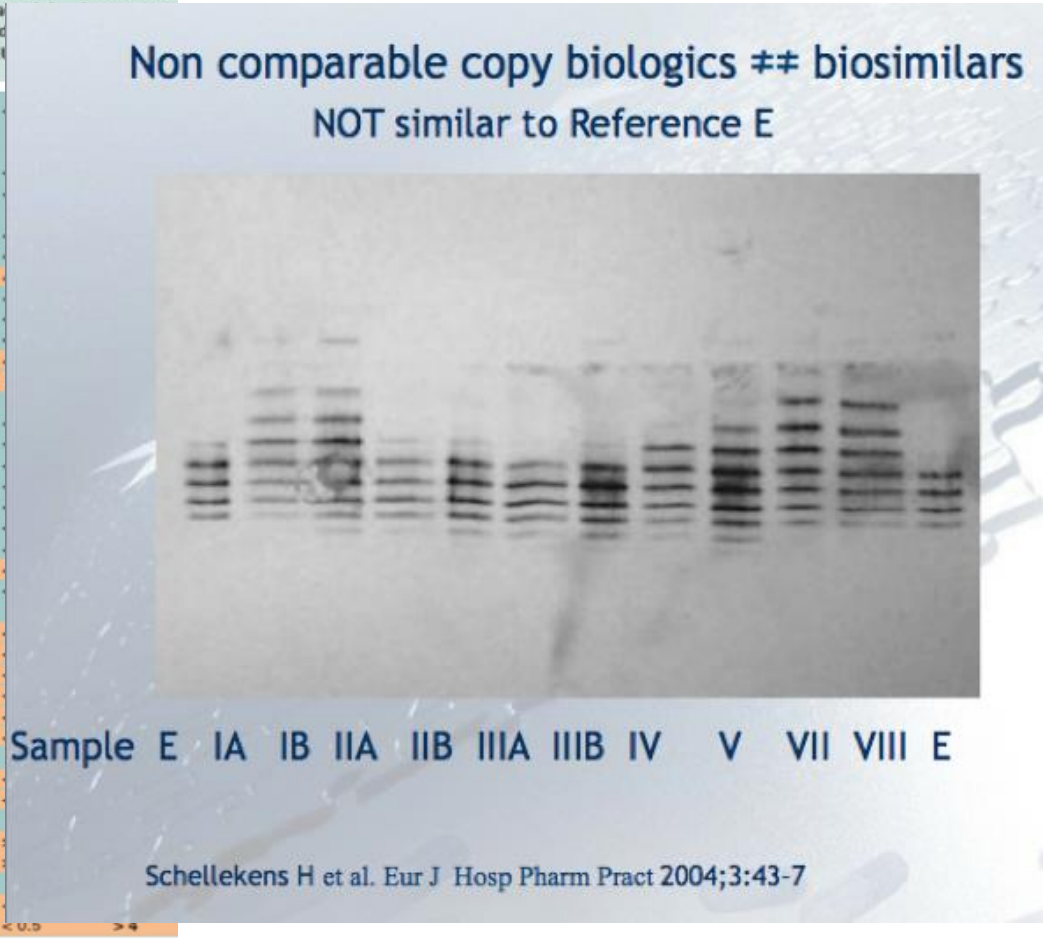
Biosymilars & „Copy biologic”

Biosimilars – approved by EMA / FDA



Copy-biologic





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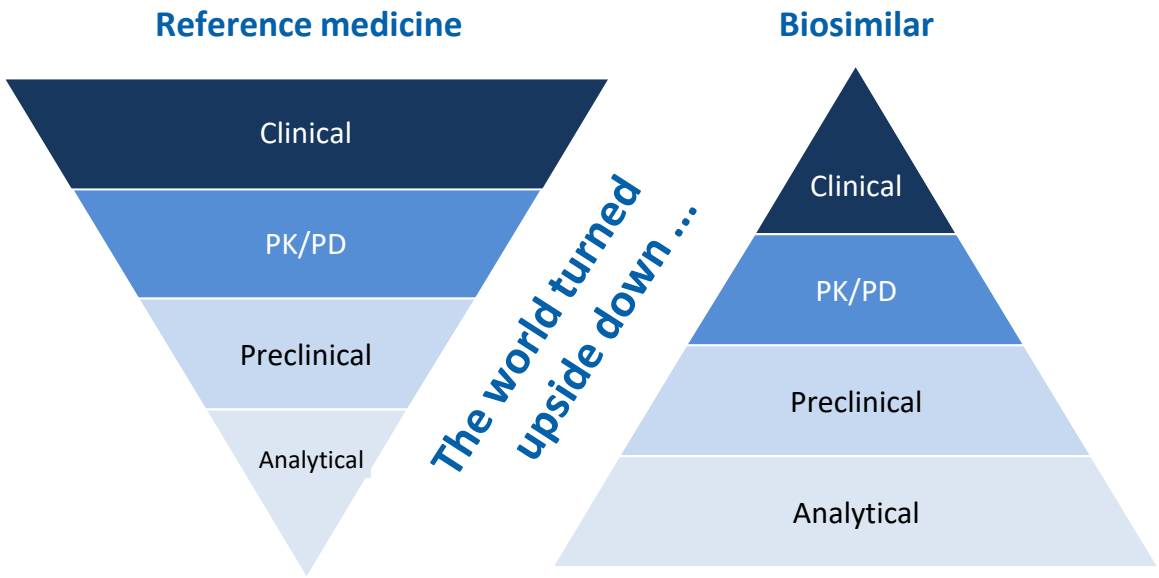
Once Biosymilar is approved it has substantial financial impact

“Biosymilars – symilar but not identical”

Different focus between originator and biosimilar development



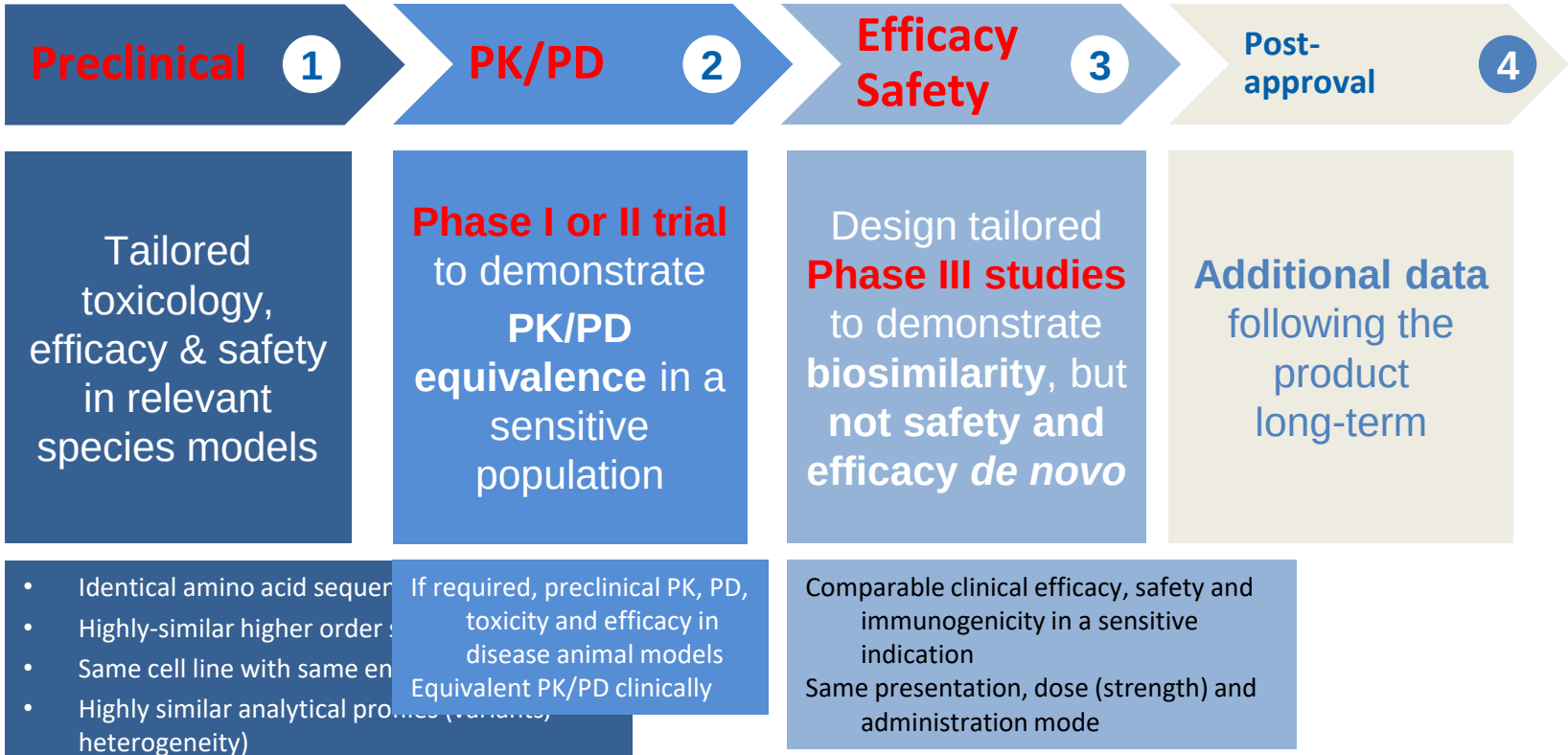
Major goal is to **determine the clinical effect**

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



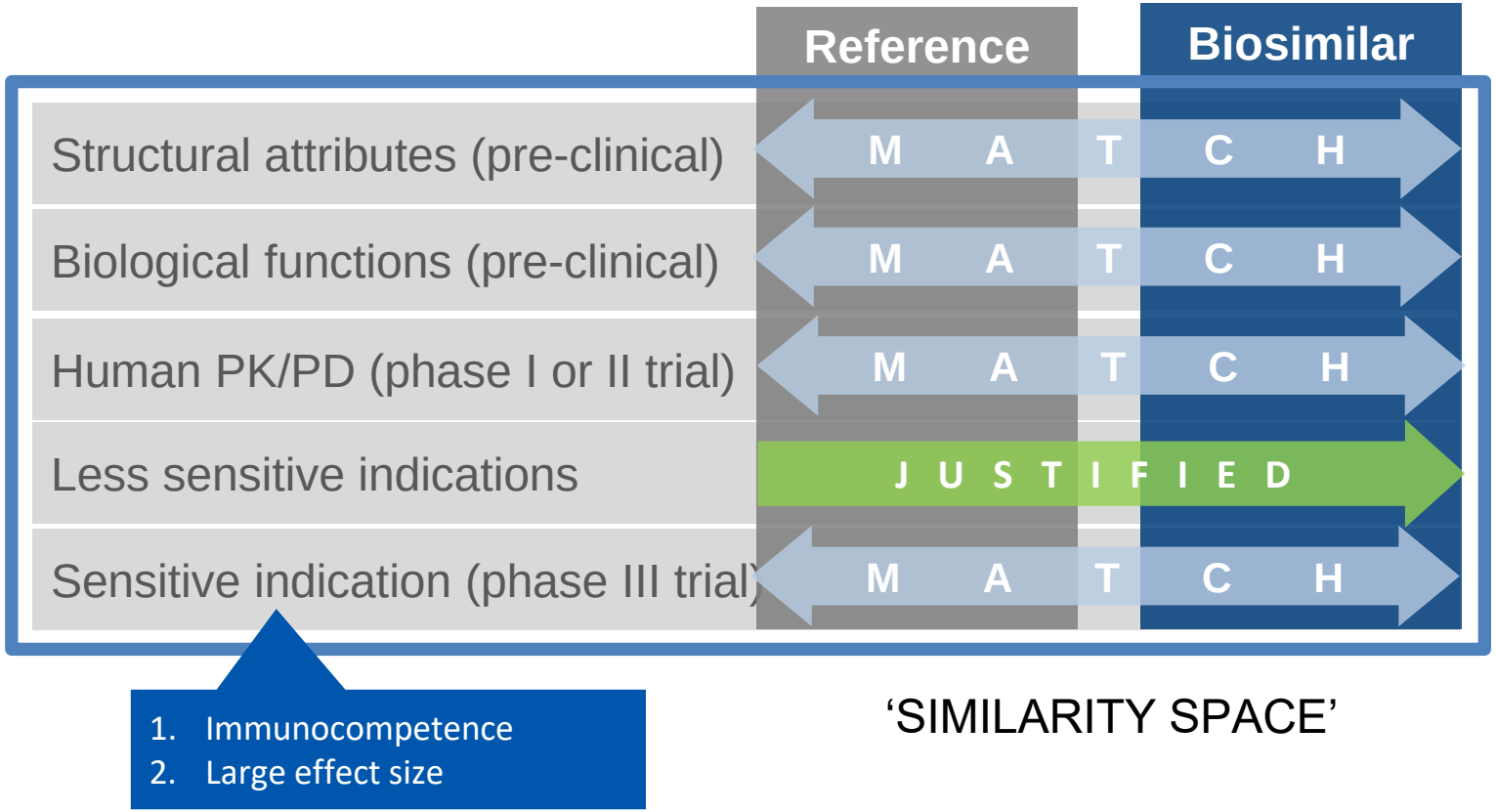
European Medicines Agency (EMA). Guideline on similar biological medicinal products. CHMP/437/04 Rev 1/2014 [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf [Accessed 2016 March 18];
US Food and Drug Administration. Guidance 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].

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].

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 Biosymilars

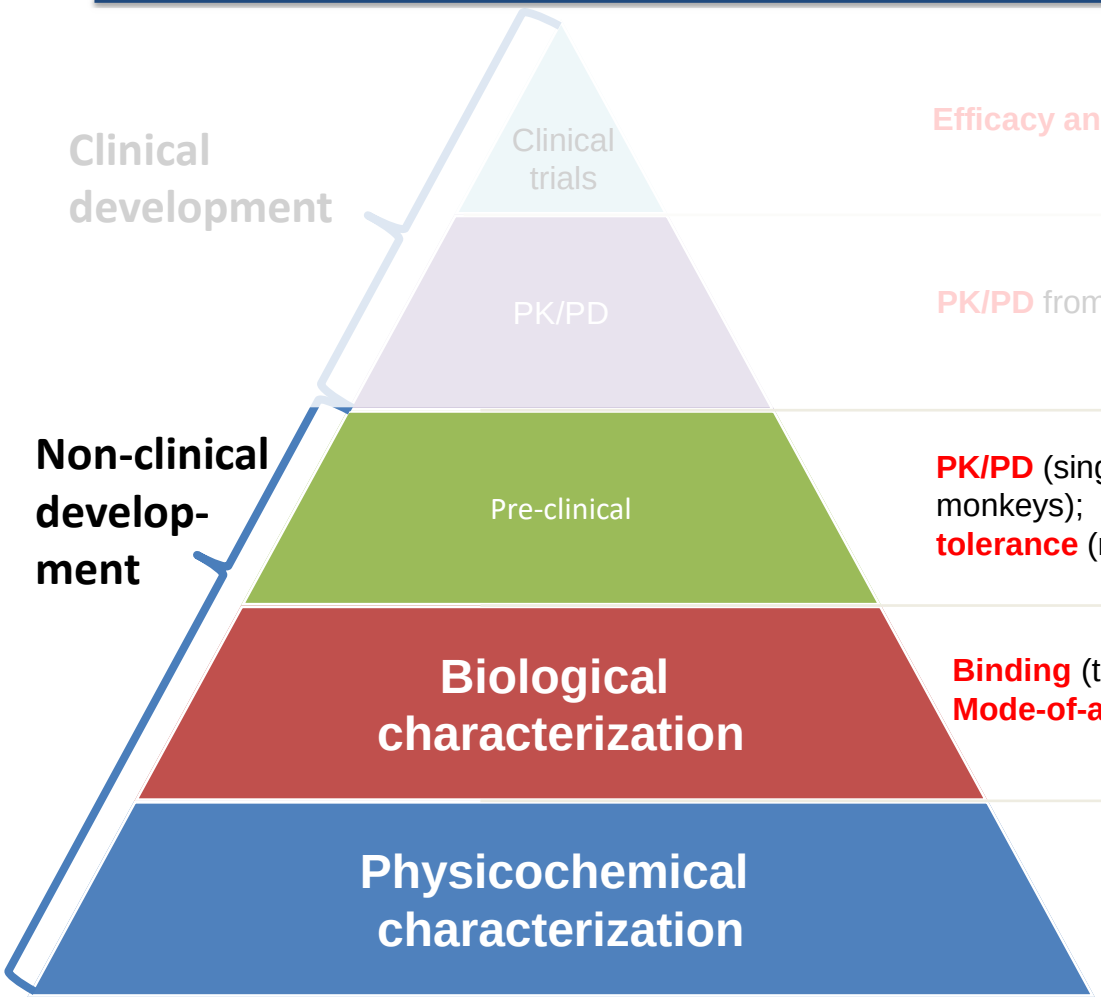
CELLTRION

CT-P10
Registered by EMA

SANDOZ A Novartis Division

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)

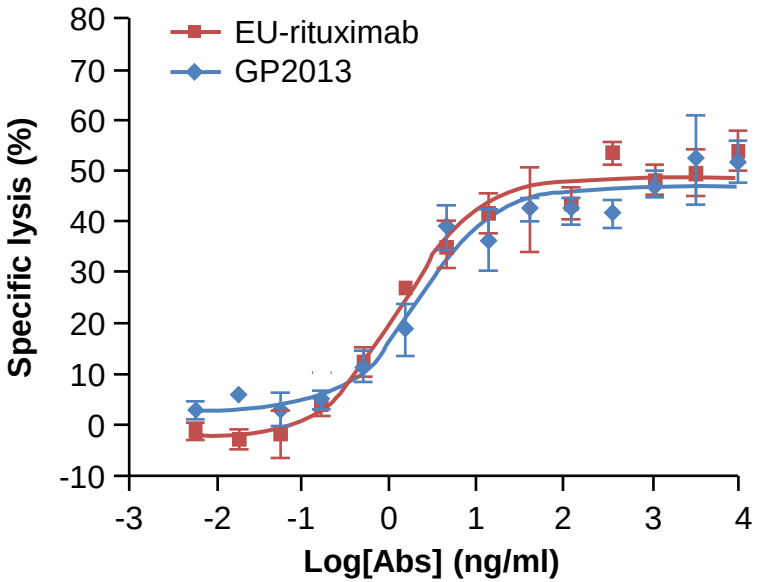
Binding (target binding, receptor binding)
Mode-of-action (programmed cell death, CDC, ADCC)

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

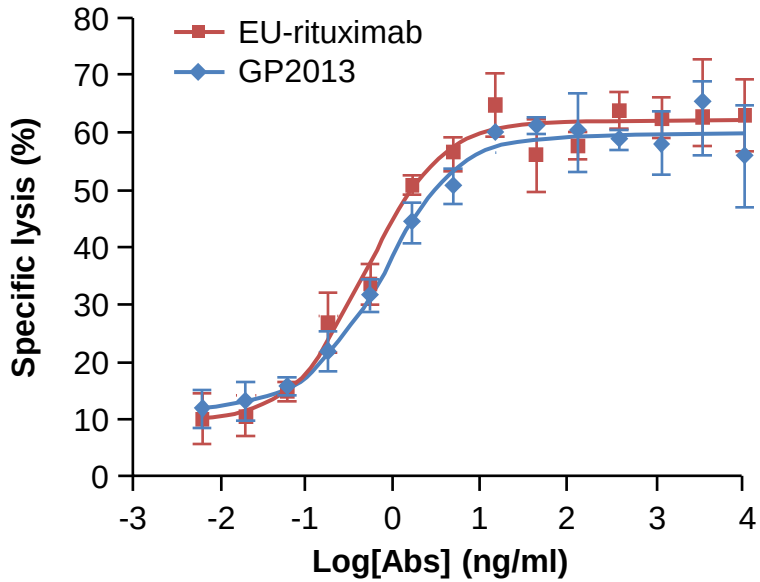
ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; FL, follicular lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency

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

Daudi cell line & fresh effector cells



SU-DHL4 & fresh effector cells



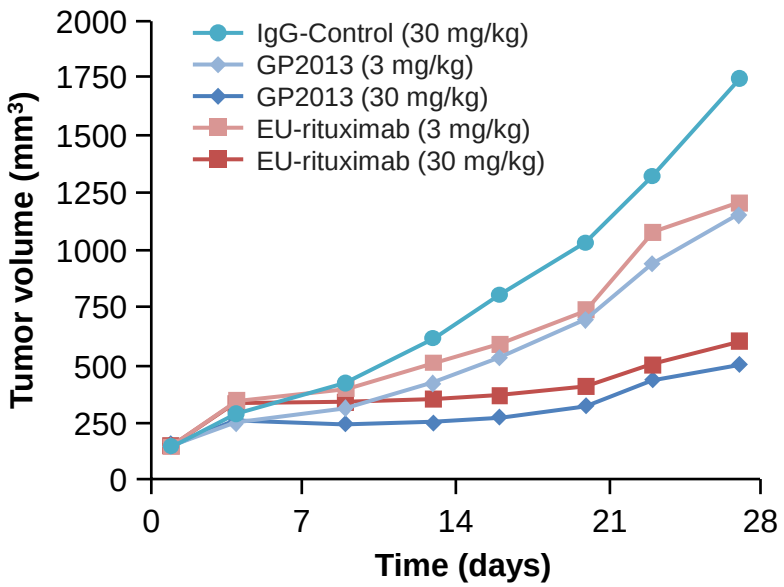
Further cell lines tested: Raji, Z138

ADCC comparable to EU-sourced reference rituximab

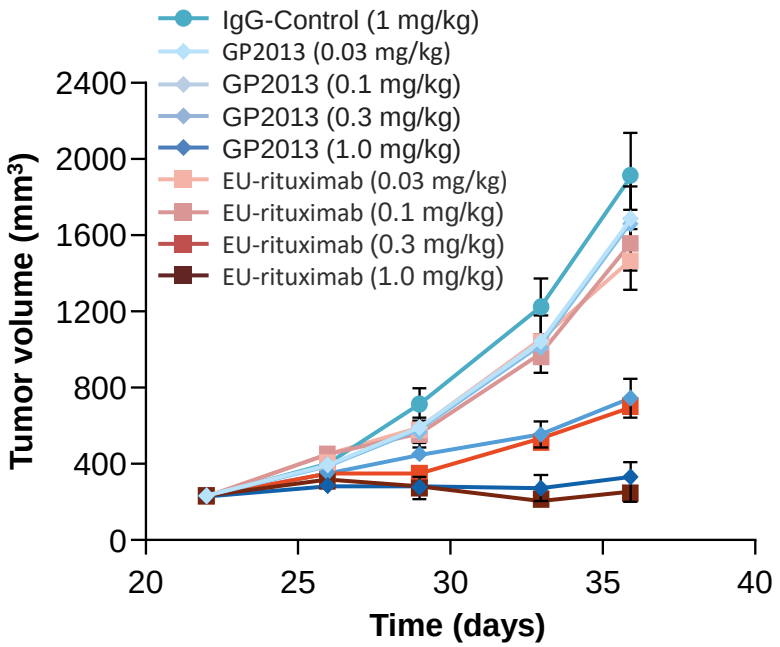
Ab, antibody; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer
da Silva et al. Leuk Lymphoma 2014;55:1609–17.

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

SU-DHL-4 model



Jeko-1 model



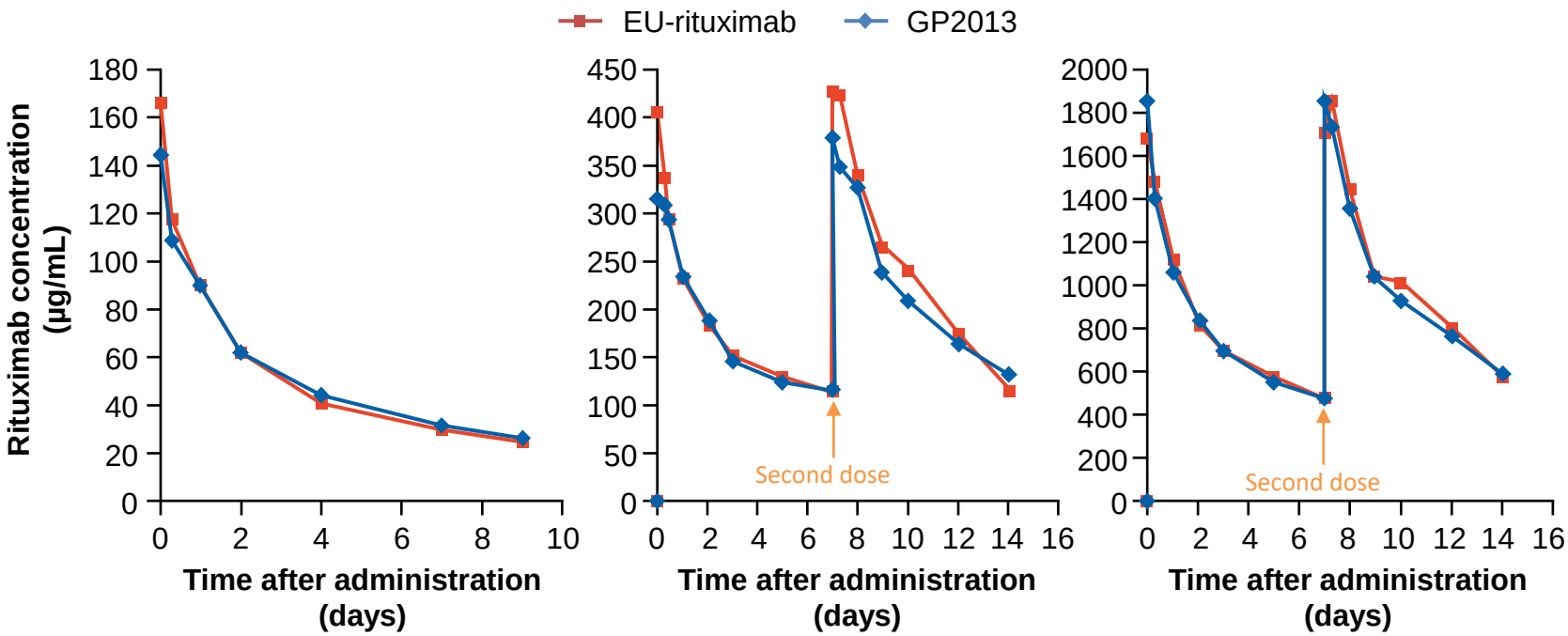
Efficacy is similar

IgG, immunoglobulin G

da Silva et al. Leuk Lymphoma 2014;55:1609–7.

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

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

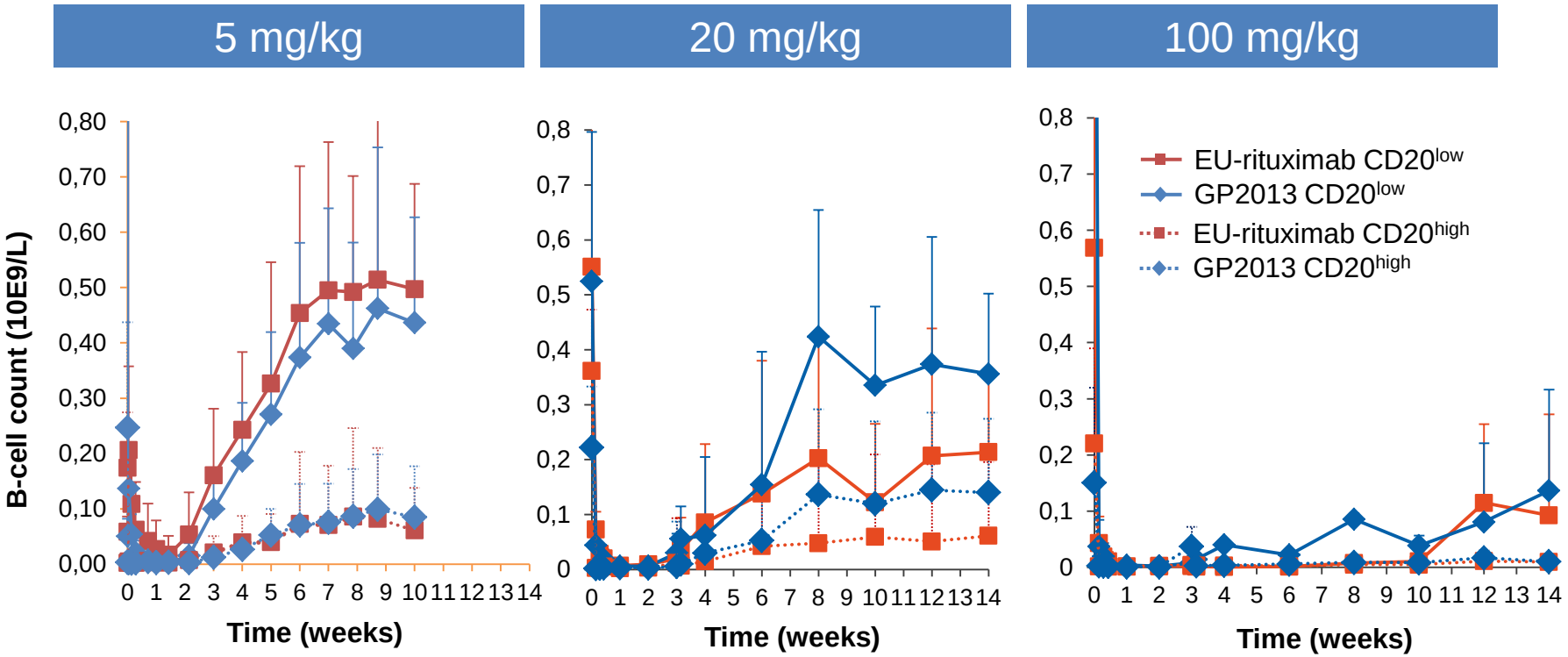


PK: AUC and C_{max} are similar

AUC, area under the curve; C_{max}, maximum concentration; IV, intravenous; PK, pharmacokinetics; SD, standard deviation

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

Pre-clinical *in vivo* comparability: B-cell depletion following IV adm to primates

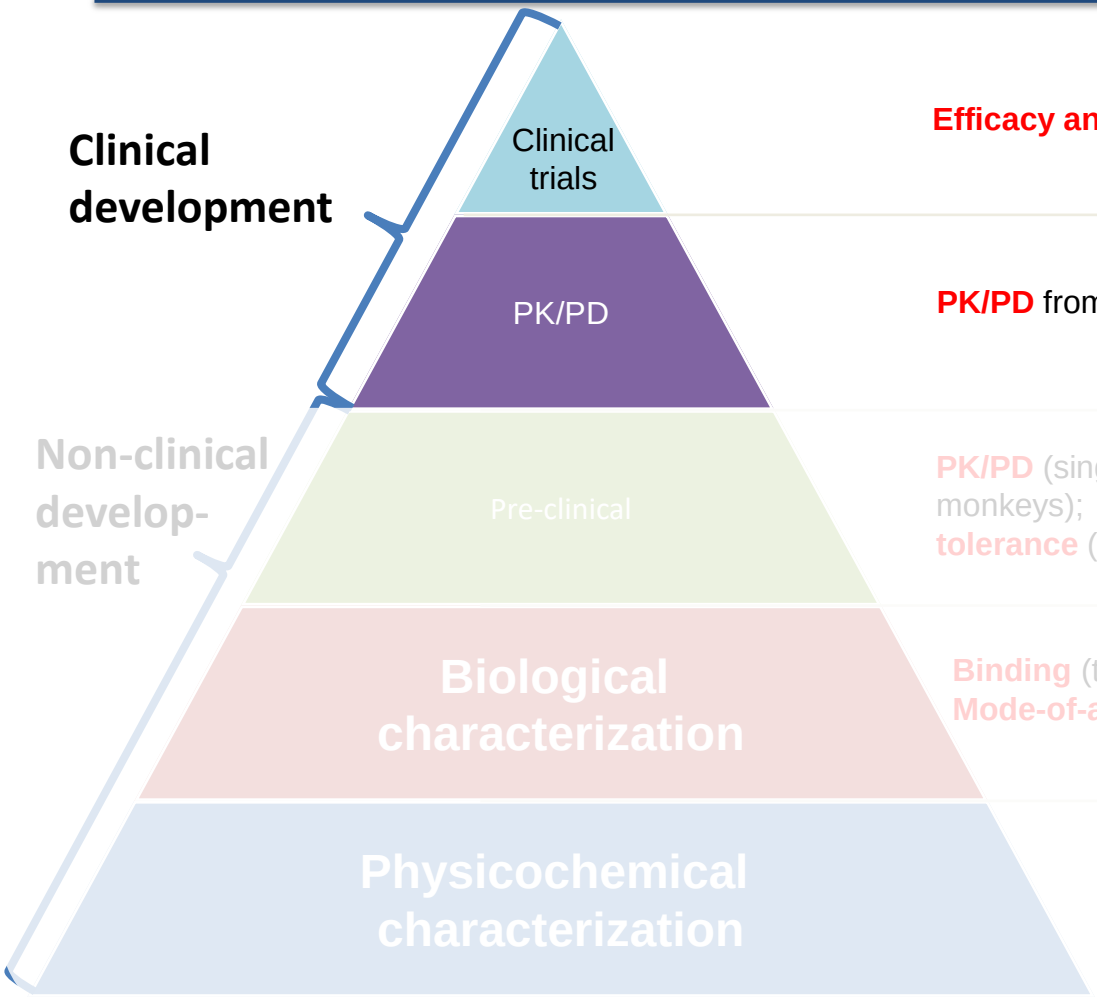


PD: B-cell depletion is similar

IV, intravenous; PD, pharmacodynamics; SD, standard deviation

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

GP2013 and CT-P10 development program



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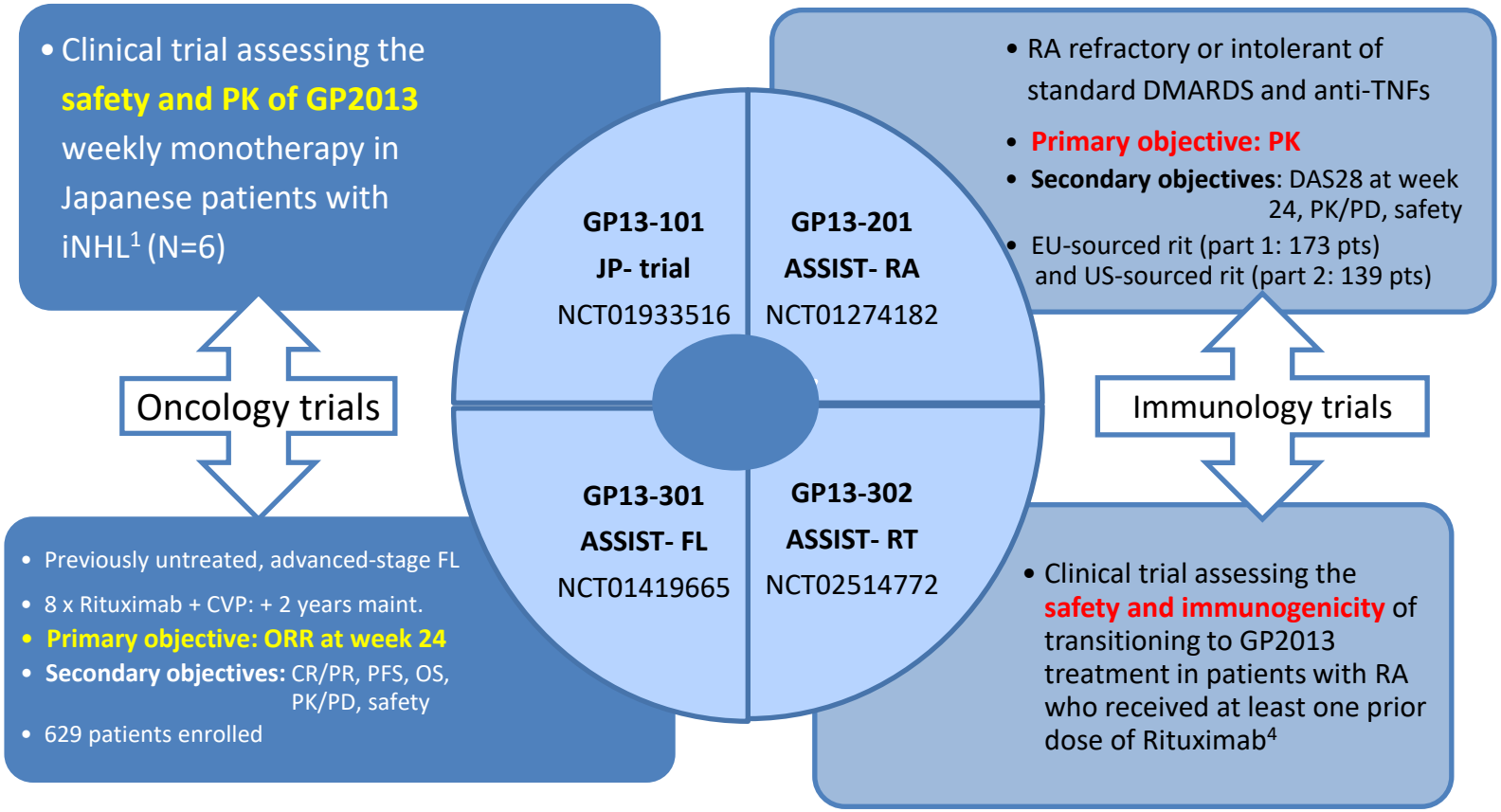
ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; FL, follicular lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency

GP2013 clinical development



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

FL: follicular lymphoma, JP: Japanese patients, NHL: non-Hodgkin's lymphoma, PK: pharmacokinetics, RA: Rheumatoid arthritis, TNF: Tumor necrosis facto

SANDOZ A Novartis Division

CT-P10 Clinical Overall Program

Study	Indication	Primary Endpoint	Sample size	Status
1.1	RA	**PK equivalence**	154	Completed
1.3 (1.1 Extension Study)	RA	Long term safety and efficacy	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**

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

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

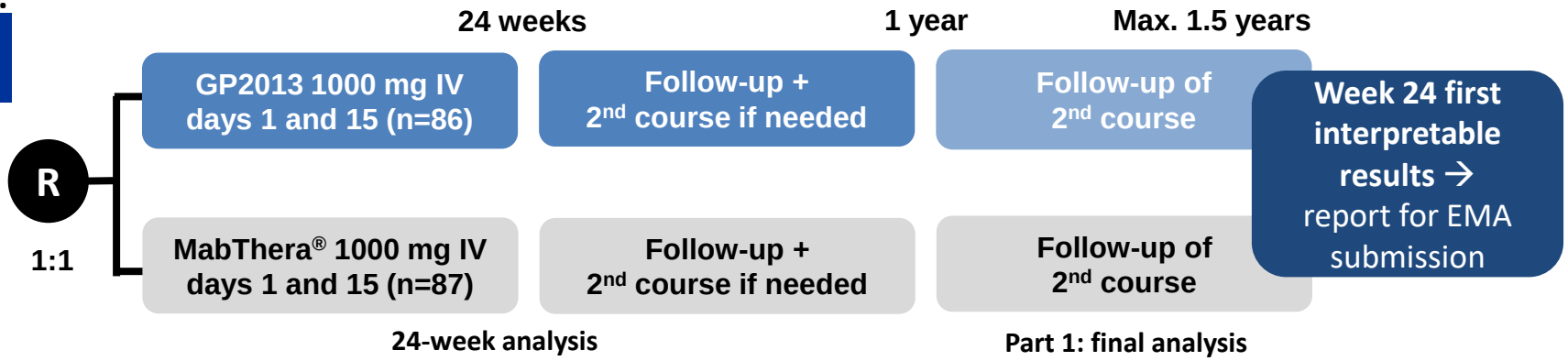
CT-P10 1.1 RA, CT-P10 3.2 RA : studies rationale

- **Rheumatoid arthritis was chosen as the most sensitive population for the PK/PD comparison** based on:
  - Establishing PK bioequivalence can not be performed in healthy subjects due to the B-cell depleting effect of rituximab
  - The **between-patient variability in terms of PK/PD is much lower** in patients with RA compared to the oncology indications (Baseline B-cell counts can vary significantly and thus affect both the PK and PD variability between patients in oncology)
  - In patients with RA the **treatment courses are given every 6 months** – less frequent than in the oncology indications, making it possible to capture the complete drug concentration-time profile before re-treatment
  - Additionally, the RA patient population is **favorable** over oncology **in terms of studying immunogenicity**

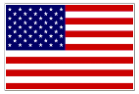
ASSIST-RA : study design

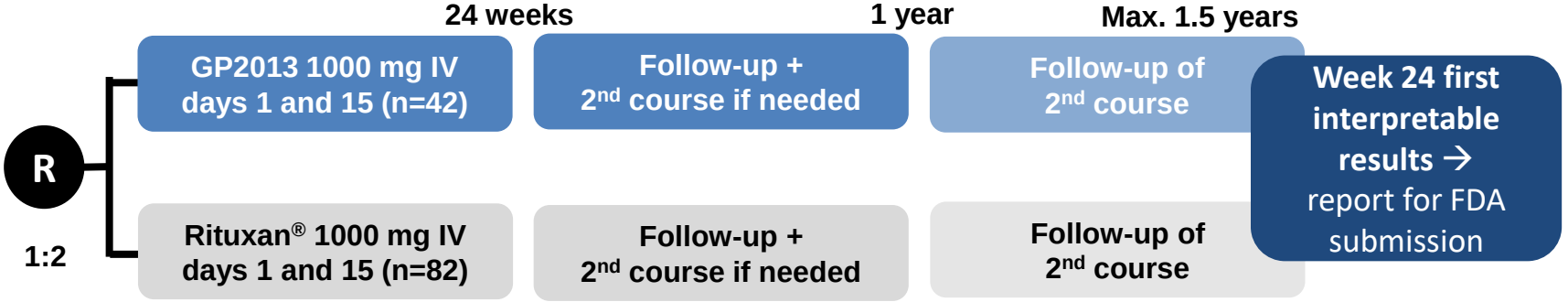
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

PART 1:



PART 2:





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

Polish Lymphoma Research Group

ASSIST-RA :primary and secondary endpoints

Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

Primary endpoint and Key secondary endpoints	Other secondary endpoints	Safety endpoints (secondary endpoints)

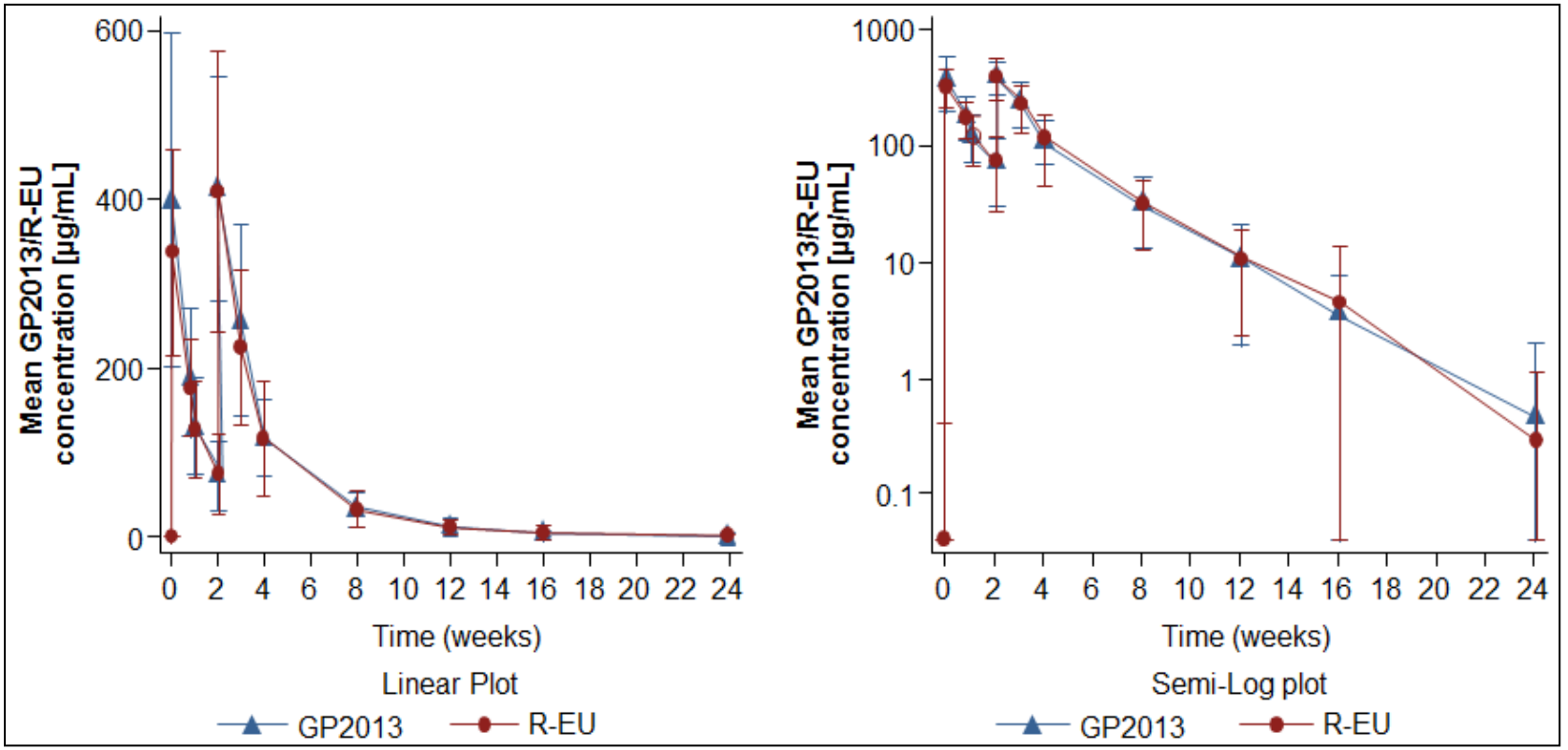
• **PK assessment: Primary endpoint**
  • **$AUC_{(0\text{-}inf)}$ of serum concentrations of the drugs**
• **Key Secondary endpoints**
  • C_{max} after the first infusion
  • $AUC_{(0\text{-}14d)}$ of percent B-cells relative to baseline
  • Change in DAS28 from baseline to week 24
	• **Efficacy: ACR20, ACR50, ACR70, EULAR response, SDAI and CDAI**
	• **PK:** $AUC_{(0\text{-}12w)}$, $AUC_{(0\text{-}24w)}$ and C_{max} following the second infusion ($C_{max}2$) and T_{max} (for both infusions; $T_{max}1$ and $T_{max}2$) and change in AUCEs
	• **PD:** Peripheral blood B-cell levels relative to baseline
	• **QoL:** HAQ-DI and FACIT fatigue scale
		• **Safety assessments:** AEs and SAEs, with their severity and relationship to the study drug; pregnancies; monitoring of hematology; blood chemistry and urine; vital signs, performance status; ECG; and body weight
		• **Immunogenicity:** ADA formation

CT-P10 3.2 RA
PK being the primary target of part 1,
while efficacy issues - the primary target of pat 2.

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

Primary efficacy results ($AUC_{(0\text{-}inf)}$)- (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

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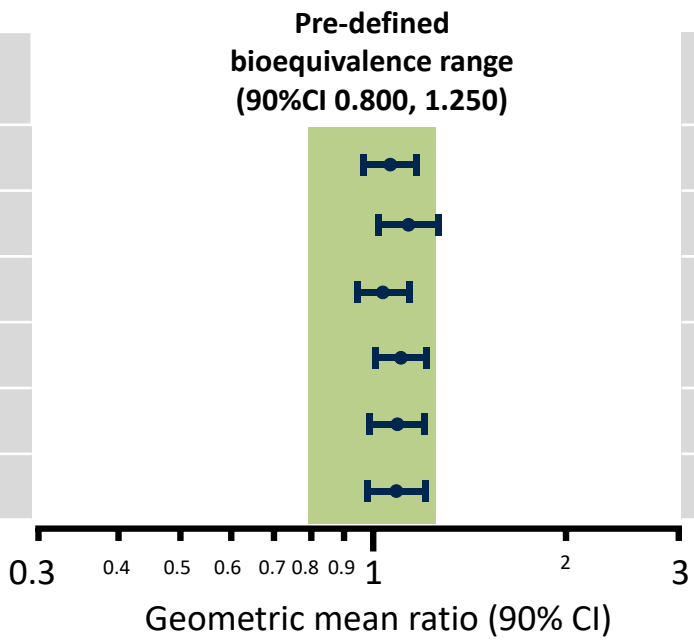
ASSIST-RA (part 1): primary and secondary pharmacokinetic endpoints

Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

- **The study met the primary endpoint of bioequivalence in PK ($AUC_{0\text{-}inf}$)**
  - **The geometric mean $AUC_{0\text{-}inf}$ was 6738.5 with GP2013 and 6334.4 with reference rituximab**
- The study also met all other secondary PK objectives with the exception of C_{max1}, which was attributed to a high variability in infusion rates and durations during the first infusion

PK parameter (unit)	n	Geom. mean ratio (90%CI)
$AUC_{0\text{-}inf}$ (primary endpoint)	145	1.064 (0.968, 1.169)
C_{max1} (1st inf.)	156	1.133 (1.017, 1.262)
C_{max2} (2nd inf.)	151	1.036 (0.944, 1.138)
$AUC_{(0\text{-}14d)}$	152	1.106 (1.010, 1.210)
$AUC_{(0\text{-}12w)}$	148	1.091 (0.988, 1.205)
$AUC_{(0\text{-}24w)}$	145	1.087 (0.980, 1.206)



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

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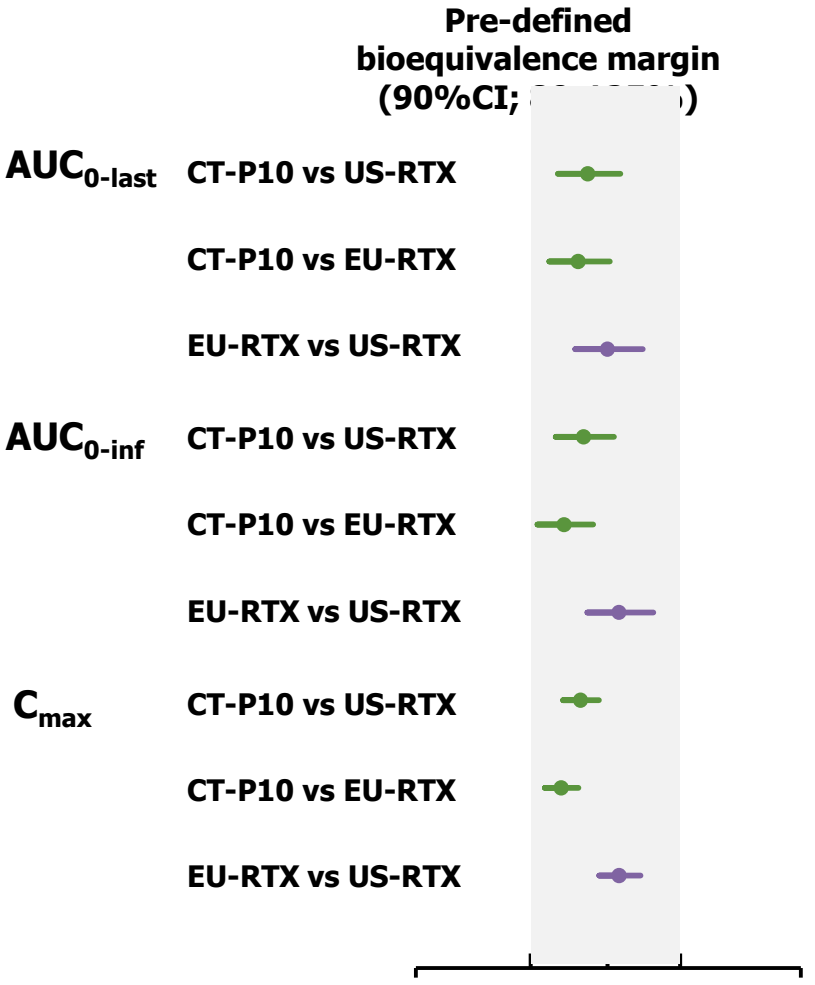
CT-P10 3.2 RA Pharmacokinetics: Primary Endpoints

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)

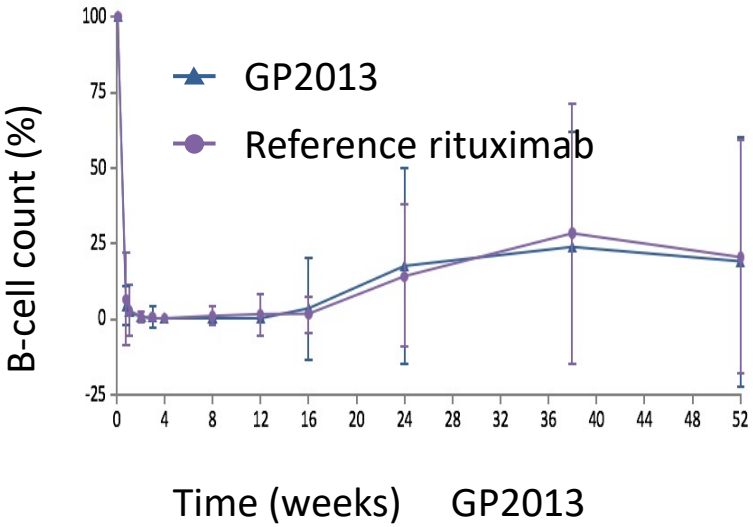


ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

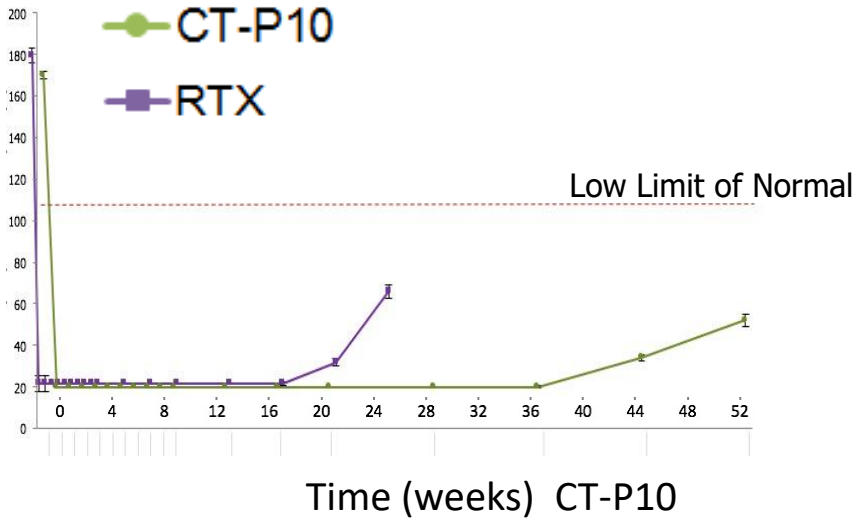
CT-P10 3.2 RA

Pharmacodynamics
Peripheral B cell depletion

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



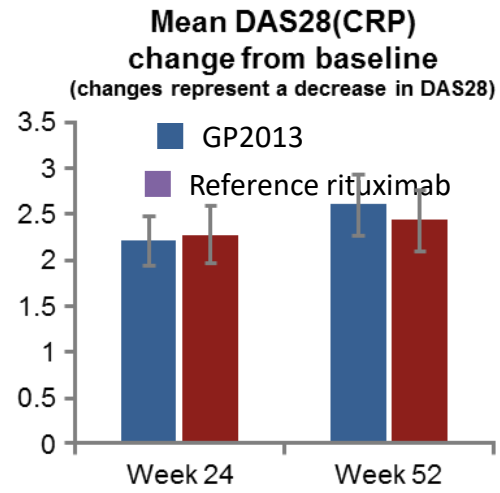
Median (±SE) B-cell Kinetics (cells/µL

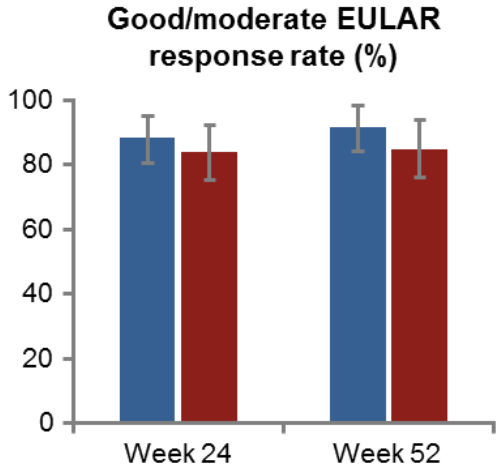


ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

CT-P10 3.2 RA

Efficacy DAS (Disesse Activity Score)





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

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ASSIST-RA (part 1): safety profiles of GP2013 and reference rituximab

Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

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 Summary up to Week 48

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-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

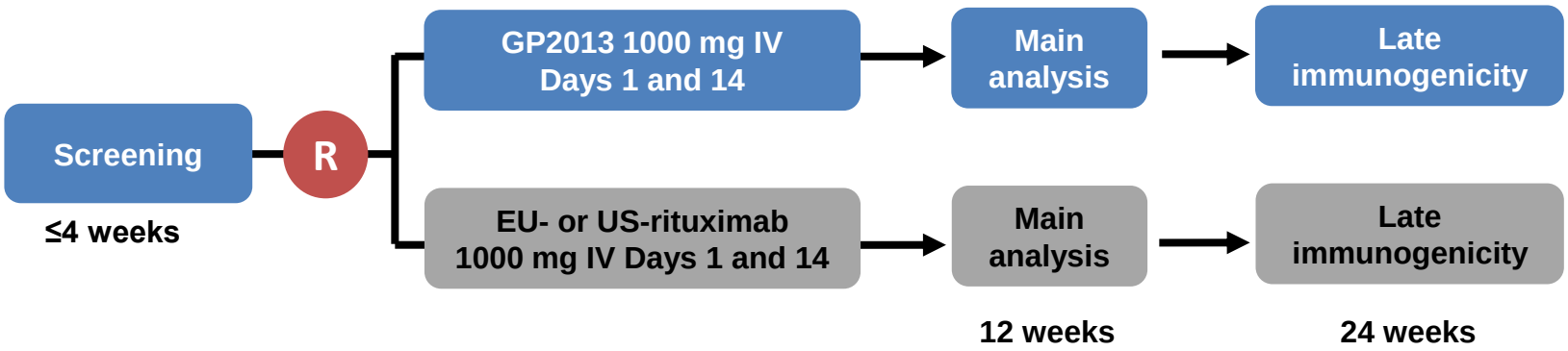
CT-P10 1.1 RA, CT-P10 3.2 RA : summary

In patients with active rheumatoid arthritis, the ASSIST-RA study shows:

1. PK bioequivalence between the proposed biosimilar rituximab, (GP2013 and CT-P10), and EU-approved reference rituximab
2. similar pharmacodynamic, efficacy and safety profiles with GP2013 and CT-P10 compared with EU-approved reference rituximab

ASSIST-RT : study design

Patients with active rheumatoid arthritis previously treated with EU- or US-sourced rituximab



Patients with ≥1 full course of EU- or US-sourced rituximab 6–18 months before randomization

Stable dose of methotrexate 7.5–25 mg/week, other allowed DMARDS and folic acid ≥5 mg/week for ≥4 weeks before randomization and throughout study; IV steroids, antihistamines and antipyretics pre-infusion

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

CT-P10 3.3 AFL

: study rationale

- ASSIST-FL was **designed to confirm non-inferior clinical effectiveness** of GP2013 as compared to originator rituximab in a sensitive population

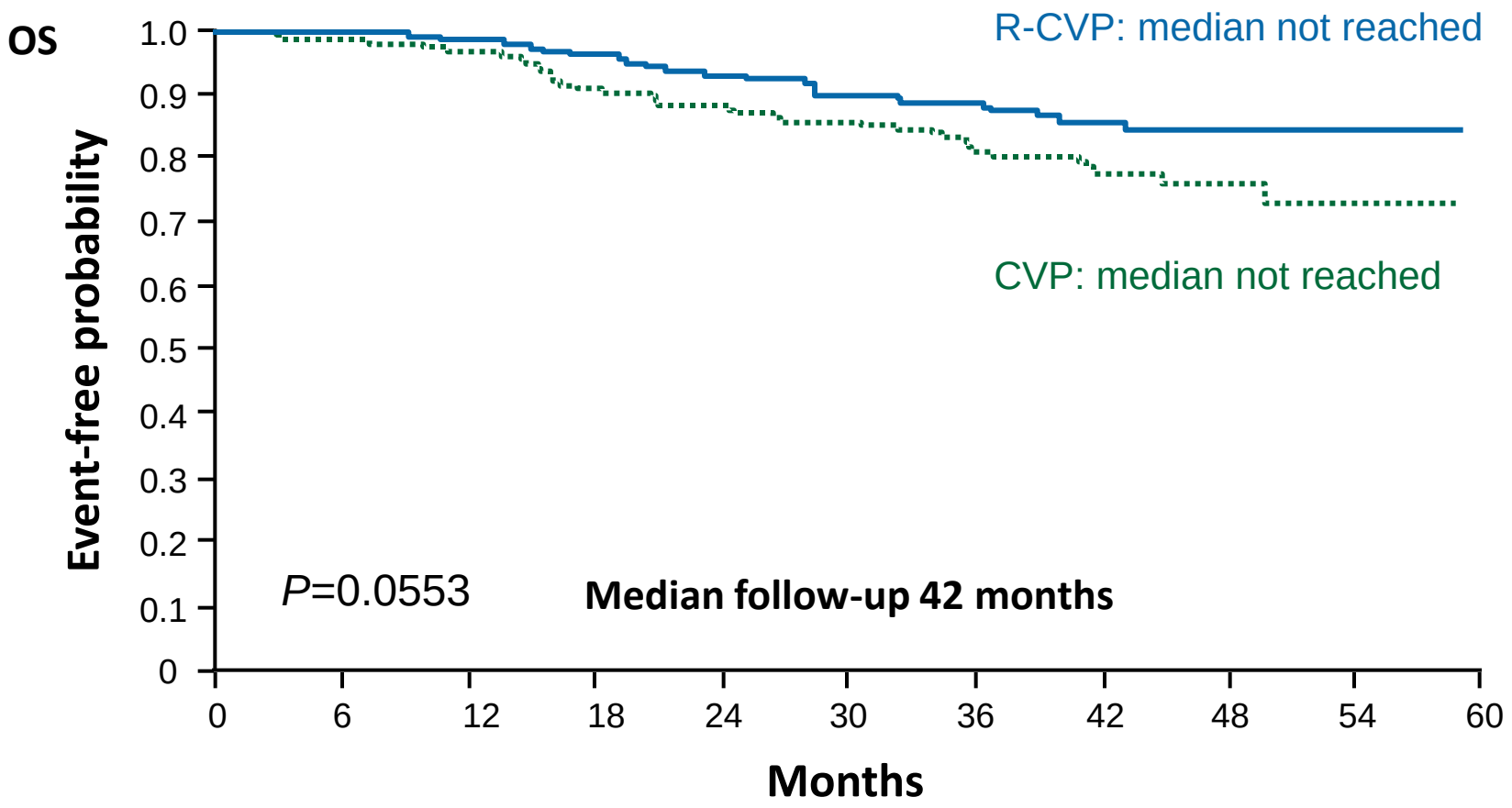
- **Follicular lymphoma** was chosen as the most appropriate indication as the disease **has a more homogeneous nature** amongst the approved oncology indications of rituximab

- 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

- Immunochemotherapy with Rituximab **remains the current standard of care** for previously untreated patients , the combination regimen increases the **RR** and prolongs both PFS and **OS**

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.

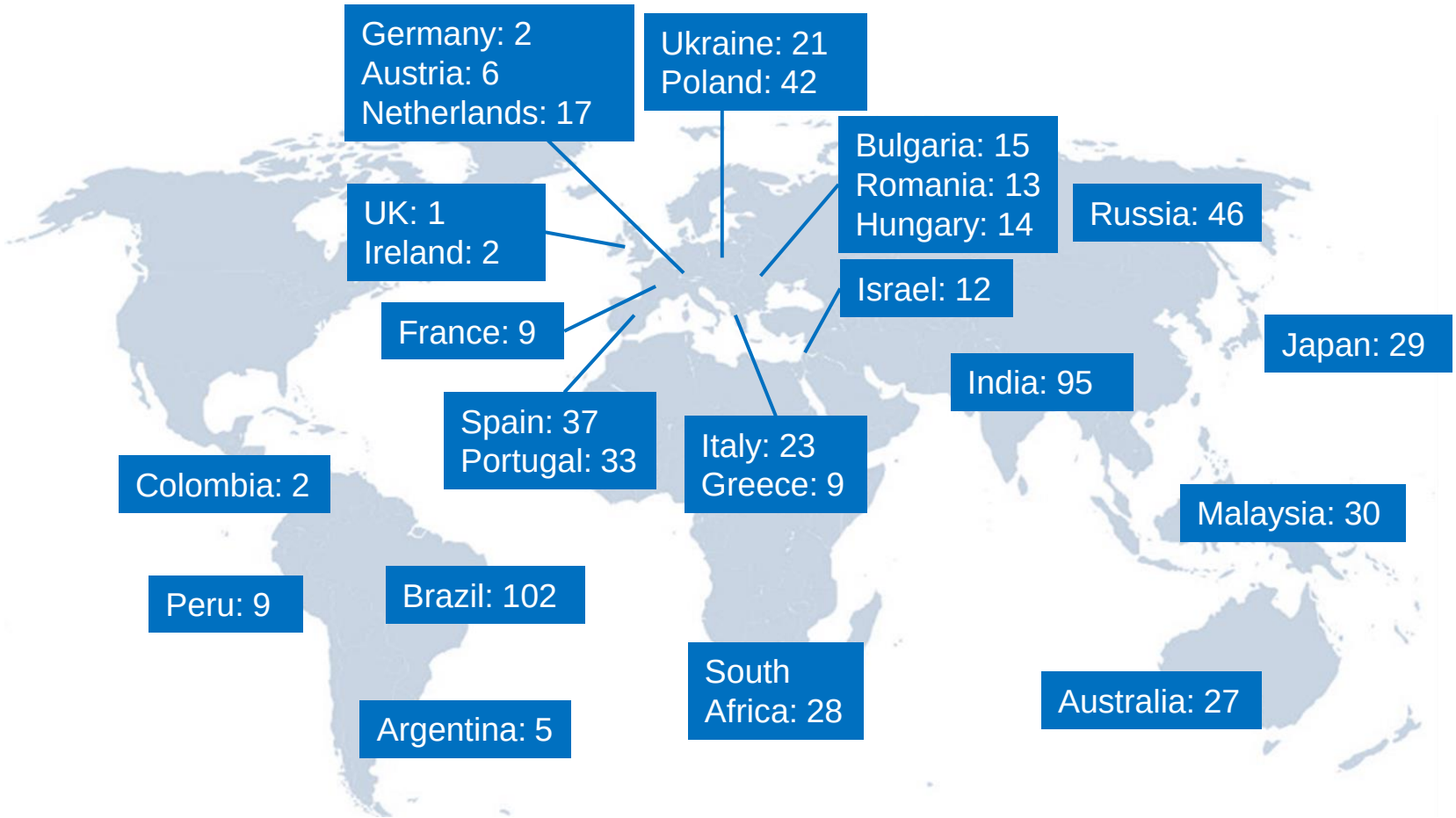
CVP ± Rituximab in Previously Untreated FL



Solal-Celigny et al. Blood. 2005;106:106a. Abstract 350

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

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



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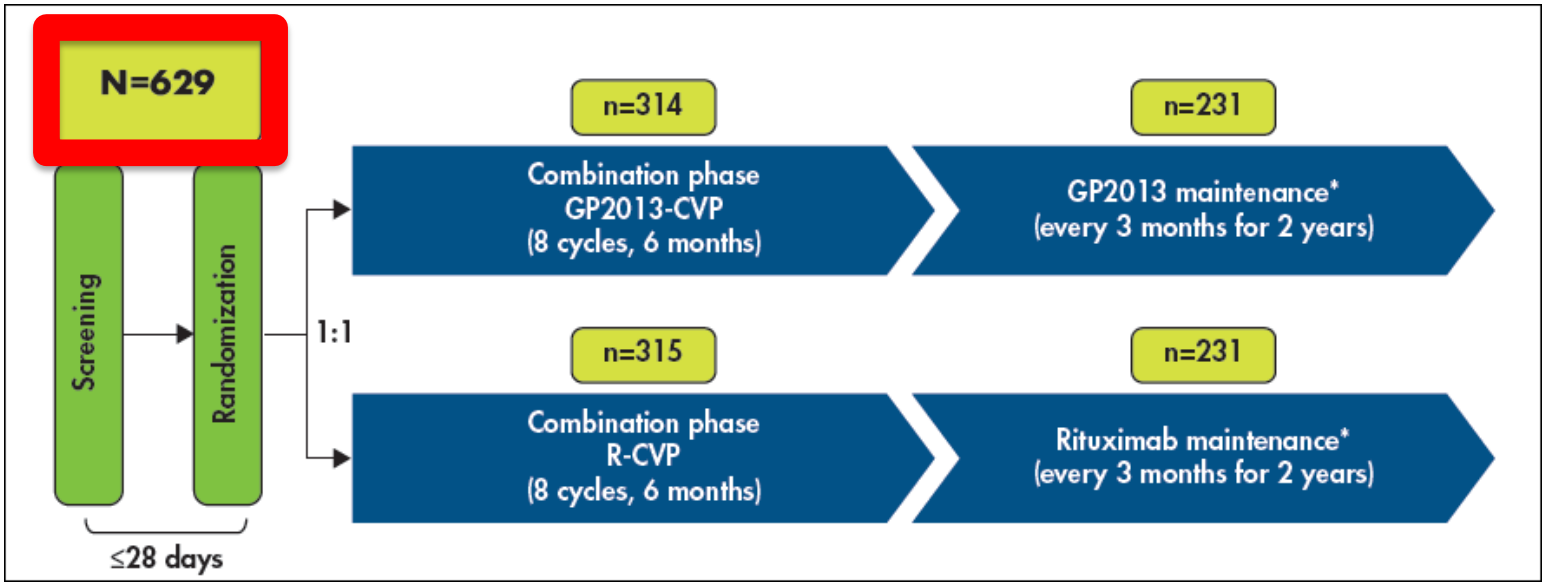
ASSIST-FL Study design

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



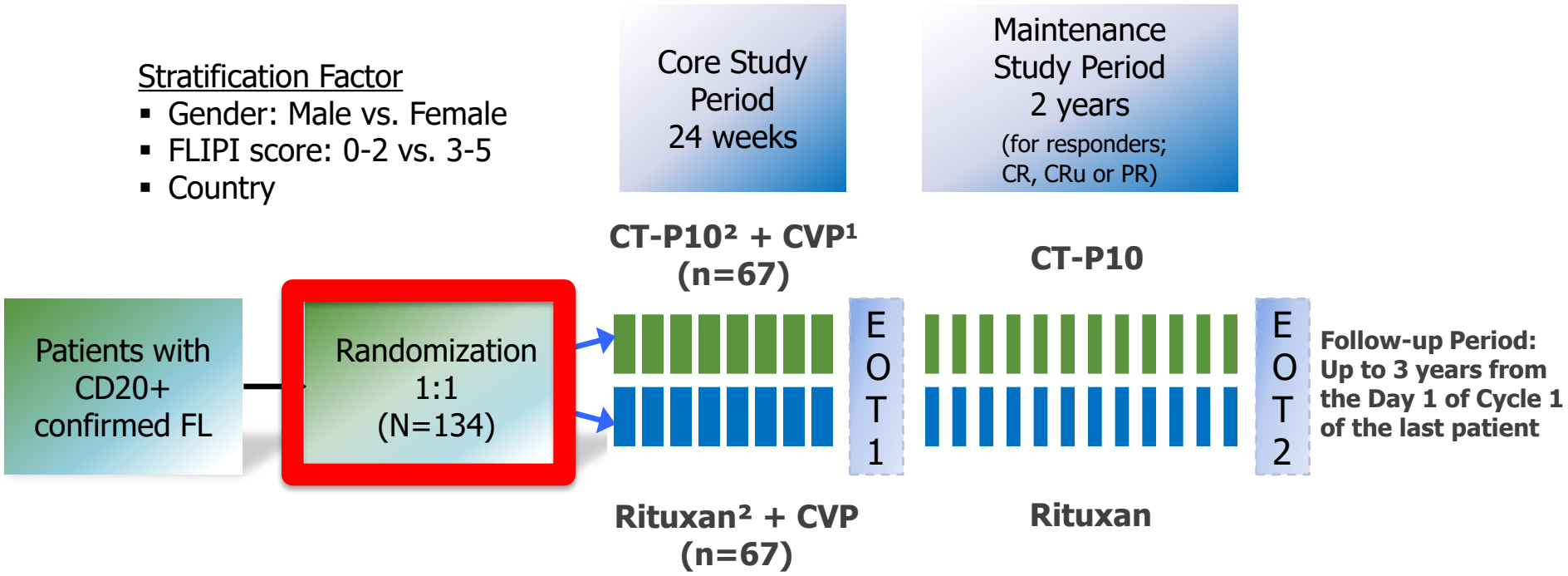
GP-2013 (375 mg/m^2) + cyclophosphamide (750 mg/m^2 IV D1) + vincristine (1.4 mg/m^2 D1) + prednisone (100 mg p.o. D1–D5)
Rituximab (375 mg/m^2) + cyclophosphamide (750 mg/m^2 IV D1) + vincristine (1.4 mg/m^2 D1) + prednisone (100 mg p.o. D1–D5)

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

R-CVP: Rituximab-cyclophosphamide, vincristine, prednisone, FL: follicular lymphoma

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

CT-P10 3.3 AFL Study Design



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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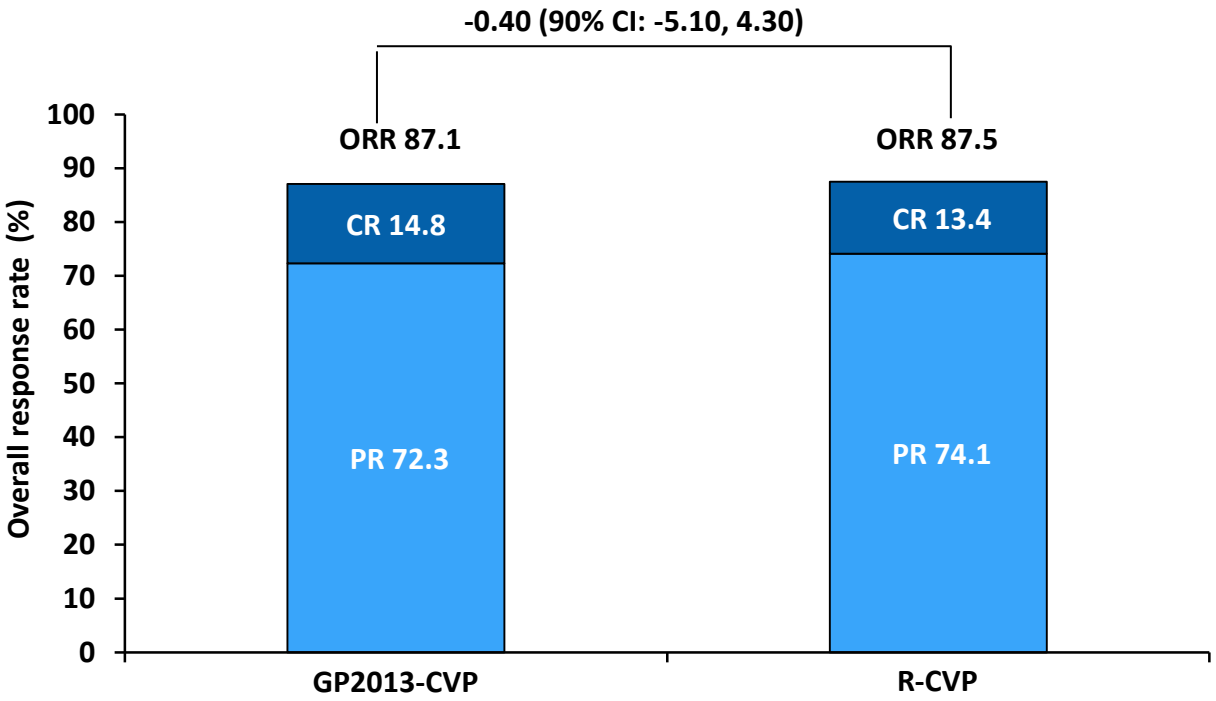
Primary efficacy results (ORR)



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.

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CT-P10 3.3 AFL Efficacy Endpoint (secondary endpt !)

ITT Population

Response	CT-P10 (N=70)	Rituxan (N=70)	Difference [lower bound of 95% CI]
ORR[1]	**67 (95.7%)**	**63 (90.0%)**	**5.7% [-3.41%]**
CR	21 (30.0%)	15 (21.4%)	-
CRu	6 (8.6%)	8 (11.4%)	-
PR	40 (57.1%)	40 (57.1%)	-

The difference between the groups lies on the positive side of -7%.
lower bound of 95% CI of differences lies on the positive side of -7%.

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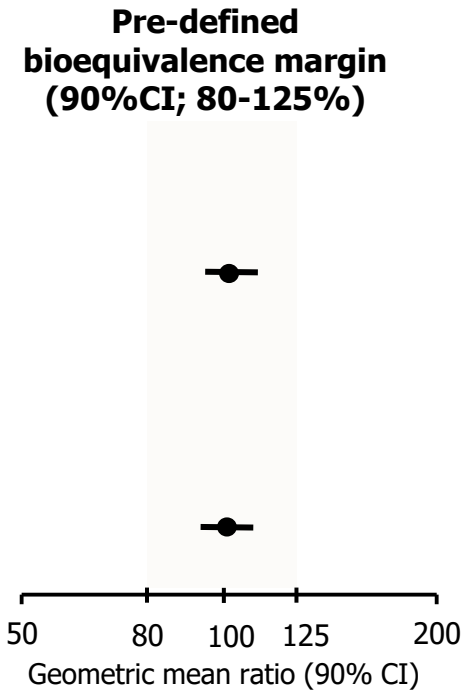
CT-P10 3.3 AFL Primary PK Endpoints (PK Equivalence)

Parameter	Treatment	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	



Abbreviations: PK, pharmacokinetics; AUC_{tau}, area under the serum concentration -time curve at steady state; $C_{maxSS,}$ Maximum serum concentration at steady state; LS, Least squares; CI, confidence interval

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ASSIST-FL: secondary endpoint results

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

- The median **PFS and OS were not reached as data are still maturing**
- **Pharmacokinetics and pharmacodynamics**
  - Geometric mean ratio between GP2013 and reference rituximab was
    - 1.00 (90% CI 0.925, 1.09) for C_{max} at Cycle 4, Day 1
    - 0.939 (90% CI 0.845,1.04) for the area under effect-time curve in CD19+ B-cell count ($AUEC_{(0–21days)}$)
  - Comparable results observed between GP2013 and reference rituximab for $AUC_{(0–21days)}$, AUC_{all} and C_{trough}

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

CT-P10 3.3 AFL

Immunogenicity: ADA

	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)

	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-FL summary of safety

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

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 3.3 AFL Safety Summary

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 3.3 AFL

: 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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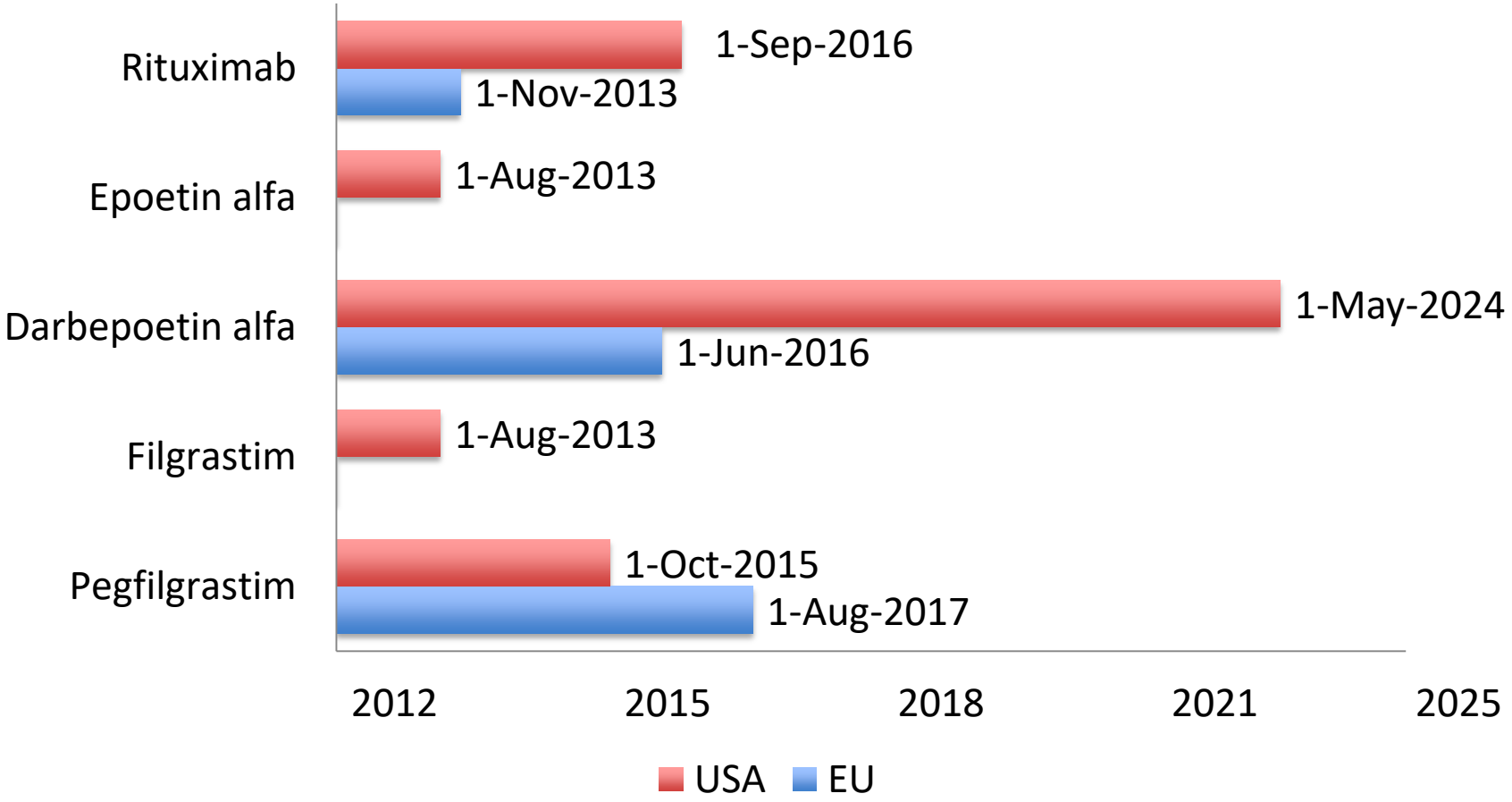
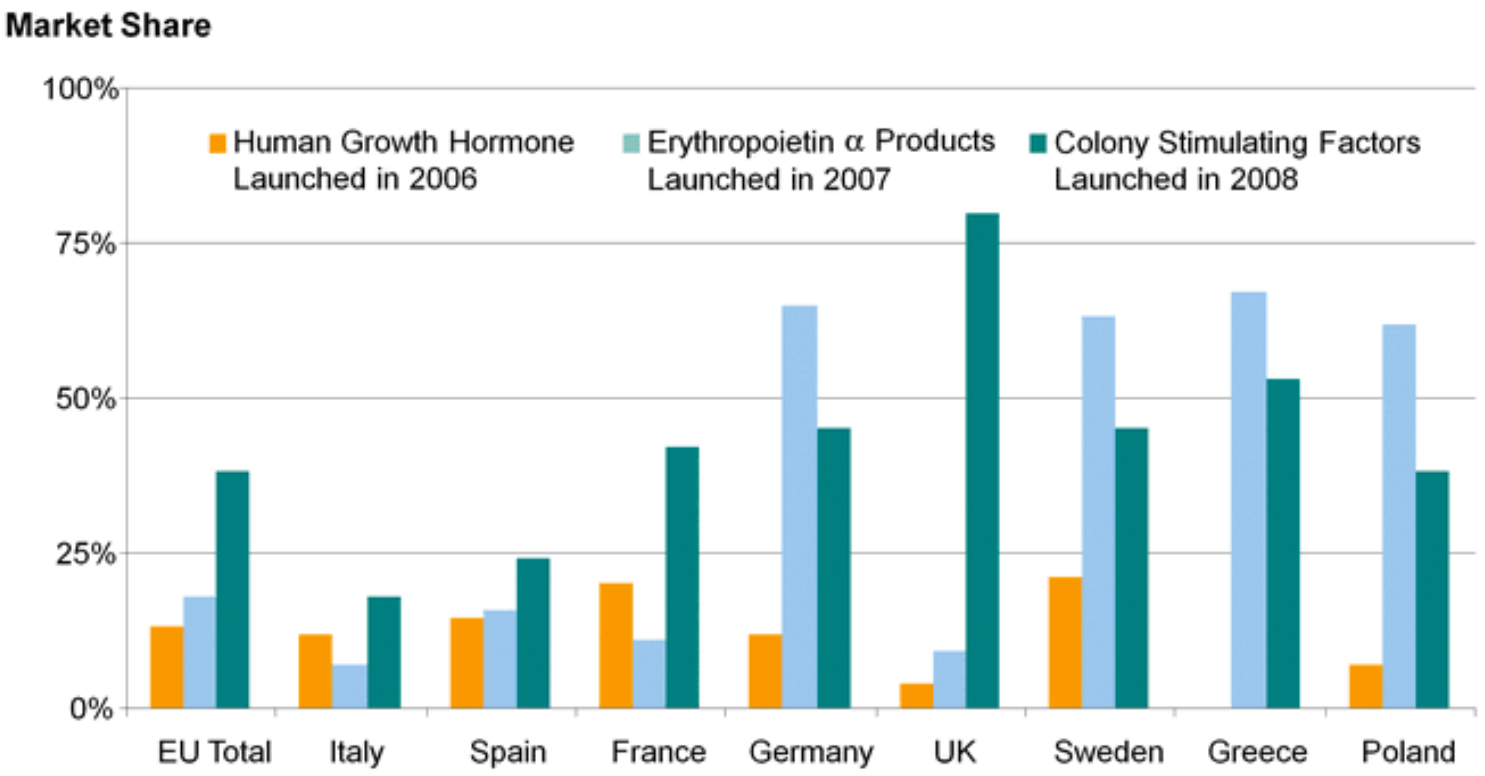
Biosimilars in Hematology: supportive care → MoAb



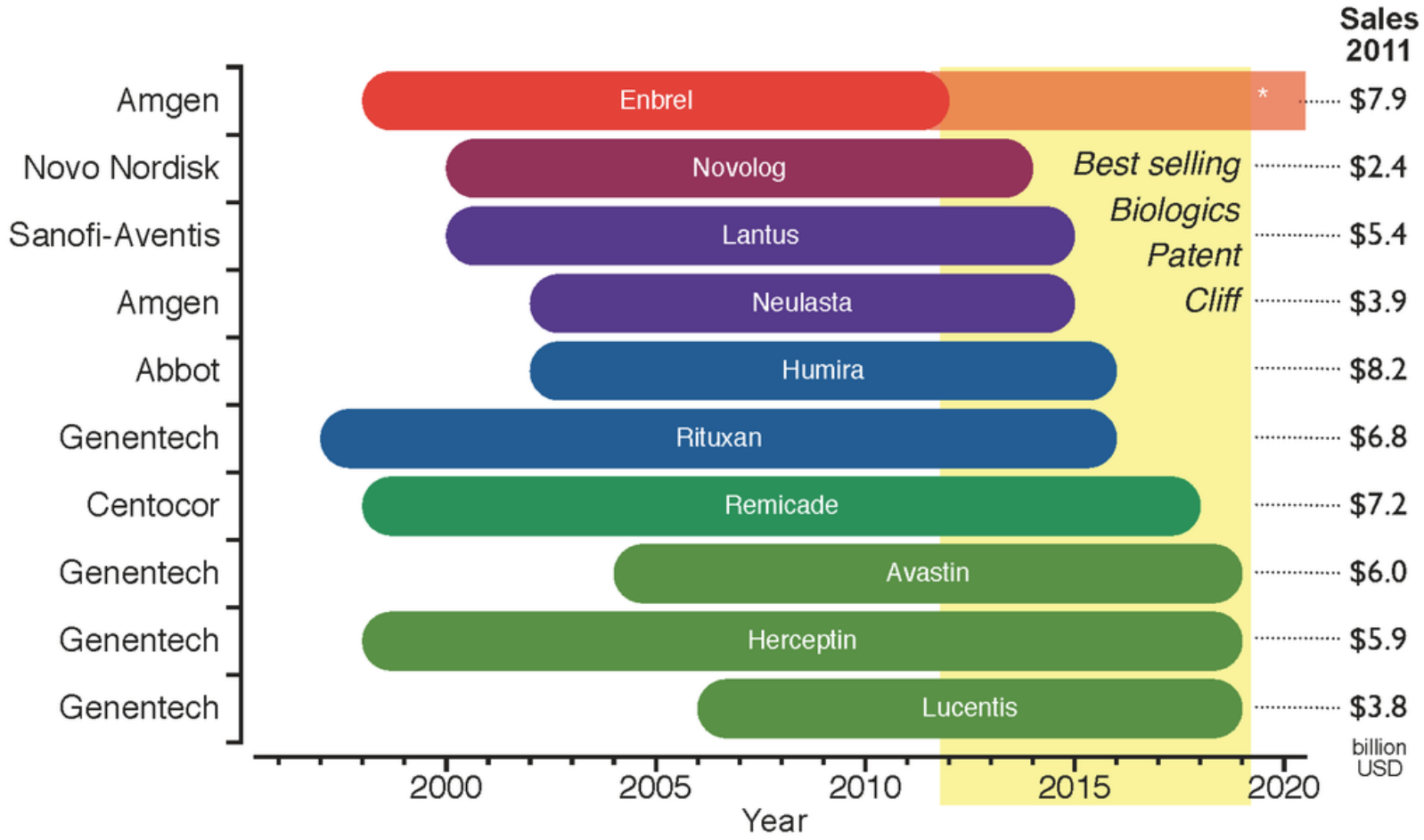
Biosimiliar use is increasing in EU



Biosimilar products have achieved market share >50% in select countries.

IMS MIDAS/MTA Global database: March 2011

Biosymilars may be potentially developed for several inovstive biologics in the next 10 years



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