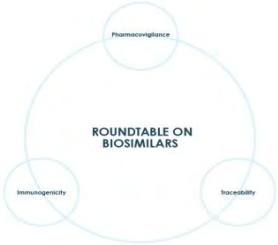
Sol Ruiz, PhD, Spain

- Head of Sector, Biotechnology and Advanced Therapies, Spanish Agency for Medicines and Medical Devices (*Agencia Española de Medicamentos y Productos Sanitarios*)
- Chair, Biosimilar Medicinal Product Working Party, European Medicines Agency
- Member of the Committee for Advanced Therapies, European Medicines Agency
- Co-opted member of the Committee for Medicinal Products for Human Use, Quality and Safety (biological)

GaBI Scientific Meetings

ROUNDTABLE ON BIOSIMILARS
Pharmacovigilance, Traceability, Immunogenicity

15 November 2016, Real Academia Nacional de Farmacia, Madrid, Spain



EMA approval requirements on biosimilars: clinical aspects

Sol Ruiz, PhD, Spain

15 November 2016

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

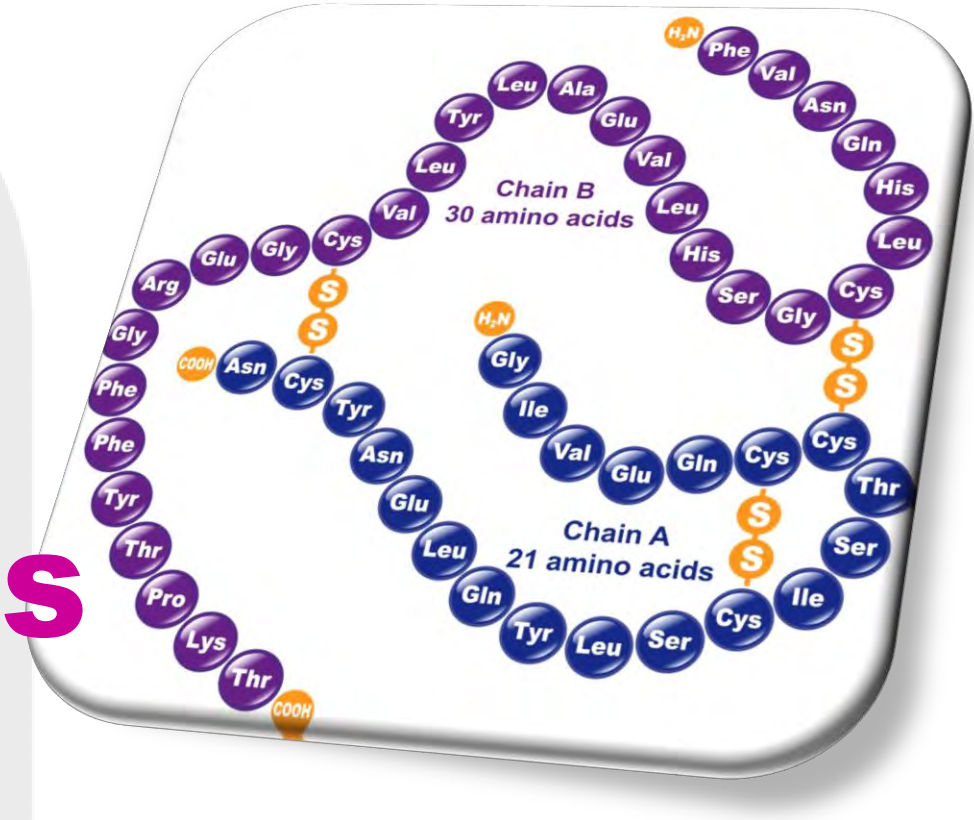
Universidad de Alcalá

PPCI
Pro Pharma Communications International

GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

Biosimilars
Clinical aspects



Agencia Española de Medicamentos y Productos Sanitarios

Sol Ruiz - AEMPS

GaBI 15-11-2016

Medicine Name	Active Substance	MAH	Status	Author date
Abasaglar (Abasria)	insulin glargine	Eli Lilly Reg	Authorised	09/09/2014
Abseamed	epoetin alfa	Medice Arzneimittel Pütter	Authorised	28/08/2007
Accofil	filgrastim	Accord Healthcare Ltd	Authorised	18/09/2014
Alpheon	**rh IFN alfa-2a**	**BioPartners GmbH**	**Refused**	-
Bemfola	follitropin alfa	Finox Biotech AG	Authorised	27/03/2014
Benepali	**etanercept**	Samsung Bioepis UK Ltd	Authorised	14/01/2016
Binocrit	epoetin alfa	Sandoz GmbH	Authorised	28/08/2007
Biograstim	filgrastim	AbZ-Pharma GmbH	Authorised	15/09/2008
Epoetin Alfa Hexal	epoetin alfa	Hexal AG	Authorised	28/08/2007
Filgrastim Hexal	filgrastim	Hexal AG	Authorised	06/02/2009
Filgrastim ratiopharm	**filgrastim**	**Ratiopharm GmbH**	**Withdrawn**	15/09/2008
Flixabi	**infliximab**	Samsung Bioepis UK Ltd	Authorised	26/05/2016
Grastofil	filgrastim	Apotex Europe BV	Authorised	18/10/2013
Inflectra	**infliximab**	Hospira UK Limited	Authorised	10/09/2013
Nivestim	filgrastim	Hospira UK Ltd	Authorised	08/06/2010
Omnitrope	somatropin	Sandoz GmbH	Authorised	12/04/2006
Ovaleap	follitropin alfa	Teva Pharma B.V.	Authorised	27/09/2013
Ratiograstim	filgrastim	Ratiopharm GmbH	Authorised	15/09/2008
Remsima	**infliximab**	Celltrion Healthcare Hung	Authorised	10/09/2013
Retacrit	epoetin zeta	Hospira UK Limited	Authorised	18/12/2007
Silapo	epoetin zeta	Stada Arzneimittel AG	Authorised	18/12/2007
Solumarv	**insulin human**	**Marvel Lifesciences Ltd**	**Refused**	-
Tevagrastim	filgrastim	Teva GmbH	Authorised	15/09/2008
Valtropin	**somatropin**	**BioPartners GmbH**	**Withdrawn**	24/04/2006
Zarzio	filgrastim	Sandoz GmbH	Authorised	06/02/2009

News and press release archive
Committee meeting highlights
Calendar
Public consultations
Statistics
What's new
Press contacts
Social media
Disease areas
Publications
Open letters
Public health threats and pandemics
Outcome of UK referendum

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 29 March - 1 April 2016

News

01/04/2016

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 29 March - 1 April 2016

Seven new medicines, including one advanced therapy, recommended for approval

A biosimilarmonoclonal antibody, **Flixabi** (infliximab), was granted a positive opinion by the Committee for the treatment of rheumatoid arthritis, adult and paediatric Crohn's disease, ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

The Committee recommended granting a conditional marketing authorisation for **Darzalex** (daratumumab) for the treatment of relapsed and refractory multiple myeloma. Darzalex has an orphan designation and was reviewed under EMA's accelerated assessment scheme. For more information, please see the press release in the grid below.

The Committee recommended granting a marketing authorisation for **Galafold** (migalastat) for the treatment of Fabry disease, a rare genetic disorder. Galafold has an orphan designation. For more information, please see the press release in the grid below.

Pandemic influenza vaccine H5N1 MedImmune also received a positive opinion from the CHMP. This is the first pandemic live attenuated influenza vaccine against avian influenza (H5N1) to be recommended for approval in the European Union (EU). The vaccine is intended for pandemic preparedness.

A biosimilarmonoclonal antibody, **Flixabi** (infliximab), was granted a positive opinion by the Committee for the treatment of rheumatoid arthritis, adult and paediatric Crohn's disease, ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

News and press release archive
Committee meeting highlights
Calendar
Public consultations
Statistics
What's new
Press contacts
Logo and visual identity
Leaflets
RSS feeds
Public health threats and pandemics
Outcome of UK referendum

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 18-21 July 2016

News

22/07/2016

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 18-21 July 2016

Eight medicines recommended for approval; use of Truvada extended to include pre-exposure prophylaxis (PrEP) against HIV-1 infection

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended eight medicines for approval at its July meeting.

The CHMP recommended granting marketing authorisations for two medicines for the treatment of advanced renal cell carcinoma (kidney cancer). **Cabometyx** (cabozantinib) and **Kisplyx** (lenvatinib) are indicated for the treatment of adult patients with advanced renal cell carcinoma who have been previously treated with a

Two biosimilar medicines, **Inhixa** and **Thorinane** (both containing enoxaparin sodium), received positive opinions for the prevention and treatment of various disorders related to blood clots in adults.

recommended a PUMA since the introduction of this type of marketing authorisation by the Paediatric Regulation, which came into force in 2007. Please see the questions and answers document in the grid below for more information on this opinion.

The Committee recommended granting a marketing authorisation for the orphan medicine **Onivyde** (irinotecan) for the treatment of metastatic adenocarcinoma of the pancreas.

Truberzi (eluxadoline) was recommended for approval for the treatment of irritable bowel syndrome with diarrhoea.

A generic medicine, **Tenofovir disoproxil Zentiva** (tenofovir disoproxil), was recommended for approval by the CHMP for the treatment of HIV-1 infection and chronic hepatitis B.

Two biosimilar medicines, **Inhixa** and **Thorinane** (both containing enoxaparin sodium), received positive opinions for the prevention and treatment of various disorders related to blood clots in adults.

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 7-10 November 2016

News

11/11/2016

Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 7-10 November 2016

Nine medicines recommended

The European Medicines Agency's
Use (CHMP) recommended nine m

The CHMP recommended granting
alfa) for the prevention and treatm

Vemlidy (tenofovir alafenamide)
treatment of chronic hepatitis B.

Fiasp (insulin aspart) was recommended for approval by the CHMP for the treatment of diabetes.

Suliqua (insulin glargine / lixisenatide) was recommended for approval for the treatment of type 2 diabetes.

Three biosimilar medicines were recommended for approval by the Committee: **Lusduna** (insulin glargine) for the treatment of diabetes, and **Movymia** and **Terrosa** (both containing teriparatide) for the treatment of osteoporosis. A biosimilar medicine is a biological medicine that is similar to another biological medicine that is already authorised for use.

Two generic medicines were recommended for approval: **Darunavir Mylan** (darunavir) for the treatment of human immunodeficiency virus (HIV-1) infection and **Tadalafil Generics** (tadalafil) for the treatment of pulmonary arterial hypertension.

Three biosimilar medicines were recommended for approval by the Committee: **Lusduna** (insulin glargine) for the treatment of diabetes, and **Movymia** and **Terrosa** (both containing teriparatide) for the treatment of osteoporosis. A biosimilar medicine is a biological medicine that is similar to another biological medicine that is already authorised for use.

How to establish biosimilarity?

1. **extensive characterization** *(physico-chemical, biological)*

2. ***in vitro* functional activity** *(analyzing all possible MoA of the molecule)*

3. **efficacy and safety** *(most sensitive population to detect differences)*

Analytical comparability
Clinical
PK/PD
Preclinical
Biological characterization
Physicochemical characterization
Lower
Higher
Sensitivity to detect differences

How to establish biosimilarity?

1. **extensive characterization** *(physico-chemical, biological)*

2. ***in vitro* functional activity** *(analyzing all possible MoA of the molecule)*

3. **efficacy and safety** *(most sensitive population to detect differences)*

Step 1: PK/PD
Step 2: E & S

Primary objective:

to show comparable PK in a sufficiently sensitive and homogeneous population.

Healthy volunteers OK
(patients, if a toxic MoA)

PK studies

Use of **multiple PD markers** recommended (if possible)

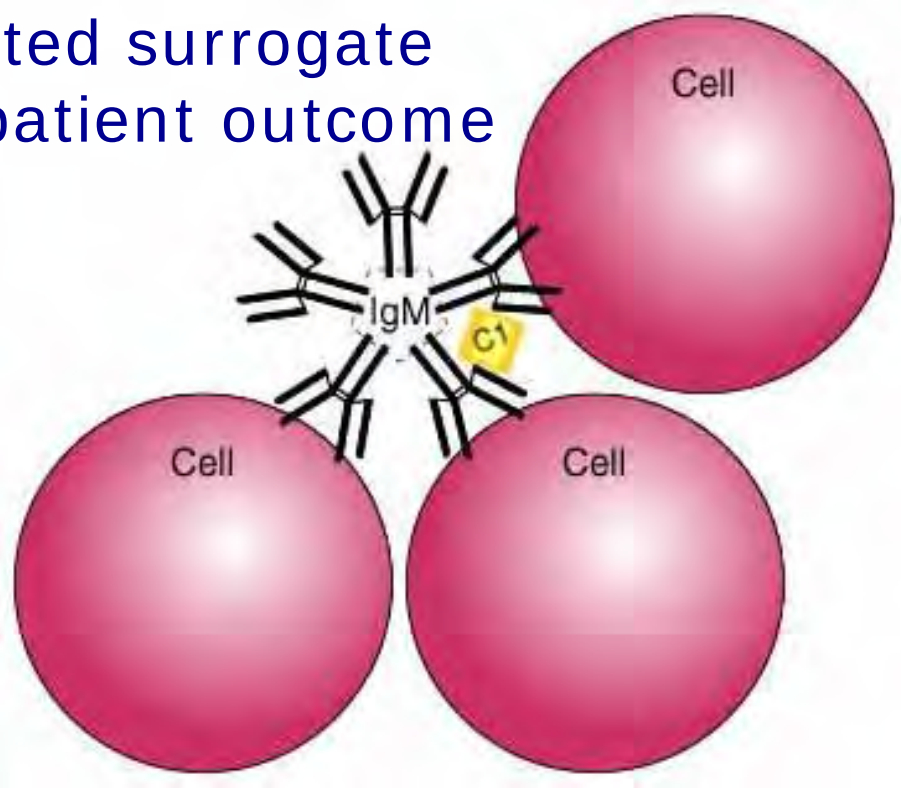
Explore dose-concentration-response or time-response relationships

PD markers as **pivotal evidence** for comparable efficacy if:

- Clear dose-response relationship shown
- At least one PD marker is an accepted surrogate marker and can be related to patient outcome

If not ⟶ Step 2

PD STUDIES



E & S

- Adequately powered, randomised, parallel group comparative clinical trial, preferably double-blind, normally equivalence trials.
- Deviation from relevant efficacy guidelines should be justified
- Most sensitive patient population and clinical EP preferred
- Comparative S data (immunogenicity)
- Extrapolation of indications: possible; based on the overall evidence of comparability

REMSIMA (infliximab)

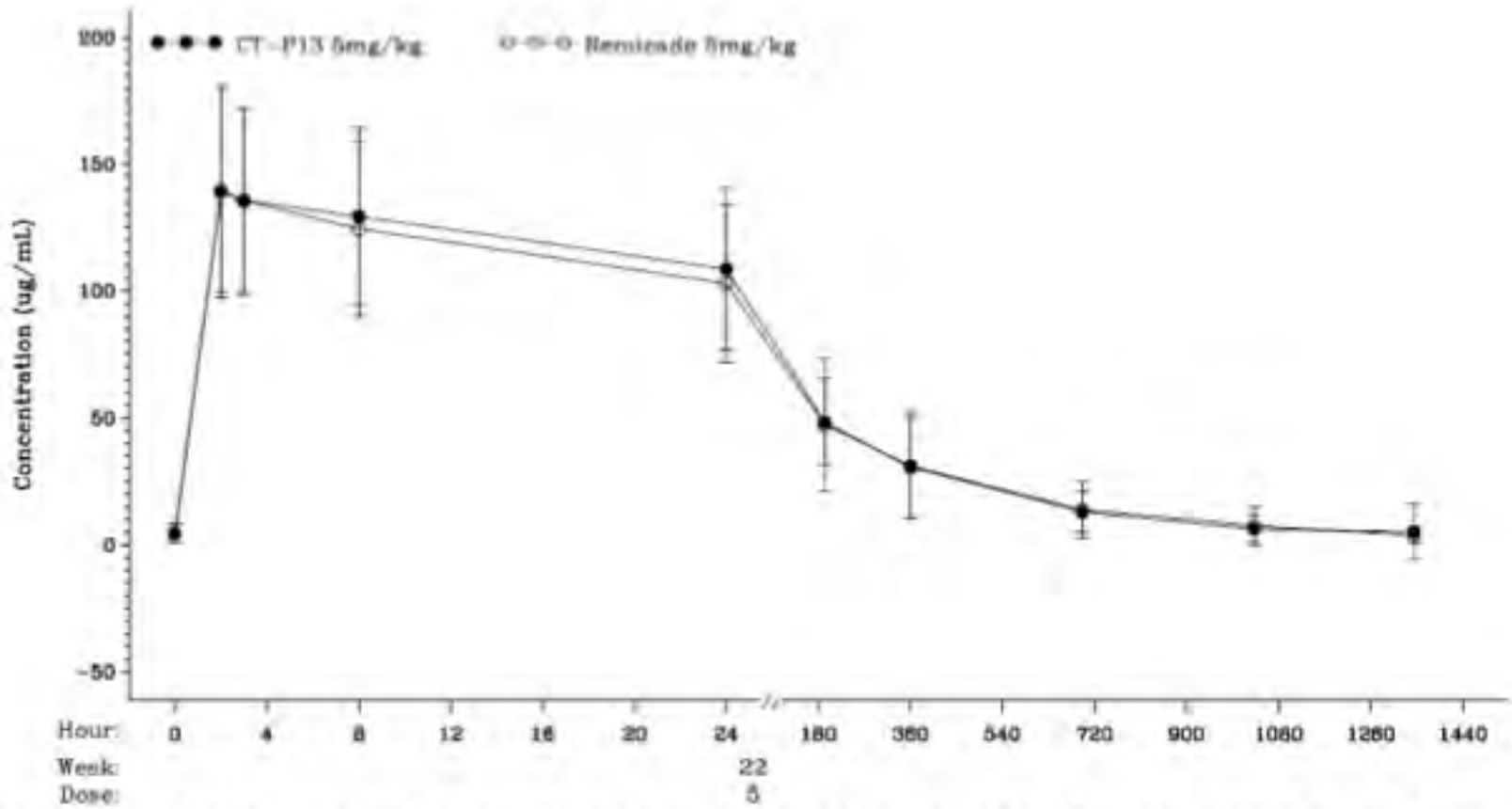
- A large -250 patients-, multiple-dose, **PK study** in patients with **ankylosing spondylitis** showed BE of the biosimilar and the reference product (supportive evidence for comparable safety, efficacy, and immunogenicity)

- Equivalent **efficacy** and comparable **safety** and **immunogenicity** (randomized, controlled clinical trial in **rheumatoid arthritis**; 606 patients)

Table 13 Tabular overview of clinical studies

Protocol	Design	Objectives	Treatment	Study population
CT-P13 1.2 (pilot study)	Prospective Phase 1, randomised double-blind, parallel-group, multiple single-dose intravenous (i.v.) infusion, multicentre	Primary: To determine C_{max}, PK profiles of CT-P13 and Remicade at Weeks 0, 2 and 6 Secondary: PK profile, PD, efficacy, and safety of CT-P13 in comparison to Remicade up to Week 102.	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 20 Randomised: 19 CT-P13: 9 Remicade: 10
CT-P13 1.1 PK equivalence (Study name: PLANET AS)	Prospective Phase 1, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group	Primary: To demonstrate comparable PK at steady state in terms AUC_T, $C_{max,ss}$ between CT-P13 and Remicade determined between Weeks 22 and 30. Secondary: long-term efficacy, PK and overall safety up to Week 54	CT-P13 or Remicade	AS patients with active disease Planned: 246 (ratio: 1:1) Randomised: 250 CT-P13: 125 Remicade: 125
CT-P13 3.1 Therapeutic equivalence (Study name: PLANET RA)	Prospective Phase 3, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group	Primary: To demonstrate that CT-P13 is equivalent to Remicade, in terms of efficacy as determined by clinical response according to ACR20 at Week 30. Secondary: long-term efficacy, PK, PD, and overall safety up to Week 54	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 584 (ratio: 1:1) Randomised: 606 CT-P13: 302 Remicade: 304

ACR20=20% improvement according to the ACR criteria; AS=Ankylosing spondylitis; AUC_T=Area under the concentration-time curve over the dosing interval; Cmax=maximum serum concentration; i.v.=intravenous; MTX=methotrexate; PK=Pharmacokinetics; PD=Pharmacodynamics; RA=Rheumatoid arthritis



Mean (±SD) serum concentrations (µg/ml) of infliximab vs time (h) by treatment for dose 5; PK population

Supportive PK data

Study CT-P13 3.1

Methods

Supportive PK data were generated from the pivotal efficacy trial, which was designed to show therapeutic equivalence of CT-P13 and Remicade. PK parameters were included as secondary endpoints. Blood samples were taken at each dose as in the pivotal PK study (without additional sampling after Dose 5) and the same PK parameters were estimated. The study treatment was the same as in the pivotal PK trial except for the dose, 3 mg/kg. In addition, MTX (12.5 to 25 mg/week oral or parenteral) with folate was co-administered.

Outcomes and estimation

Primary endpoint

In the all-randomised population, the proportion of ACR20 responders at Week 30 was similar in the CT-P13 and Remicade treatment arms (184 [60.9%] patients and 178 [58.6%] patients, respectively). The 95% CI for the estimate of the treatment difference was entirely contained within the range -0.15 to + 0.15 (95% CI: -0.06, 0.10) indicating therapeutic equivalence between the treatment arms. The results for the PP population supported the results for the all-randomised population. The sensitivity analysis including patients from the potentially fraudulent study centre indicated a similar trend to the main analysis.

Table 28 Proportion of ACR20 responders at Week 30 (exact binomial method)

Treatment Group	n/N' (%)	Estimate of Treatment Difference[1]	95% CI of Treatment Difference[2]
All-Randomized Population			
CT-P13	184/302 (60.9)	0.02	(–0.06, 0.10)
Remicade	178/304 (58.6)		
Per-Protocol Population			
CT-P13	182/248 (73.4)	0.04	(–0.04, 0.12)
Remicade	175/251 (69.7)		

ACR20, American College of Rheumatology definition of a 20% improvement; CI, confidence interval.
Note: N'=the number of patients with an assessment, n=the number of patients with the event, (%)=n/N'×100.

1. Estimate of the difference in proportions between the 2 treatment groups (CT-P13 – Remicade) using the exact binomial test.
2. Therapeutic equivalence was concluded if the 95% CI for the difference in proportions between the 2 treatment groups was entirely contained within the range -15% to 15%.

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol & All-randomised At Week 30		
Descriptive statistics and estimate variability	Treatment group	CT-P13	Remicade
	Number of subjects	302	304
	ACR20 W30 (%) ALL-R	184/302 (60.9)	178/304 (58.6)
	PP	182/248 (73.4)	175/251 (69.7)
	ACR20 W14 (%) PP	180/248 (72.6)	164/251 (65.3)
	ACR50 W14 (%) PP	98/248 (39.5)	85/251 (33.9)
	ACR50 W30 (%) PP	105/248 (42.3)	102/251 (40.6)
	DAS28 (ESR) W14 Mean (SD) change PP	-2.22 ± 1.22	-2.10 ± 1.11
	DAS28 (ESR) W30 Mean (SD) change PP	-2.44 ± 1.39	-2.31 ± 1.27
	SF36 PF W14 Mean (SD) change PP	7.49 ± 9.42	5.90 ± 8.22

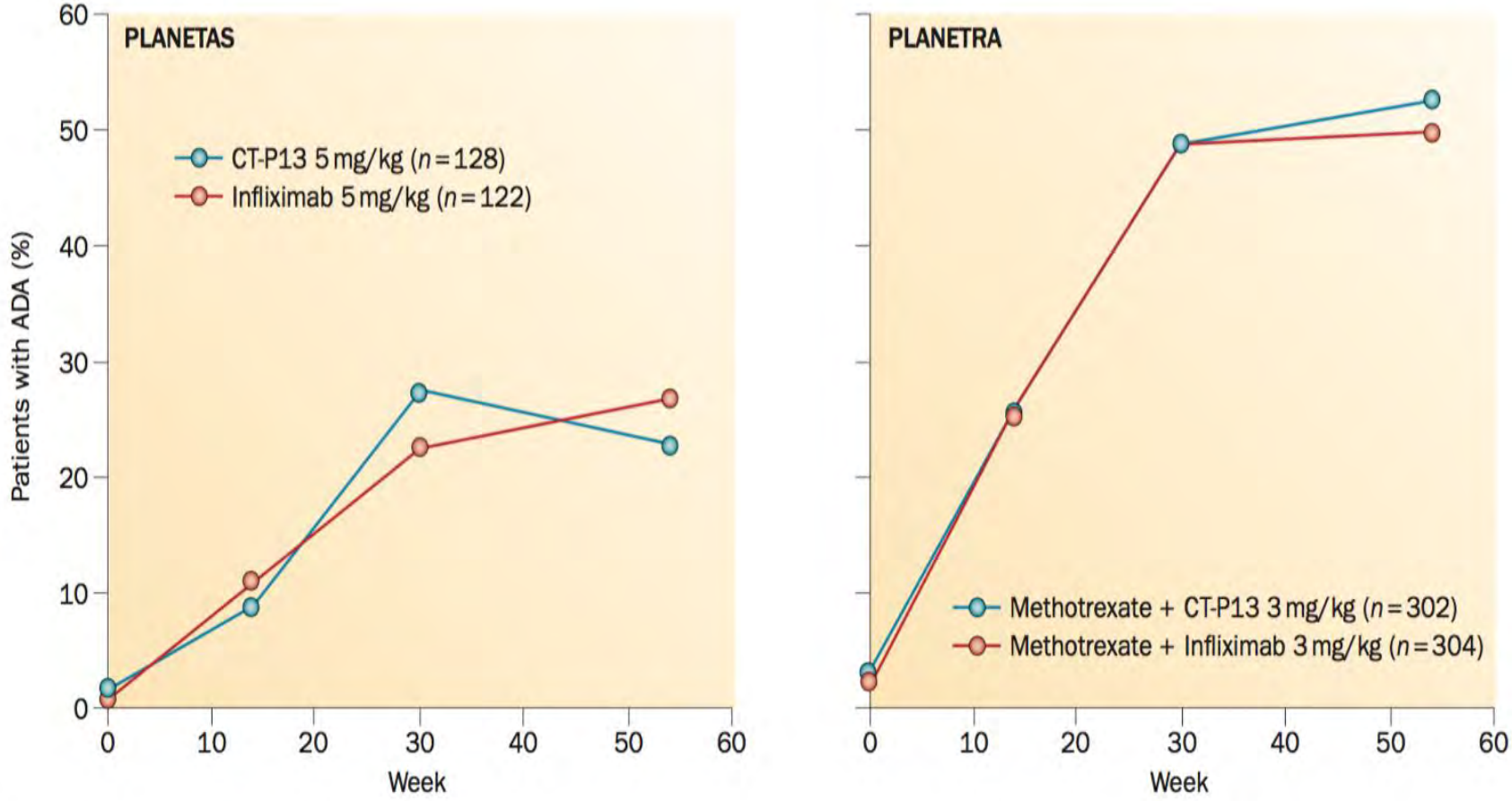


Figure 3 | ADA induction after treatment with infliximab or CT-P13. Comparative induction of ADAs against reference infliximab and CT-P13 in patients with ankylosing spondylitis (left) and rheumatoid arthritis (right) during two clinical studies (PLANETAS and PLANETRA, respectively).[14,15,32] ADAs were assessed by electrochemical-luminescent immunoassay technology (Meso Scale Discovery). Abbreviation: ADA, antidrug antibody.

Relevance of the PK results to all approved indications

Remicade is approved in several indications in inflammatory diseases, including RA, AS, PsA, adults and paediatric CD, adults and paediatric UC and Ps. Study CT-P13 1.1 designed to demonstrate PK equivalence of CT-P13 and Remicade was conducted in patients with AS. In accordance with the guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), the primary objective of PK studies performed to support a MAA for a similar biological medicinal product is to show comparability in PK of the biosimilar with the reference product in a sufficiently sensitive and homogeneous population. Patients with AS were considered as a sensitive population, because these patients are generally young, otherwise healthy and not receiving concomitant medication such as MTX, which has been shown to have an effect on anti-infliximab antibody status and thus on infliximab clearance (Xu et al. 2008). Furthermore, the available data and published literature on Remicade indicate that there are no significant differences in PK profiles for Remicade in patients with RA, adult and paediatric CD, and Ps (Klotz et al. 2007, Nestorov 2005) and there are no data to indicate that the PK profile in these three indications differ from the PK profile in AS patients. Also, infliximab serum levels in paediatric patients with CD were similar to those in adult CD patients.

A recent retrospective analysis of data from 2 phase III clinical trials in CD patients found that age did not influence infliximab PK in the range of 6 – 76 years (Fasanmade et al. 2011). Although the balance of data report similarities for infliximab PK profiles in different patient populations, it is noted that some studies report differences but these are attributed to differences in immunological responses in different populations. For example, the systemic clearance of infliximab was reported to be similar in patients with AS and RA (0.27 L/day), but lower than in patients with CD (0.36 L/day). In this PK study, it was concluded that of all the covariates evaluated, it was anti-infliximab antibody status that had the most significant influence on infliximab clearance being associated with accelerated clearance (Xu et al. 2008).

1 April 2016
EMA/CHMP/272283/2016
Committee for Medicinal Products for Human Use (CHMP)

FLIXABI (infliximab)

CHMP assessment report

Study	Study Objectives	Design	Study Population	Primary Endpoints
SB2-G11-NHV Phase I (Germany) Healthy subjects	Comparative PK, safety, tolerability, immunogenicity To investigate and compare the PK profiles of SB2 and EU-Remicade in healthy subjects.	Randomised, single-blind, three-arm, parallel group, single-dose study; Total duration: 10 weeks Single dose *i.v.* infusion of 5 mg/kg either SB2, EU- or US-Remicade	159 healthy subjects (53/arm)	AUCinf

SB2-G31-RA Phase III (UK,Czech Republic, Bulgaria, Lithuania, Latvia, Poland, Romania, Bosnia, Ukraine, Korea, India, Mexico, Philippines) RA subjects	Safety, efficacy, immunogenicity, and PK To demonstrate the equivalence of SB2 to EU-Remicade at Week 30, in terms of the ACR20 response rate in subjects with moderate to severe RA despite methotrexate (MTX) therapy	Randomised, double-blind, parallel group, multicentre study; Total duration: 78 weeks Randomised, Double- Blind period: 54 weeks *i.v.* infusions of 3 mg/kg SB2 or EU-Remicade at Weeks 0, 2, 6 and then every 8 weeks until Week 46. After Week 30 dose increments by 1.5 mg/kg per visit up to 7.5 mg/kg allowed if the subject`s RA symptoms are not well controlled by the existing dose. Transition-Extension period: 24 weeks *i.v.* infusions of 3 to 7.5 mg/kg SB2 or EU Remicade® every 8 weeks at Weeks 54, 62 and 70.	584 RA subjects (291 for SB2, 293 for EU-Remicade)	Efficacy: ACR20 at Week 30 PK: Ctrough

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Per Protocol Set week 30			
Descriptive statistics and estimate variability	Treatment group	SB2	Remicade	
	Number of subject	231	247	
	ACR20 at week 30 (Response rate)	64.1%	66.0%	
	ACR50 at week 30 (Response rate)	35.5%	38.1%	
	ACR70 at week 30 (Response rate)	18.2%	19.0%	
Effect estimate per comparison	Primary endpoint ACR20 at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-1.88%	
		95%-CI	(-10.26%, 6.51%)	
		P-value	N/A	
	Secondary endpoint ACR50 at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-2.13%	
		95%-CI	(-10.69%, 6.43%)	
		P-value	N/A	
	Secondary endpoint ACR70 at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-0.25%	
		95%-CI	(-7.26%, 6.75%)	
		P-value	N/A	

Analysis description	**Secondary analysis**			
Analysis population and time point description	Full Analysis Set week 30			
Descriptive statistics and estimate variability	Treatment group	SB2	Remicade	
	Number of subject	290	293	
	ACR20 at week 30 (Response rate)	55.5%	59.0%	
	ACR50 at week 30 (Response rate)	30.7%	33.8%	
	ACR70 at week 30 (Response rate)	15.5%	17.1%	
Effect estimate per comparison	Primary endpoint ACR20* at week 30	Comparison groups	SB2 - Remicade	
		Difference in response	-2.95%	

		95%-CI	(-10.88%, 4.97%)
		P-value	N/A
	Secondary endpoint ACR50* at week 30	Comparison groups	SB2 - Remicade
		Difference in response	-2.53%
		95%-CI	(-10.07%, 5.00%)
		P-value	N/A
	Secondary endpoint ACR70* at week 30	Comparison groups	SB2 - Remicade
		Difference in response	-1.08%
		95%-CI	(-7.06%, 4.91%)
		P-value	N/A
	Secondary endpoint Change in DAS28 at week 30	Comparison groups	SB2 – Remicade
		Adjusted mean difference	0.044
		95%-CI	(-0.186, 0.274)
		P-value	N/A
Notes	*subjects with missing values imputed as non-responder		

Figure 10. ACR 20 response curves by ADA status at each time-point in Study SB2-G31-RA, PPS2

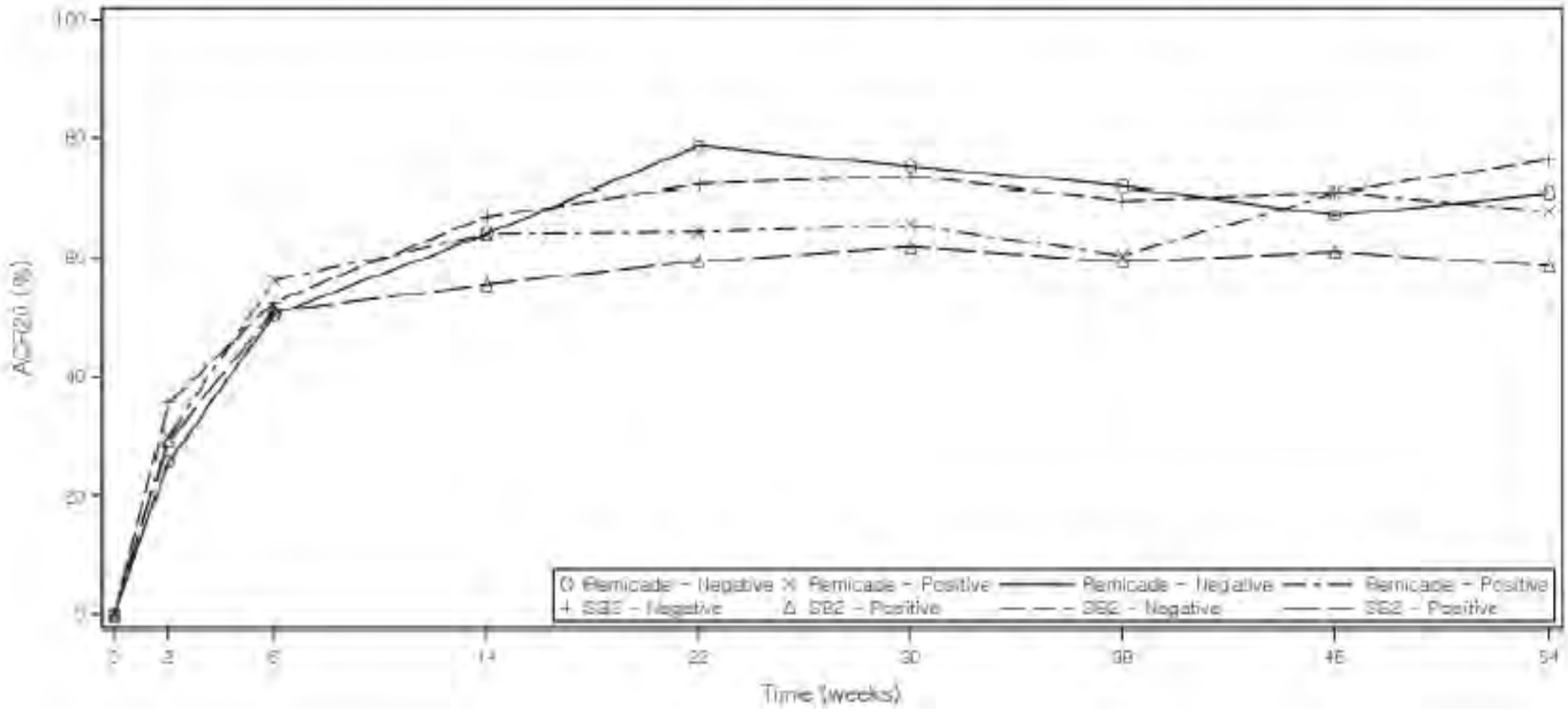


Figure 7. Mean and SD of trough concentrations of SB2 and EU Remicade by overall ADA up to Week 30 in Study SB2-G31-RA

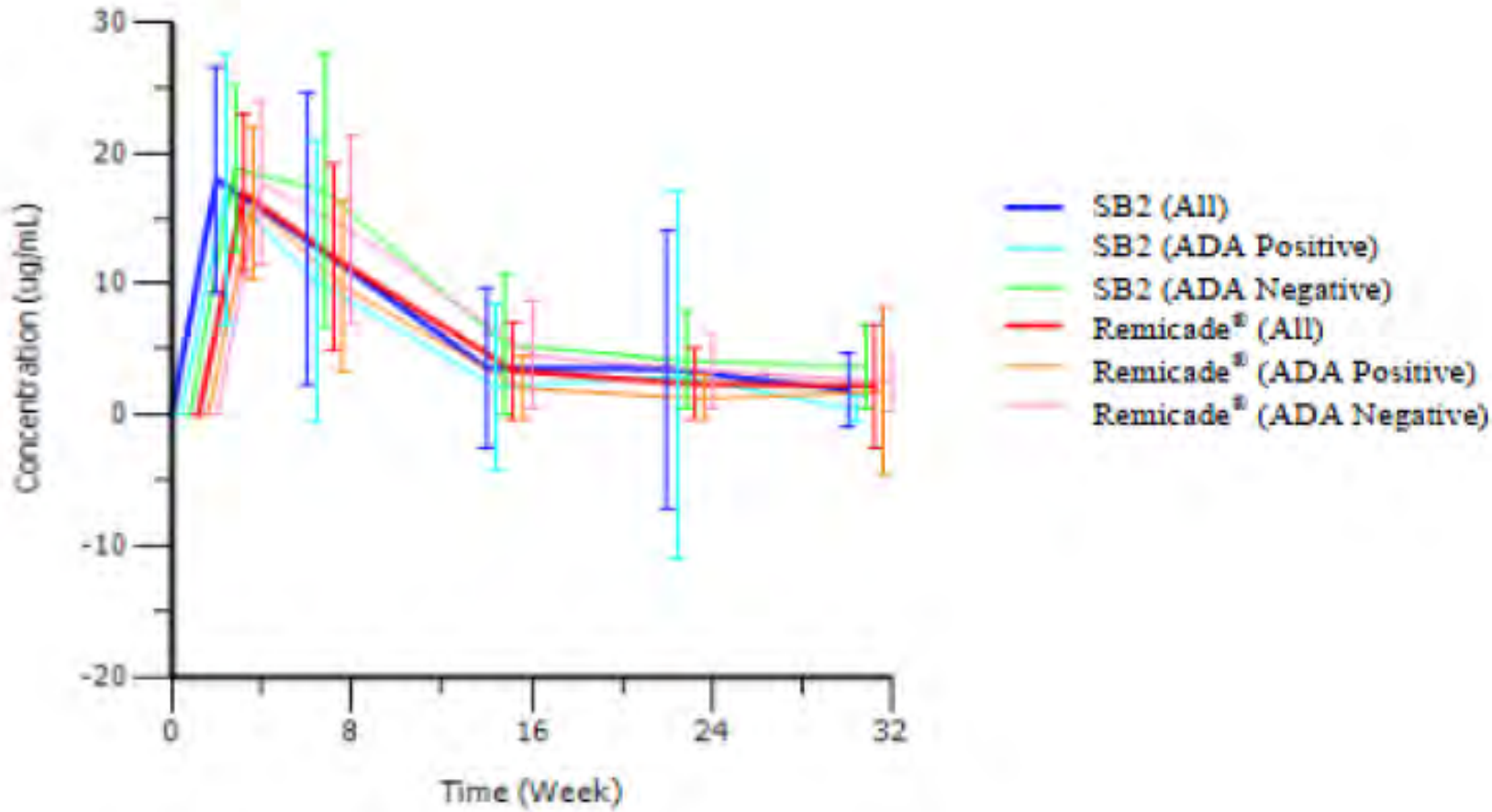
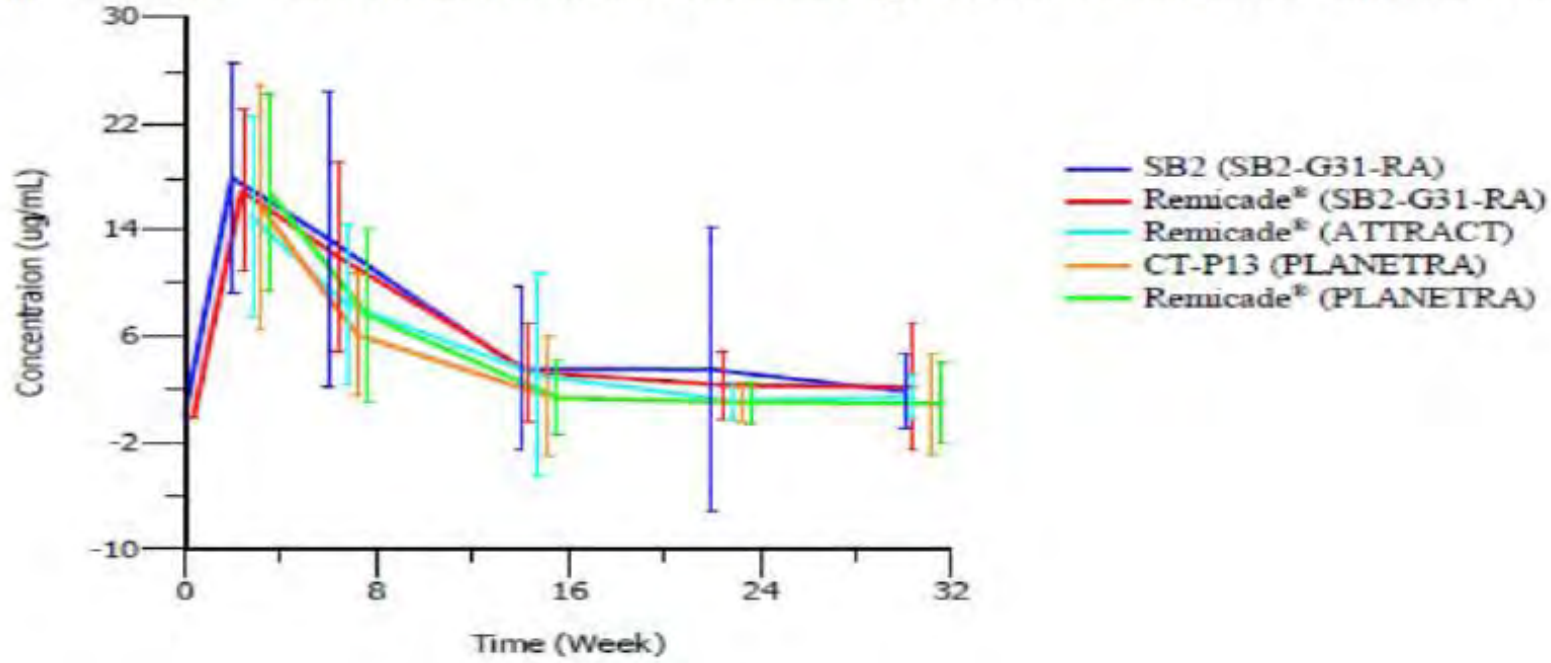


Figure 6. Mean and standard deviation of infliximab serum trough concentrations from different clinical studies



2.5.4. Conclusions on the clinical efficacy

The main efficacy study SB2-G31-RA conducted in RA patients provided robust evidence of equivalence between Flixabi and Remicade based on ACR20 response at Week 30, the primary endpoint, and this was supported by secondary efficacy parameters and sensitivity analyses.

The numerically higher rate of ADA that was observed in subjects treated with SB2 compared to EU-Remicade did not result in any meaningful differences in efficacy. Significantly, the number of subjects which required a dose increase was similar between the two treatment arms, and was not impacted by ADA status which provides further evidence of similarity in terms of efficacy.

In addition, PK was similar in the most sensitive model (PK study in healthy volunteers).

Therefore these results demonstrate equivalence in efficacy between the proposed biosimilar Flixabi and the reference product Remicade.

2.6. Clinical safety

The safety data base consisted of two studies, the phase III study in patients with RA and the phase I PK study in healthy volunteers. The safety results from the phase I PK study have been described in Section 2.4.2 of this report, and are considered supportive in characterising the short term safety profile of SB2.

Dose increase and impact of ADA

Dose increased patients were comparable in the SB2 treatment group compared to the EU Remicade treatment group. Among ADA positive patients (up to W30 ADA), the proportion of ever dose increased patients was also comparable; 55/158 (34.8%) vs. 56/145 (38.6%) in the SB2 and the EU Remicade treatment groups.

For PPS2, the ACR20 response rates for those who had a dose increase were 38.0% vs. 35.4% at Week 30 and 52.0% vs. 51.9% at Week 54. From these findings, the baseline efficacy at Week 30 as well as the overall improvement of efficacy after dose increase was considered to be comparable between the two treatment groups.

The similar trend was observed for the ACR50 and ACR70 response rates in PPS2.

Discussion on the benefit-risk balance

In accordance with the EU guidelines, the development of Flixabi comprised similarity exercises with comparison of the structural characteristics, physicochemical properties and biological activities between Flixabi and Remicade, followed by in vivo similarity studies.

In vitro and *in vivo* non-clinical studies confirmed the similarity of Flixabi and Remicade in PK and in TNF-α-related PD. Considering the mode of action of infliximab, the small differences observed in these studies were not considered to have any impact on the efficacy/safety profile of Flixabi.

Furthermore, in a sensitive clinical model (RA), the efficacy and safety of Flixabi was also shown to be similar to that of Remicade.

The historically reported rates of ADA formation for Remicade have been around 8% in patients with RA treated concomitantly with MTX, the rates observed in both Remicade and Flixabi treated patients in the submitted RA trial were considerably higher (5 to 6 fold). Thus, it can be concluded that the ADA assay used for this application has a profoundly increased sensitivity. It also follows that an increased sensitivity of the laboratory determination of ADA formation and therefore an increase in "immunogenicity" per se does not necessarily translate into a clinically relevant effect. Any observed difference in ADA formation rate therefore has to be judged in the context of clinical data observed in a trial and in this instance did not translate in any meaningful differences between Flixabi and Remicade.

For indications for which pathogenesis appears to be dominated by soluble TNF-α (ankylosing spondylitis, psoriatic arthritis and plaque psoriasis) extrapolation is supported by the TNF-α binding assay and the cell-based assay (TNF-α neutralisation assay by NF-κB reporter gene).

With respect to the membrane bound TNF-α, it has been reported that at least four distinct mechanisms are involved in the inhibition of TNF-α-bearing cells by anti-TNF agents: (i) inhibition of tmTNF-α-mediated effector functions, (ii) destruction of TNF-α-bearing cells by CDC, (iii) destruction of TNF-α-bearing cells by ADCC and (iv) destruction of TNF-α-bearing cells by outside-to-inside signal (reverse signalling). Transmembrane-TNF-α binding assays, but also Fc receptor binding assays, CDC, ADCC and apoptosis assays were performed. Overall, these results showed that Flixabi is similar to the reference product in terms of tmTNF-α related activities.

It has been described that the rate of ADA positivity is amongst other factors dependent on the population, dose, dose interruptions and co-medication. However, there is no reason to believe that the ADA formation would be affected differentially by these factors for molecules that are considered highly similar such as Flixabi and Remicade. Although, it may be argued that methotrexate used in the clinical trial may have reduced the immune response, it should be noted that anti-drug antibody development is nevertheless reportedly highest in patients with rheumatoid arthritis compared to other licensed indications of Remicade.

Biosimilars in rheumatology: current perspectives and lessons learnt

Thomas Dörner and Jonathan Kay

2015 NATURE REVIEWS | RHEUMATOLOGY

Immunogenicity of biosimilars

One of the interesting lessons provided by biosimilar research relates to aspects of immunogenicity, both for biosimilars and for reference products. Monoclonal antibodies generated *in vitro* to be administered to patients are foreign antigens that undergo a set of defined processes from transcription to various post-translational modifications (Figure 1). These processes can generate heterogeneity of the expressed monoclonal protein, which

immunogenicity. Although biosimilar age

by cell lines and undergo various purificat

studies reported to date have not found

ferences between biosimilars and their re

in the three domains rigorously studied d

development—pharmacokinetics, phar

and immunogenicity. These domains a

in the final two steps of clinical develop

fied by regulatory agencies, such as the

Interestingly, the different proprietary

to produce reference products and biosimilars have not resulted in differences in efficacy or safety, including immunogenicity. Although no definitive conclusions can be drawn from these observations, they suggest that the primary (nonproprietary) amino acid sequence is of the utmost importance in defining the characteristics of therapeutic antibodies.

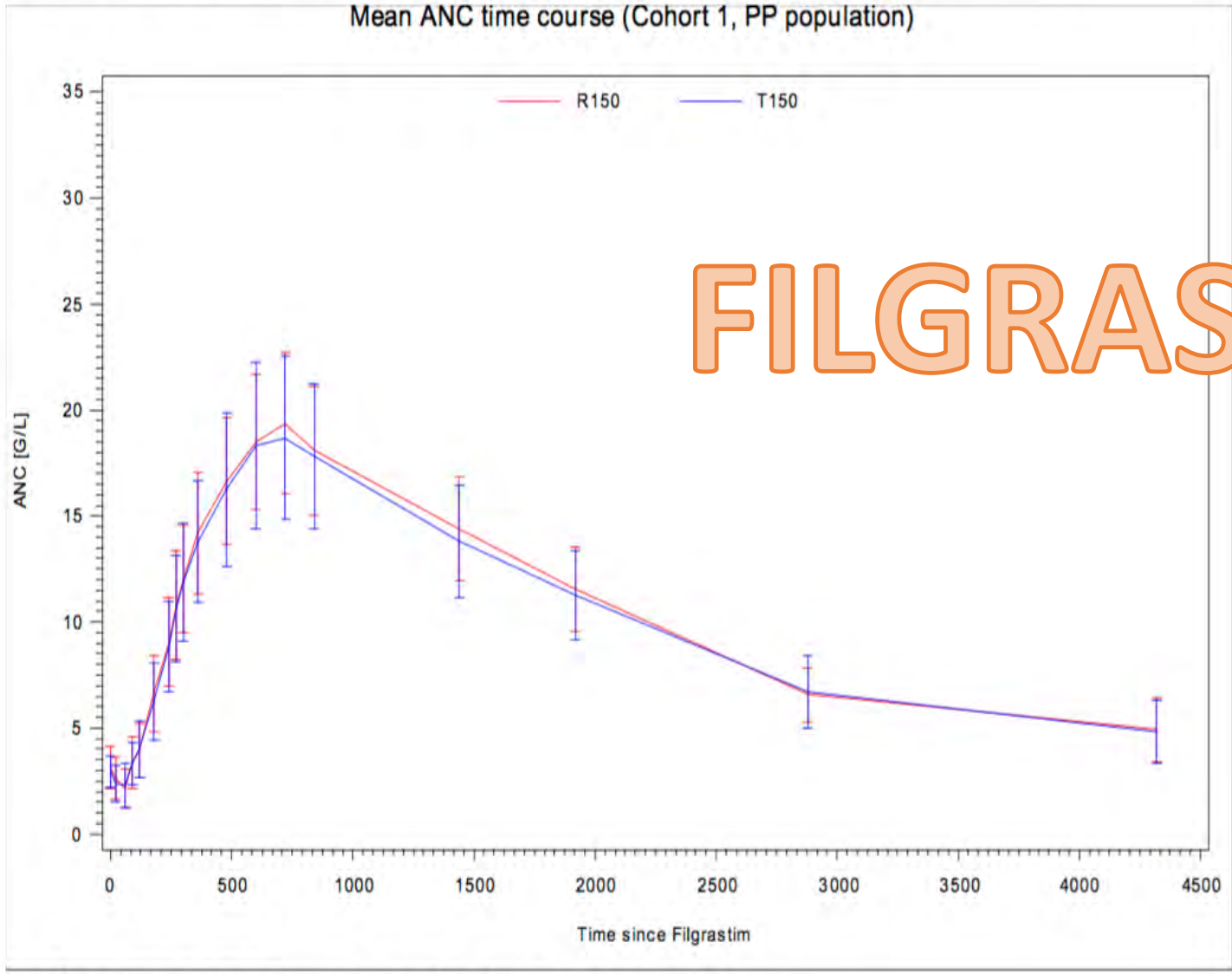
immunogenicity. Although no definitive conclusions can be drawn from these observations, they suggest that the primary (nonproprietary) amino acid sequence is of the utmost importance in defining the characteristics of therapeutic antibodies.

Therefore, with the totality of evidence, the CHMP considered that it was justifiable to extrapolate the equivalent clinical efficacy and the comparable safety profile from the Flixabi study in RA patients to all of the indications where Remicade has been approved.

The applicant intends to claim the same therapeutic indications for the biosimilar Flixabi as those granted for Remicade in the EU. Even though available data demonstrate that the numerically higher rate of ADA in Flixabi treated patients compared to Remicade as measured by the assays employed do not have an effect on the safety and efficacy in patients with RA, additional long-term data will be provided through the observational study in patients with ankylosing spondylitis and Crohn's disease.

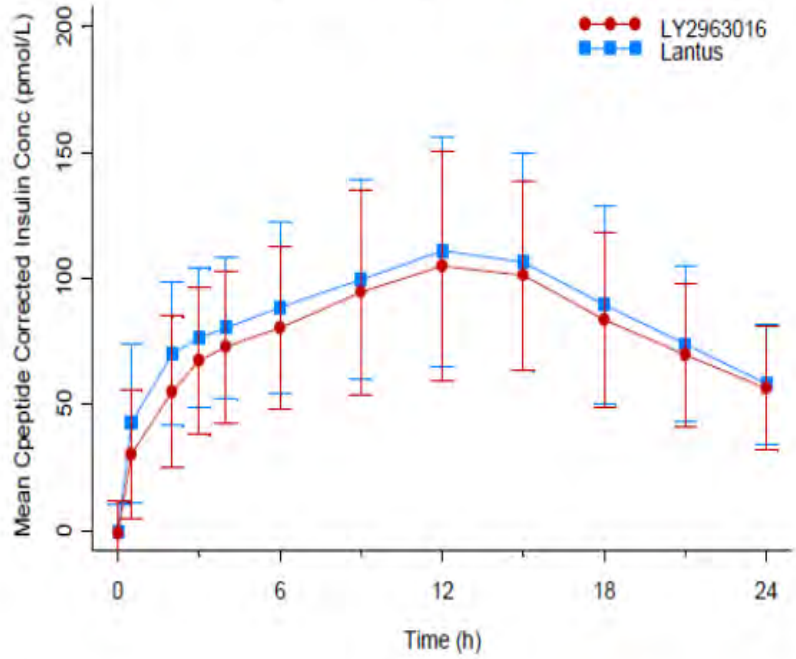
Absorption and Distribution

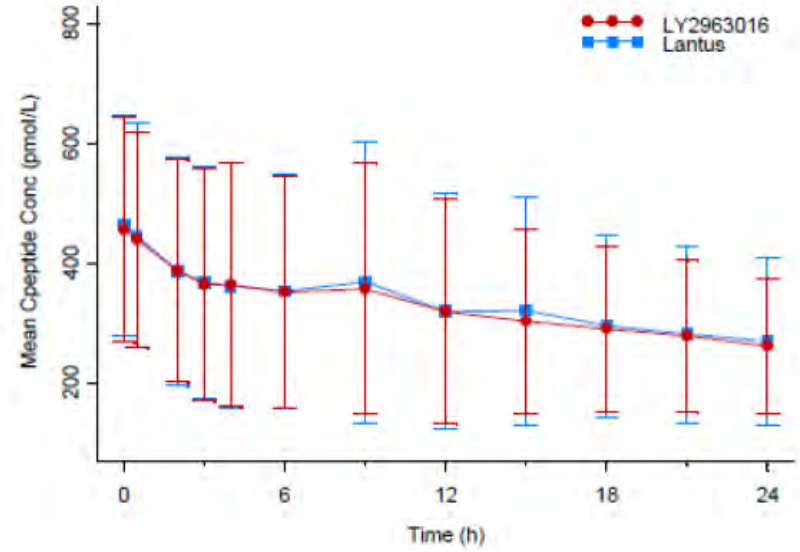
Figure 02: Study KWI-300-102: Mean ANC-Time Profile Following a Single Subcutaneous Injection of 150 µg of Apo-Filgrastim or Neupogen to Healthy Male and Female Volunteers (PP-Population)

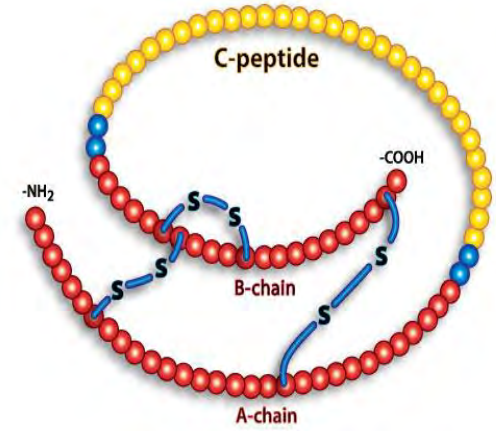


T150 = Apo-Filgrastim 150µg, R150 = Neupogen 150µg

Figure 5: PK & PD profiles in pivotal study ABEA (healthy volunteers; 0.5 U/kg)







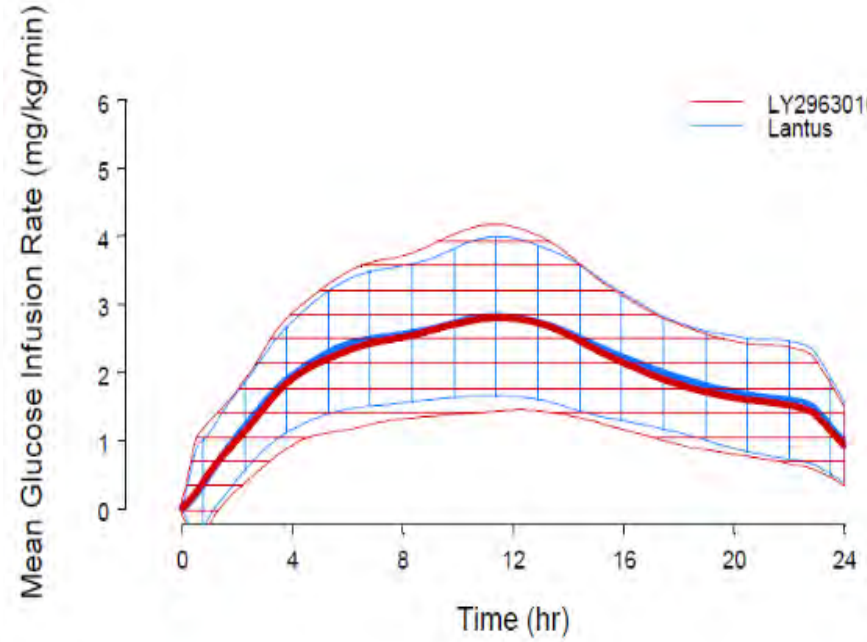
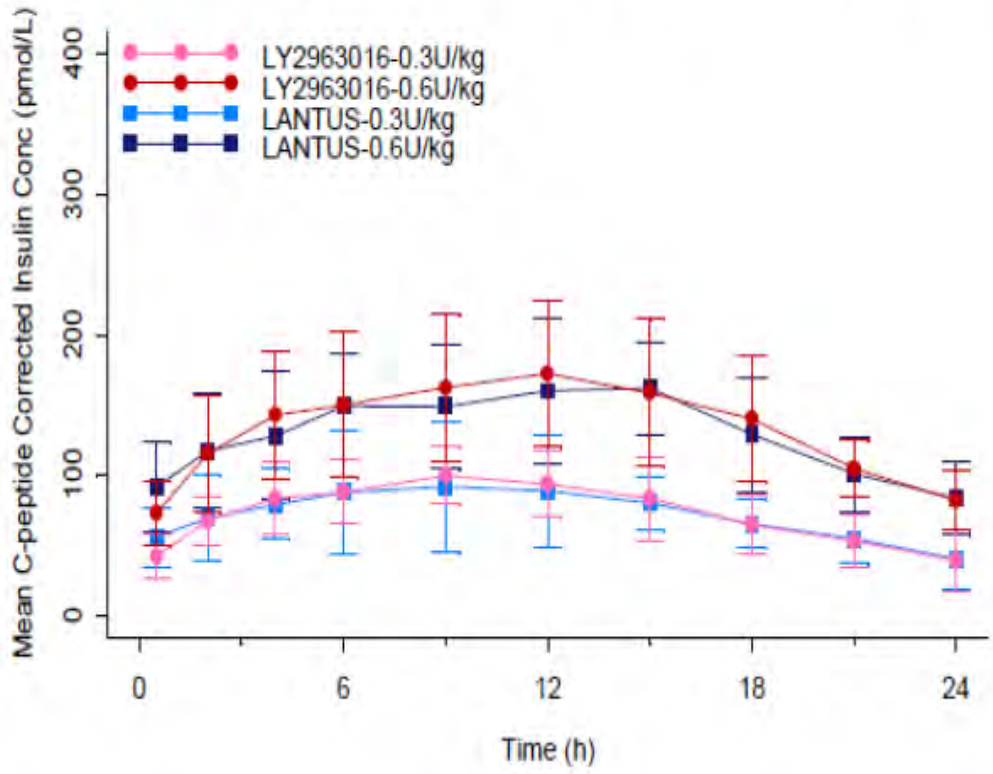
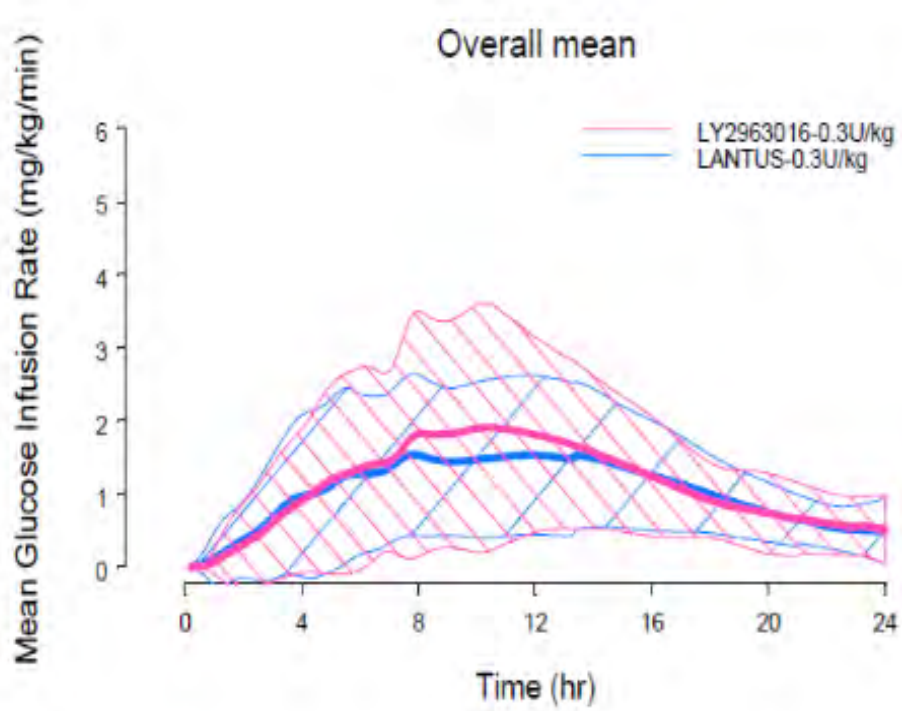
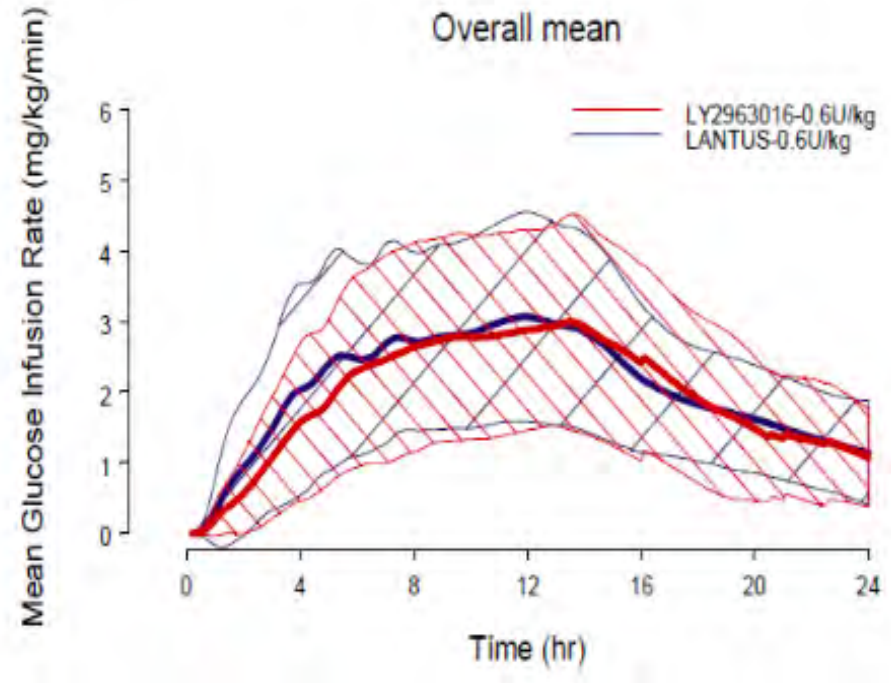


Figure 6: PK & PD profiles in study ABEM (healthy volunteers; 0.3 & 0.6 U/kg)




Overall mean
LY2963016-0.3U/kg
LANTUS-0.3U/kg
Mean Glucose Infusion Rate (mg/kg/min)
0
1
2
3
4
5
6
0
4
8
12
16
20
24
Time (hr)


Overall mean
LY2963016-0.6U/kg
LANTUS-0.6U/kg
Mean Glucose Infusion Rate (mg/kg/min)
0
1
2
3
4
5
6
0
4
8
12
16
20
24
Time (hr)

Biosimilars in rheumatology: current perspectives and lessons learnt

Thomas Dörner and Jonathan Kay

2015 NATURE REVIEWS | RHEUMATOLOGY

Key points

- Biosimilars are biopharmaceuticals that have been assessed by regulatory agencies to have efficacy and safety similar to their reference products and are expected to be marketed at substantially lower prices
- CT-P13 (an infliximab biosimilar) was the first monoclonal antibody biosimilar to be approved, but not all national regulatory agencies granted extrapolation to all infliximab indications
- A substantial proportion of patients treated with biopharmaceuticals develop antidrug antibodies, regardless of whether they received a biosimilar or the reference product
- Establishing a nomenclature system that facilitates traceability for the purpose of pharmacovigilance is a key issue in the adoption of biosimilars in clinical practice
- Extrapolation of indications for biosimilars is possible, but concerns have been raised regarding the potential efficacy and safety of a biosimilar in diseases for which it has not been studied

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMEA/CHMP/BMWP/42832/2005 Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

6. Extrapolation of indications

Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification. If pivotal evidence for comparability is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications. Applicants should support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action.

6. Extrapolation of indications

Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification. If pivotal evidence for comparability is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications. Applicants should support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action.

For example, if a reference mAb is licensed both as an immunomodulator and as an anticancer antibody, the scientific justification as regards extrapolation between the two (or more) indications is more challenging. The basis for such extrapolation forms an extensive quality and non-clinical database, including potency assay(s) and *in vitro* assays that cover the functionality of the molecule, supplemented by relevant clinical data as described further in this document. The possibility of extrapolating safety including immunogenicity data also requires careful consideration, and may have to involve more specific studies (see sections 5 and 7). For the mechanism of action, e.g. the depletion of immune cells, several mechanisms may play a role in the various clinical conditions. For example, ADCC appears to be more important in some indications than in others. To provide further evidence about the mechanism of action, it may also be helpful to perform a literature search to identify what is known, e.g. about potential signalling inhibition by the reference mAb that would not be covered by ADCC/CDC tests, in particular direct induction of apoptosis. This could provide more knowledge on potential read-outs that could be used to support comparability on a molecular level.

Extrapolation of data is already an established scientific and regulatory principle that has been exercised for many years, for example, in the case of **major changes** in the manufacturing process of **originator biologicals**.

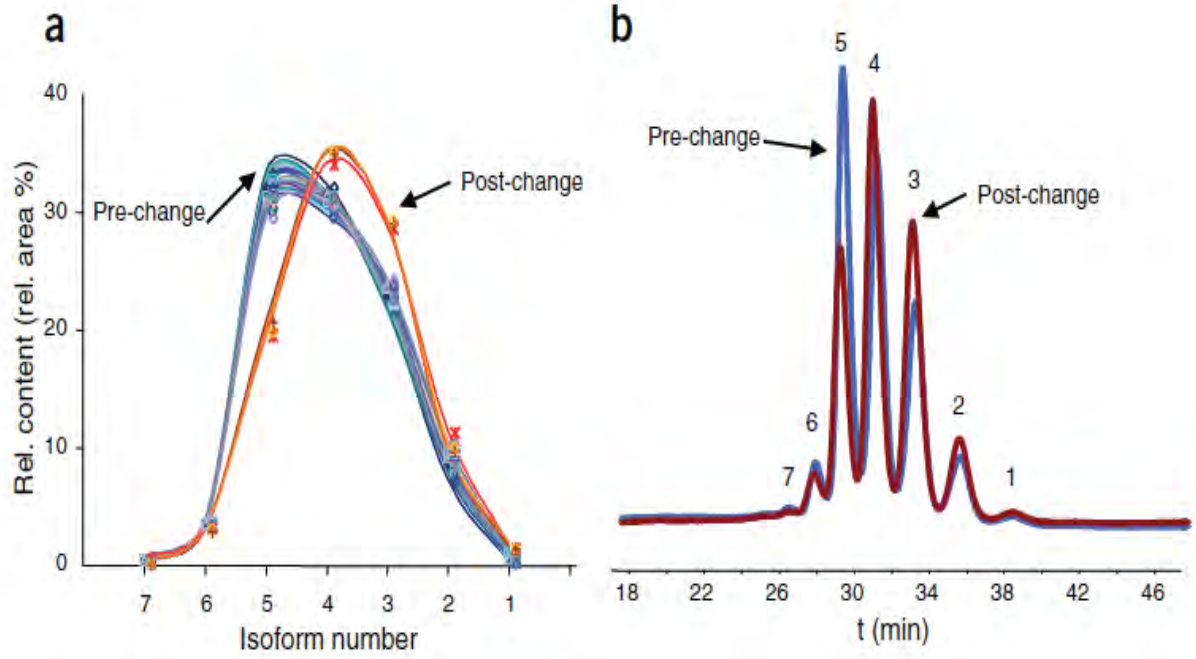


Figure 1 Comparison of the pre- and post-change Aranesp batches measured by capillary zone electrophoresis. (**a**) Relative content of the individual isoforms of the pre-change ($n = 18$) and the post-change ($n = 4$) batches. (**b**) Representative electropherograms; peaks are labeled with the isoform number.

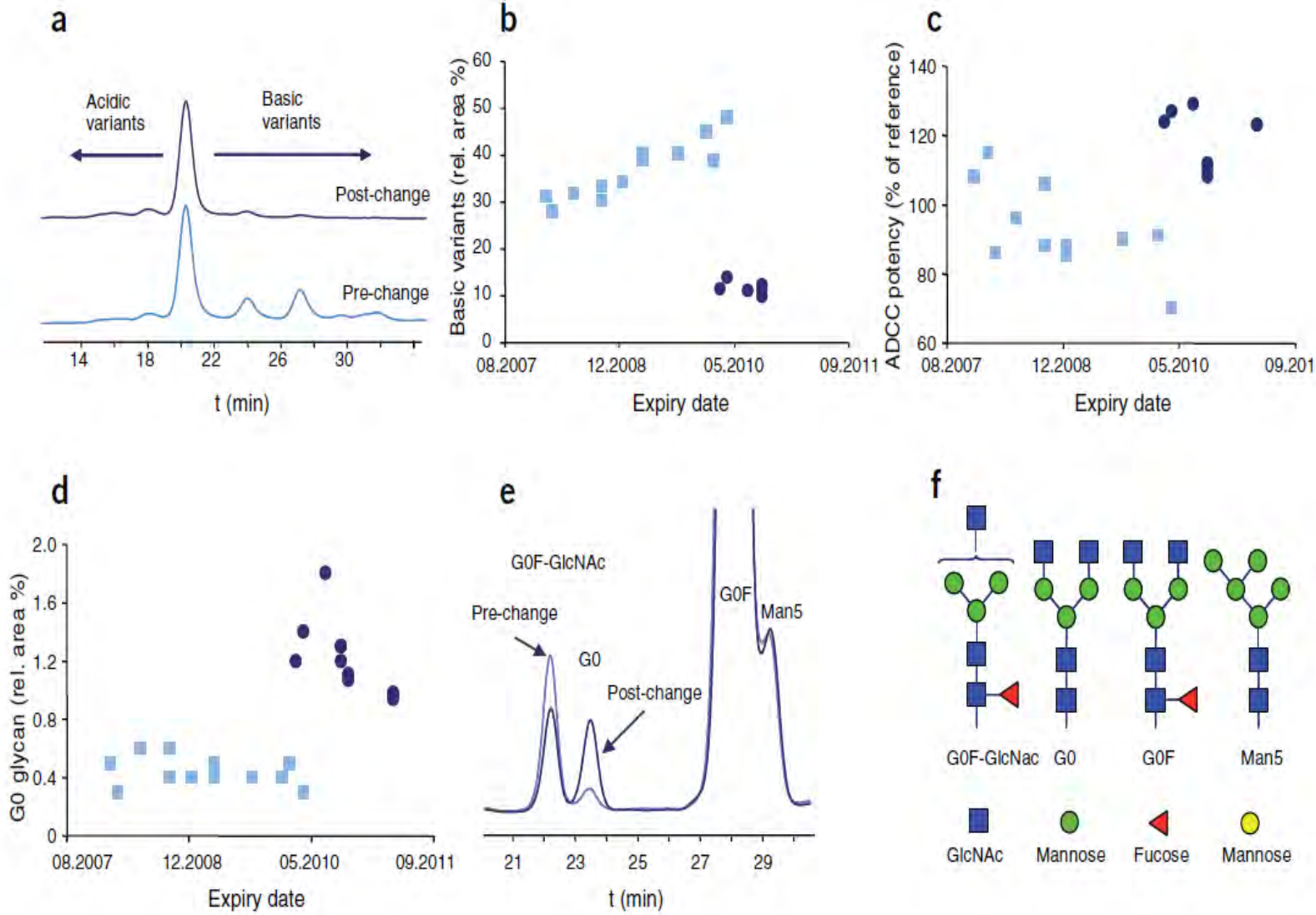
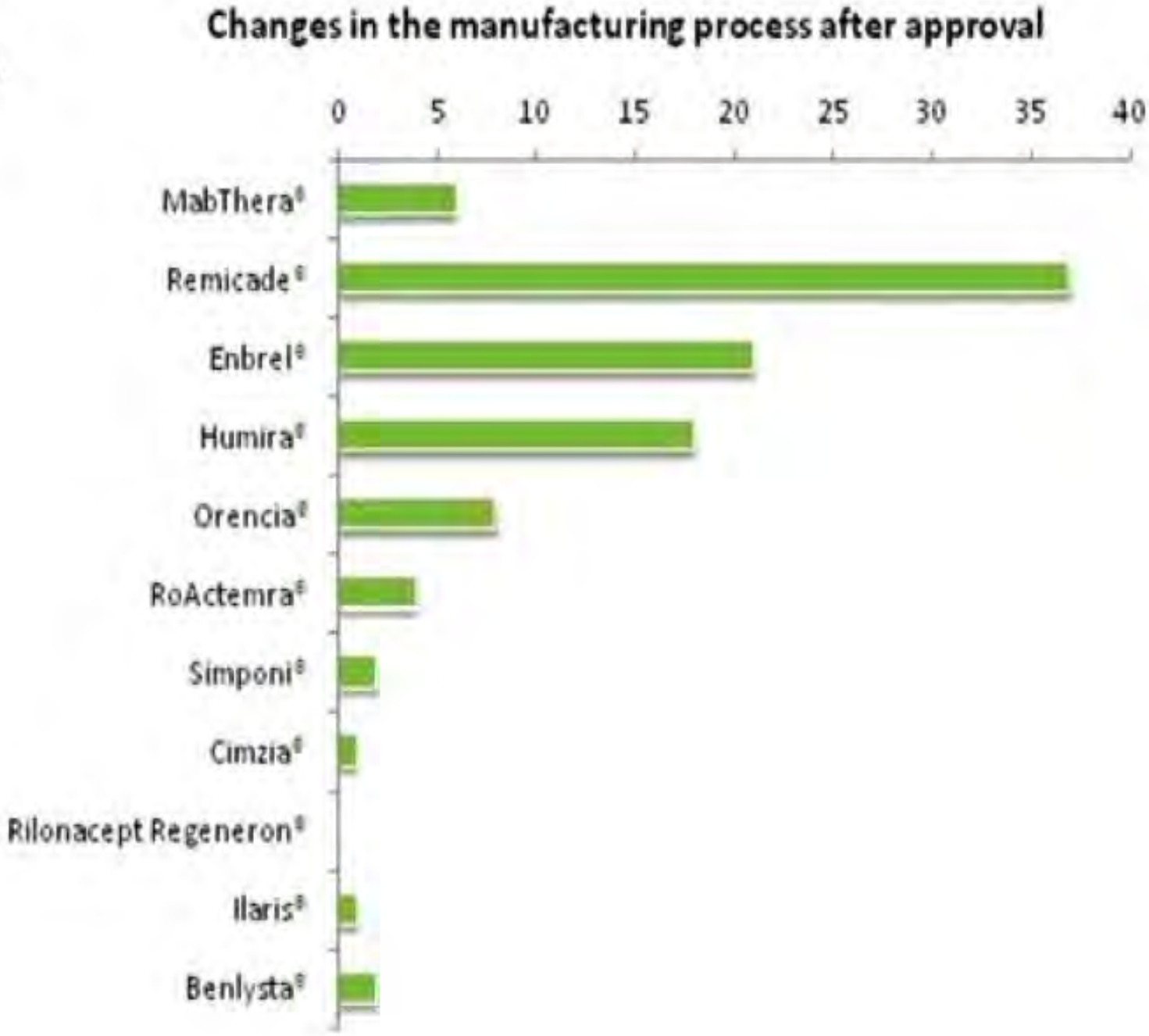


Figure 2 Comparison of the different pre- and post-change batches of Rituxan/Mabthera. (**a**) Exemplary CEX chromatograms. (**b**) Amount of basic variants of the pre-change ($n = 12$) and post-change ($n = 6$) batches as measured by CEX. (**c**) ADCC potency of the pre-change ($n = 11$) and post-change ($n = 8$) batches. (**d**) Relative amount of the G0 glycan of the pre-change ($n = 13$) and post-change ($n = 11$) batches. (**e**) Exemplary glycan mapping chromatogram (**f**) Glycan legend.

A


Changes in the manufacturing process after approval
0
5
10
15
20
25
30
35
40
MabThera®
Remicade®
Enbrel®
Humira®
Orencia®
RoActemra®
Simponi®
Cimzia®
Rilonacept Regeneron®
Ilaris®
Benlysta®

Another example where extrapolation has already been accepted is the introduction of a new subcutaneous (SC) formulation of a hitherto intravenously (IV) applied product. Although the formulation and bioavailability of the SC product will be different, one clinical study is usually sufficient to grant several, if not all, clinical indications approved for the IV product. This is illustrated by the recent approval of an SC formulation of an anti-Her2 monoclonal antibody (mAb) based on clinical data in the neoadjuvant setting, which were extrapolated to the metastatic setting based on the totality of the evidence from all data provided.[27] It is notable that the SC formulation of that antibody contains recombinant human hyaluronidase (rHuPH20) as a permeation enhancer and is thus considerably different from the IV formulation. A formulation difference of this magnitude would not be acceptable for a biosimilar compared with the reference product.

Factors to considered for **extrapolation**:

- Clinical experience with the reference product
- MoA/active site(s) of the active substance in each indication (including its degree of certainty)
- Target receptors involved
- Differences in the safety/immunogenicity profile between the therapeutic indications, including considerations on patient-related factors (comorbidities, comedication, immunologic status) and disease-related factors (reactions related to the target cells, e.g lysis of tumor cells).
- The degree to which the functional moieties of the molecule can be analytically characterized and compared.

EXTRAPOLATION OF INDICATIONS
Points to consider

- Overall evidence of comparability
- Remaining uncertainties from the data provided
- Acceptable safety profile (including immunogenicity)

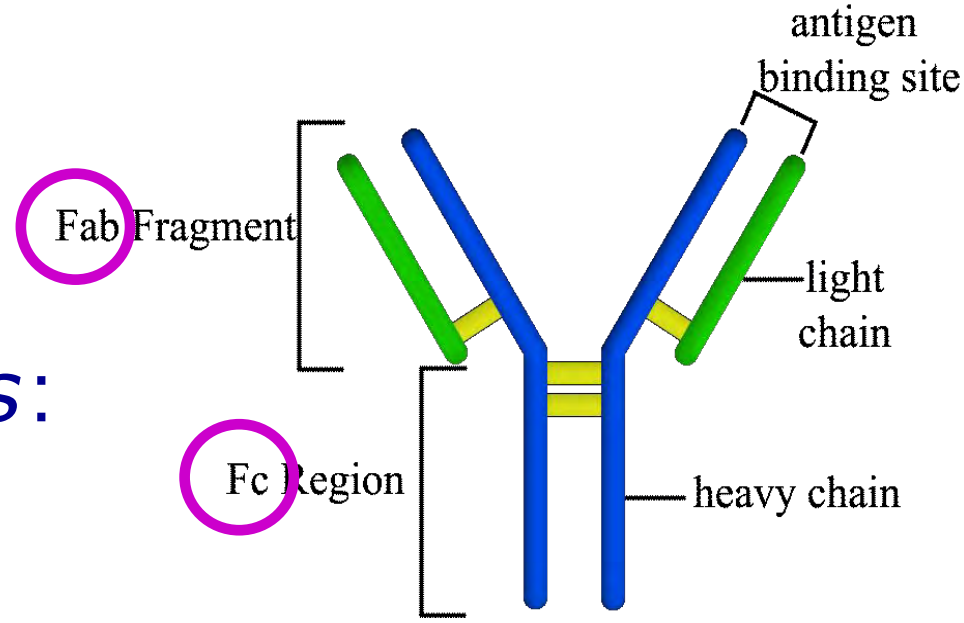
How to establish biosimilarity?

1. **extensive characterization** *(physico-chemical, biological)*

2. ***in vitro* functional activity** *(analyzing all possible MoA of the molecule)*

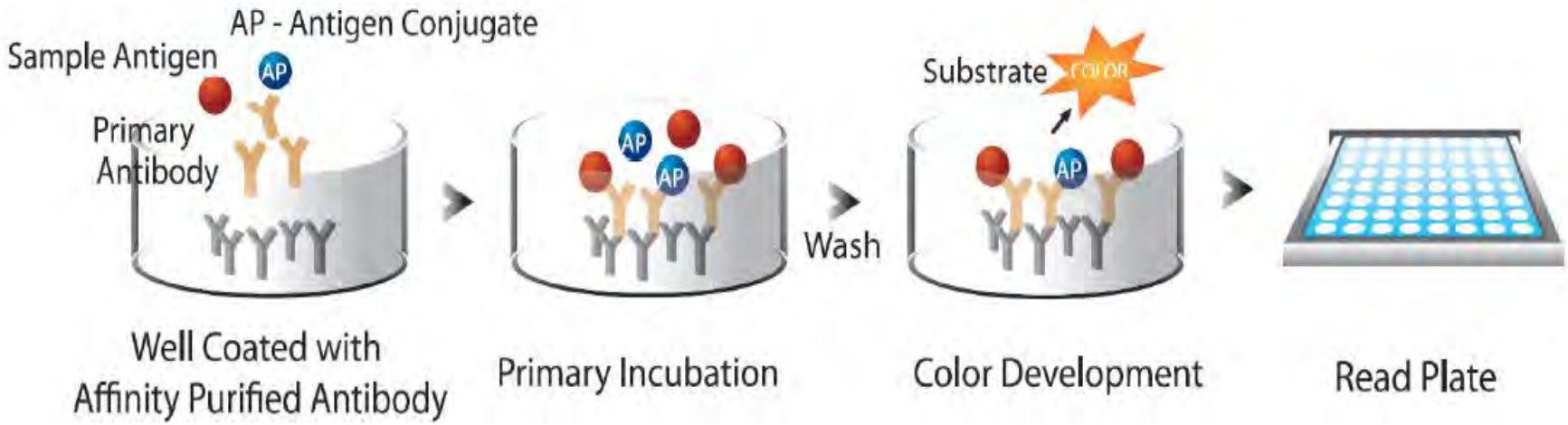
3. **efficacy and safety** *(most sensitive population to detect differences)*

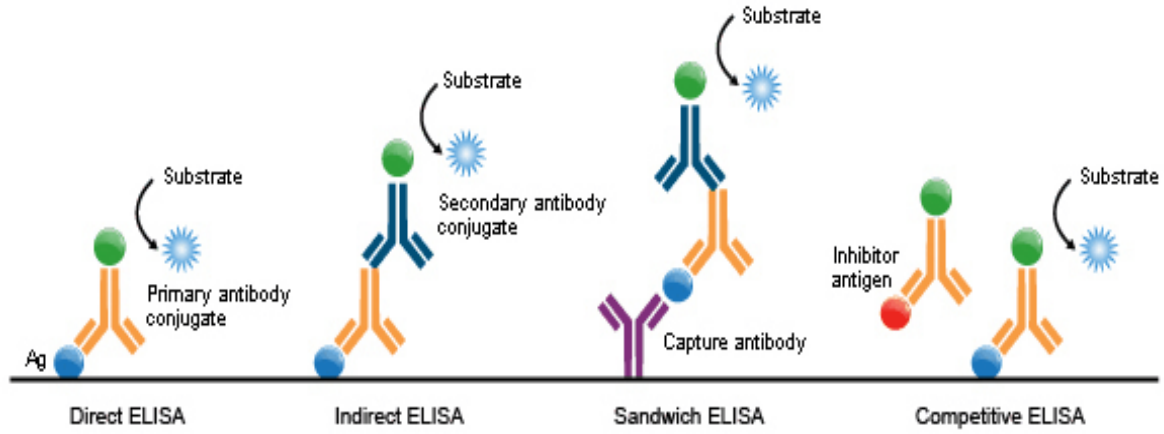
Additional *in vitro studies*:

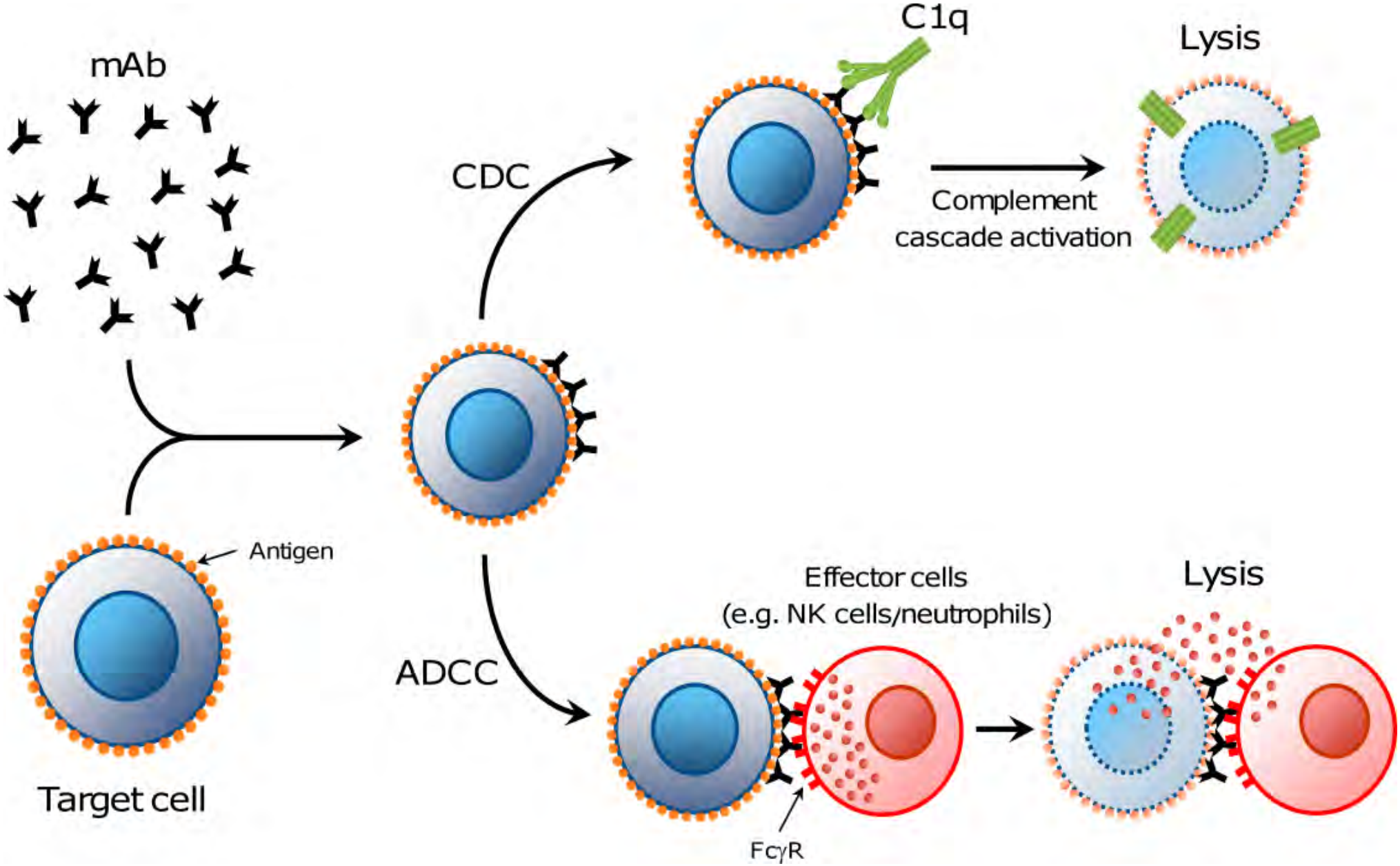


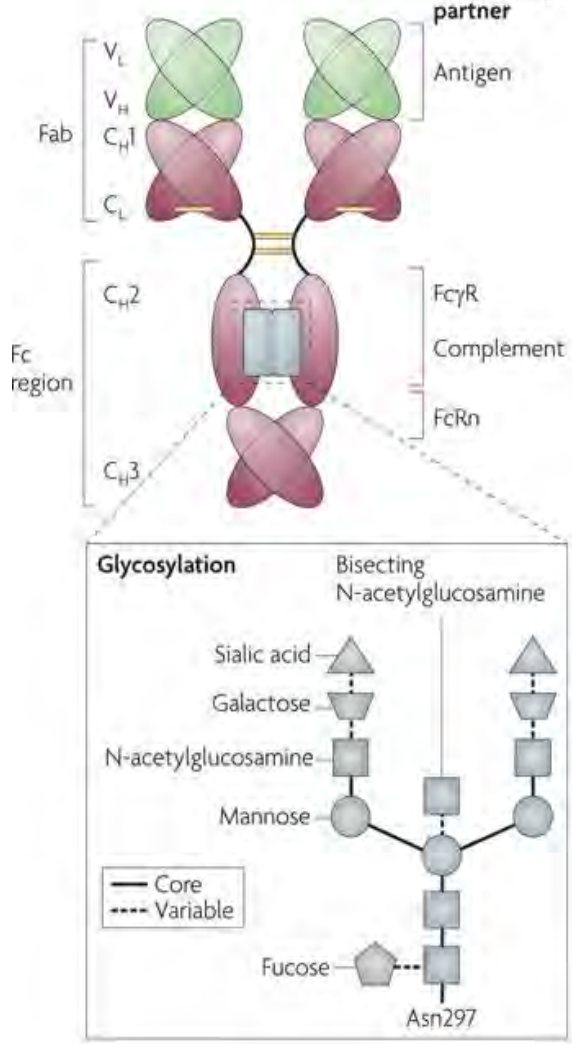
- Binding to target antigen(s)
- Binding to representative isoforms of the relevant three Fc gamma receptors (FcγRI, FcγRII and FcγRIII), FcRn and complement (C1q)
- Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation or blockade)
- Fc-associated functions (e.g. antibody-dependent cell-mediated cytotoxicity, ADCC; complement-dependent cytotoxicity, CDC; complement activation)

Critical to show comparability


AP - Antigen Conjugate
Sample Antigen
AP
Primary
Antibody
Substrate
COLOR
AP
AP
AP
Wash
Well Coated with
Affinity Purified Antibody
Primary Incubation
Color Development
Read Plate


Substrate
Substrate
Secondary antibody
conjugate
Substrate
Primary antibody
conjugate
Inhibitor
antigen
Substrate
Ag
Capture antibody
Direct ELISA
Indirect ELISA
Sandwich ELISA
Competitive ELISA


mAb
C1q
Lysis
CDC
Complement
cascade activation
Antigen
Target cell
ADCC
Effector cells
(e.g. NK cells/neutrophils)
Lysis
FcγR



IgG binding partner	Protein strategies for modifying interactions	Potential impact of modifying interaction
Antigen	Mutate V domain sequences using display libraries and/or rationale design	Altered binding affinity or specificity
FcγR Complement	Mutate Fc sequence using display libraries and/or rationale design; select IgG isotype	↑ or ↓ ADCC ↑ or ↓ ADCP ↑ or ↓ CDC
FcRn	Mutate Fc sequence using display libraries and/or rationale design	↑ or ↓ half-life
	Antibody fragment lacking Fc	↓ Half-life, ↓ CDC, ↓ ADCC and ↓ ADCP

Glycosylation strategies for modifying FcγR and complement interactions

Aglycosylation	↓ ADCC, ↓ ADCP and ↓ CDC
Bisecting N-acetylglucosamine	↑ ADCC
Non-fucosylation	↑ ADCC

REMSIMA (infliximab)

- Extensive analytical tests showed physicochemical and structural comparability except for a small difference in the proportion of afucosylated forms (associated with increased binding affinity to the FcγRIIIa receptor).

- Comparable binding of the test and reference product to the soluble and/or the membrane-bound TNFα (main MoA), functions mediated by transmembrane binding, including reverse signaling and apoptosis.

REMSIMA (infliximab)

- Similar inhibition of the direct effects of TNFα on epithelial cells that play an important role in Crohn's disease

- Similar induction of regulatory macrophages is implicated as a mode of action of infliximab in IBD

Table 1. Summary of the Flixabi *in vitro* pharmacodynamic studies

Type of Study		Results
Fab-related biological activities	TNF-α binding assay	TNF-α (soluble) binding activity of SB2 was similar to that of Remicade®.
	TNF-β binding assay	SB2 and Remicade® showed a significant lack of TNF-β (LTα3) binding activity.
	tmTNF-α binding assay	tmTNF-α binding activity of SB2 was similar to that of Remicade®.
	TNF-α neutralisation assay	Inhibitory activity of SB2 on the signal pathway was similar to that of Remicade®.
	Apoptosis assay	Apoptosis activity of SB2 was similar to that of Remicade®.
	Inhibitory activity on apoptosis in an *in vitro* IBD model	Inhibitory activity of SB2 on apoptosis was similar to that of Remicade®, which may support the extrapolation of indications to inflammatory bowel disease (IBD).
	Cytokine release activity in an *in vitro* IBD model	Cytokine IL-8 release suppression activity of SB2 was similar to that of Remicade®, which may support the extrapolation of indications to IBD.

Fc-related biological activities	FcγRIa binding assay	FcγRIa binding activity of SB2 was similar to that of Remicade®.
	FcγRIIa binding assay	FcγRIIa binding activity of SB2 was similar to that of Remicade®.
	FcγRIIIa binding assay (V/V type)	FcγRIIIa binding activity of SB2 was slightly higher than that of Remicade®, but not biologically significant as these differences did not affect ADCC activity. ADCC activity of SB2 was within the similarity range.
	FcγRIIIa binding assay (F/F type)	FcγRIIIa (F158 allotype) binding activity of SB2 was similar to that of Remicade®.
	FcγRIIIa binding assay using NK cells from PBMCs	Binding activity of SB2 to FcγRIIIa on natural killer (NK) cells of peripheral blood mononuclear cells (PBMCs) was similar to that of Remicade®.
	FcγRIIb binding assay	FcγRIIb binding activity of SB2 was slightly higher than that of Remicade®, but not significant as these differences were within assay

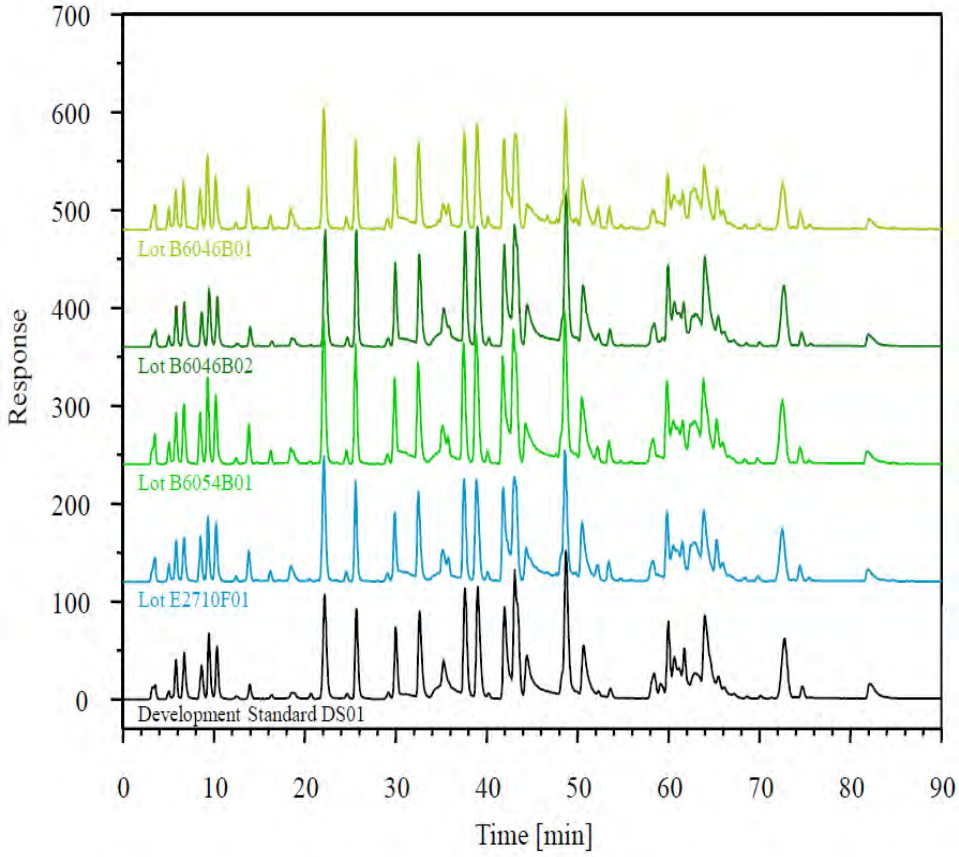
Type of Study		Results
		variability and did not affect ADCC activity. ADCC activity of SB2 was within the similarity range.
	FcγRIIIb binding assay	FcγRIIIb binding activity of SB2 was similar to that of Remicade®.
	FcγRIIIb binding assay using neutrophils	FcγRIIIb binding activity of SB2 using neutrophils was similar to that of Remicade®.
	ADCC assay using engineered NK cell line	ADCC activity (effector cell: engineered NK cell line) of SB2 was similar to that of Remicade®.
	ADCC assay using healthy donor PBMCs	ADCC activity (effector cell: healthy donor PBMCs) of SB2 was similar to that of Remicade®, which may support similarity in more representative condition of *in vivo* situation.
	C1q binding assay	C1q binding activity of SB2 was similar to that of Remicade®.
	CDC assay	CDC activity of SB2 was similar to that of Remicade®.
	FcRn binding assay	FcRn binding activity of SB2 was slightly higher than that of Remicade®, but not significant as these differences were within assay variability and were not translated into PK difference according to the PK results from the Phase I clinical study.
	Evaluation of regulatory macrophage induction function	Regulatory macrophage induction function of SB2 was similar to that of Remicade®, which may support the extrapolation of indications to IBD.

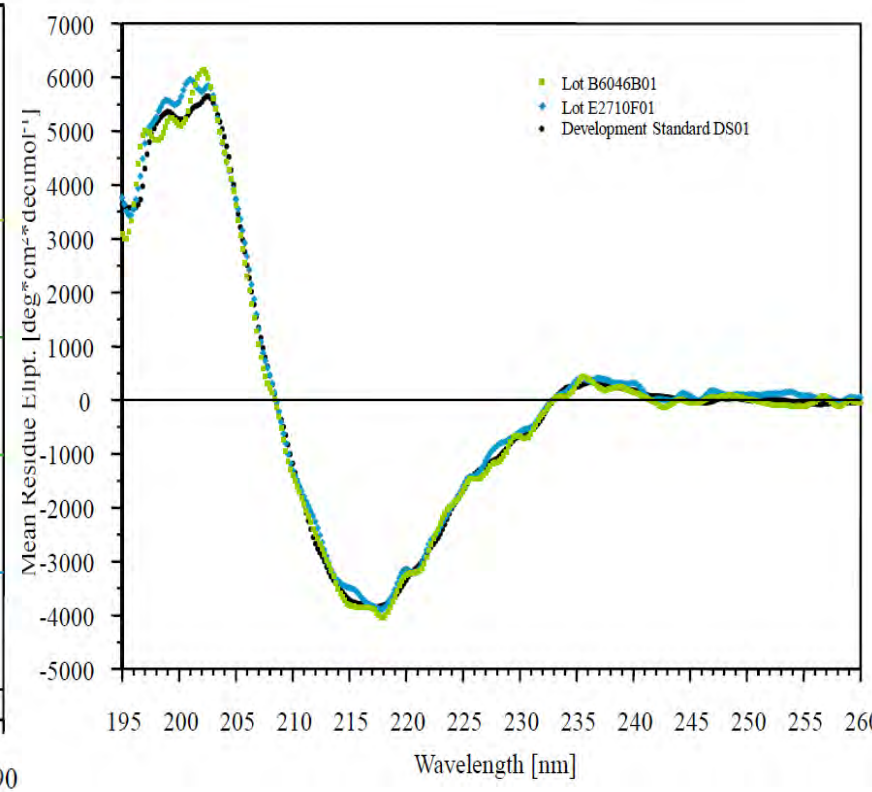
How to establish biosimilarity?

1. **extensive characterization** *(physico-chemical, biological)*

2. ***in vitro* functional activity** *(analyzing all possible MoA of the molecule)*

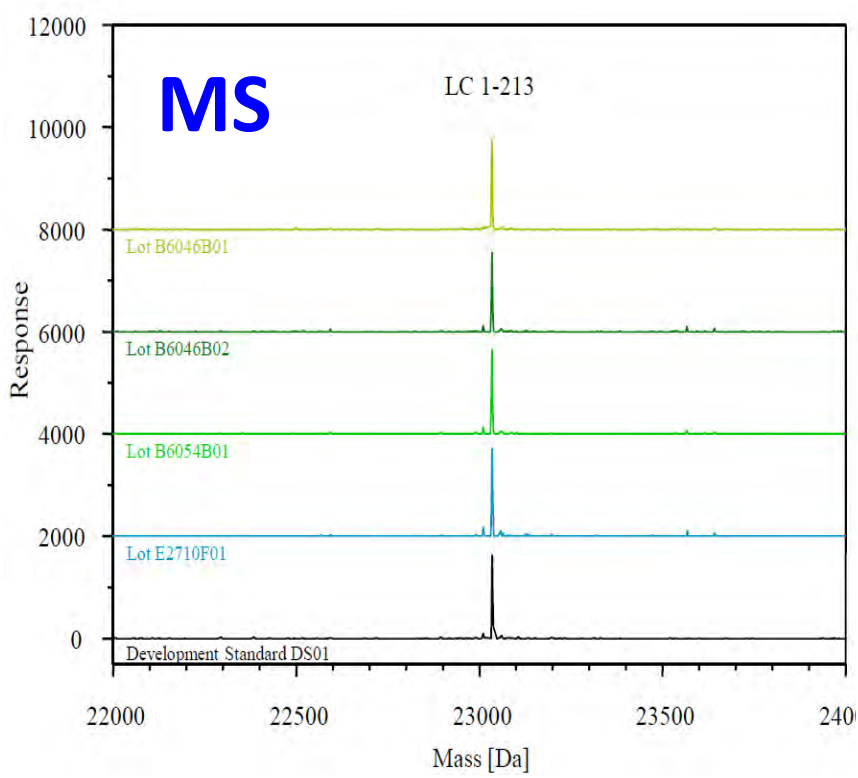
3. **efficacy and safety** *(most sensitive population to detect differences)*

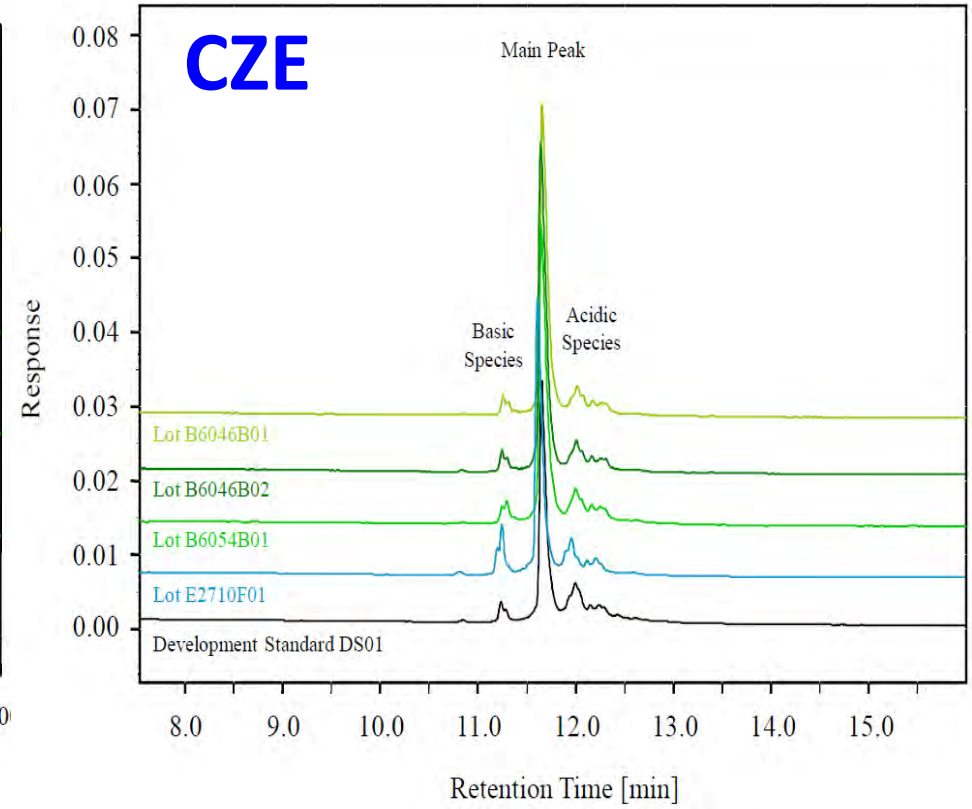


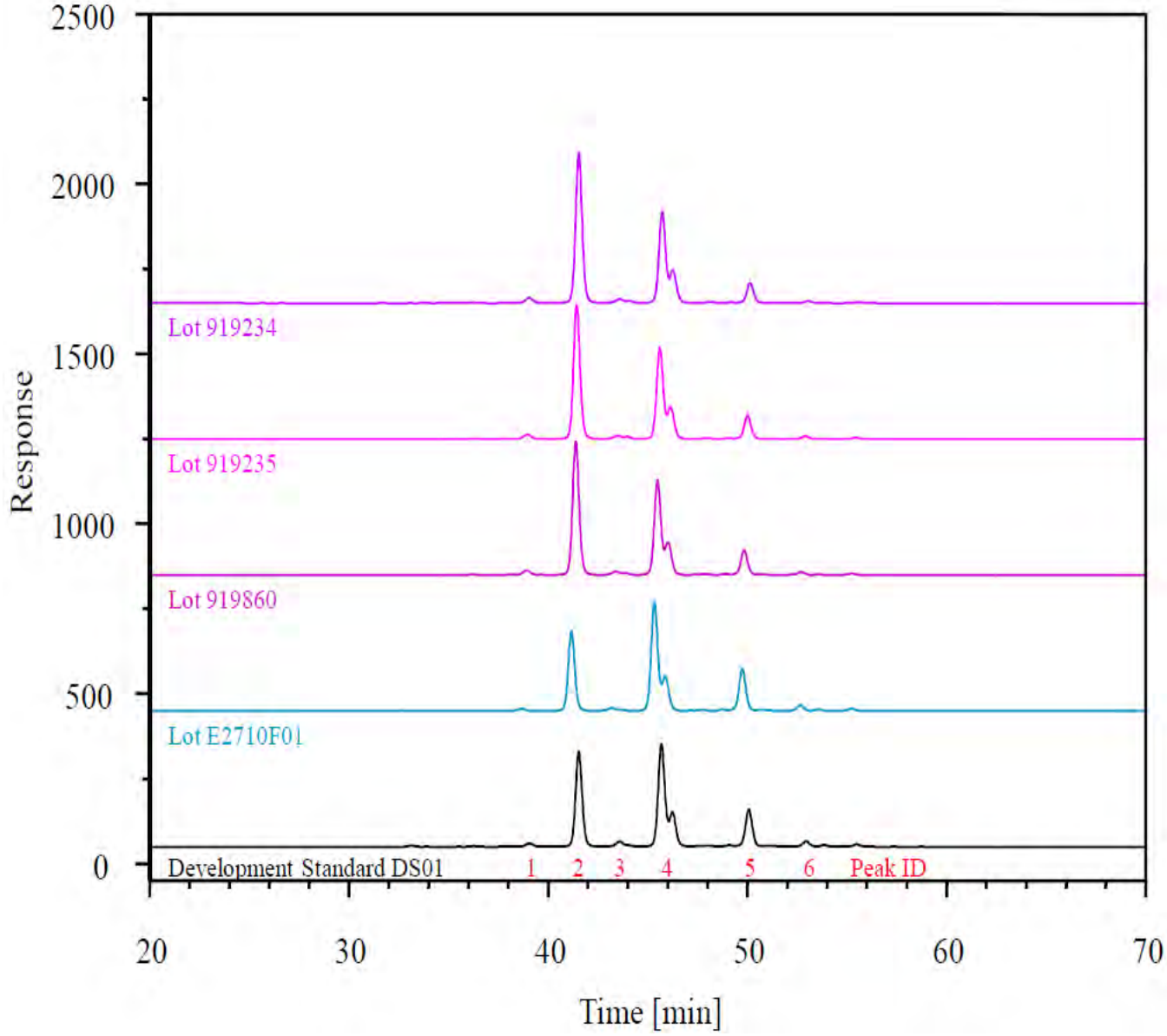


TRYPTIC MAP

CD spectra


MS
LC 1-213
Response
Mass [Da]
Lot B6046B01
Lot B6046B02
Lot B6054B01
Lot E2710F01
Development Standard DS01
12000
10000
8000
6000
4000
2000
0
22000
22500
23000
23500


CZE
Main Peak
Basic Species
Acidic Species
Response
Retention Time [min]
Lot B6046B01
Lot B6046B02
Lot B6054B01
Lot E2710F01
Development Standard DS01
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0



Oligosaccharide map

IFN-beta

FUNCTIONAL ANALYSIS

- antiviral activity
- antiproliferative activities (using different cell lines)
- immunomodulatory activities
- receptor binding
- formation of activated IFN stimulated gene factor complex
- IFN-beta inducible mRNAs

GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

Thank you!

sruiz@aemps.es