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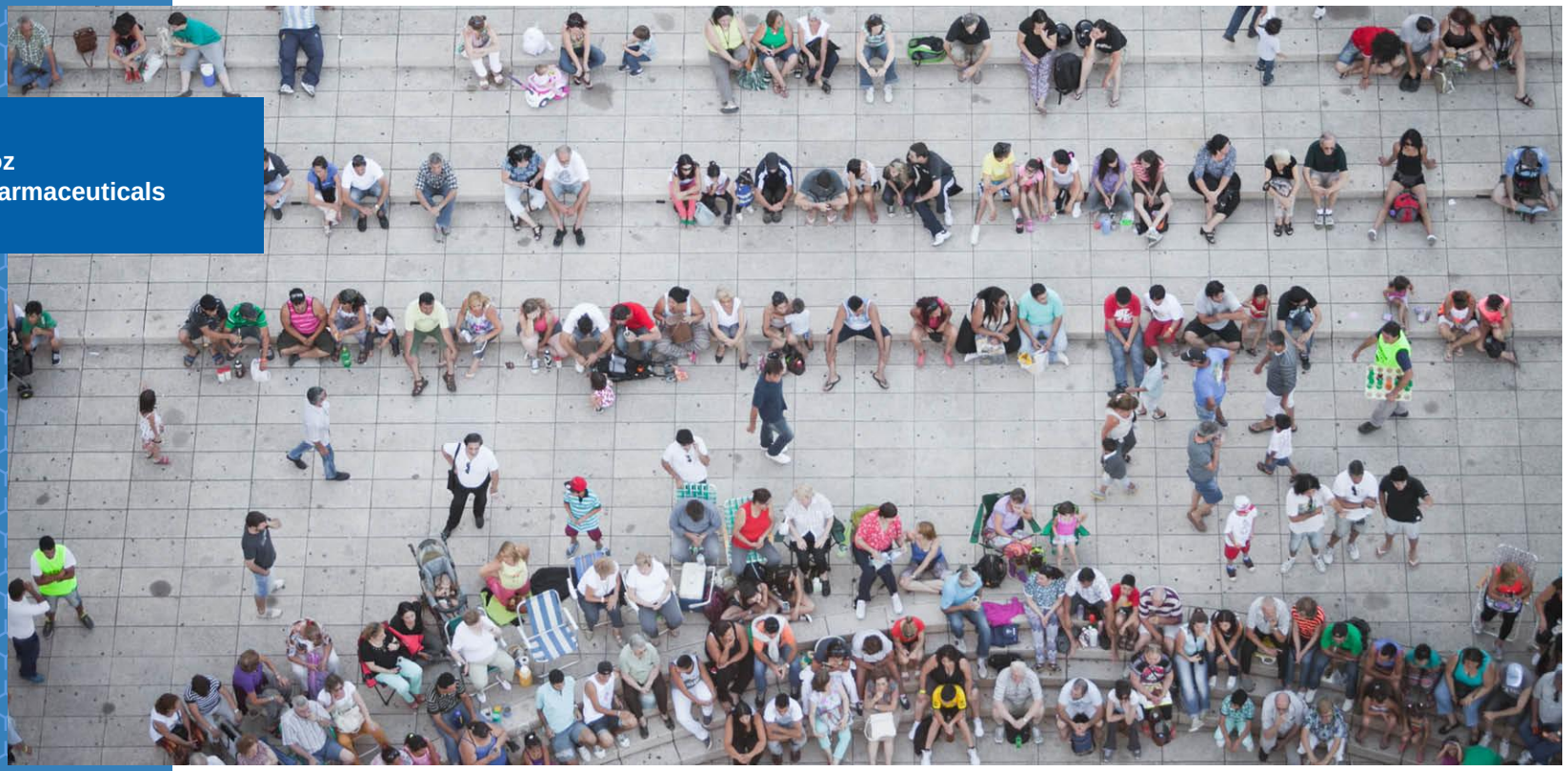

How the increase of assay sensitivity influences the immunogenicity assessment

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Agenda

1. Problem statement
2. Example of biosimilar development for etanercept
3. Root cause for identified differences
4. Reference to Samsung‘s SB4
5. Consequences and points of discussion

Problem statement

Immunogenicity is a concern for all biologics because of the impact of anti-drug antibodies (ADAs) on safety and clinical outcomes. Assessment of immunogenicity greatly depends on appropriate assays. Several assay parameters are considered critical for immunogenicity assays, i.e. assay sensitivity, drug tolerance and definition of the assay positive cut-point level

According to guidelines head-to-head comparative immunogenicity studies are required in the development of biosimilar products (EMEA/CHMP/BMWP/42832/2005 Rev. 1). *Differences in immunogenicity will question the comparability of a biosimilar and its reference product as well as of new and old versions of an approved product, and thorough root cause analysis is warranted.*

The presented example assesses a real case of a biosimilar development and the relevance of the assay sensitivity and the assumptions of cut-point validation.

Example of biosimilar development for etanercept

Erelzi® an etanercept biosimilar

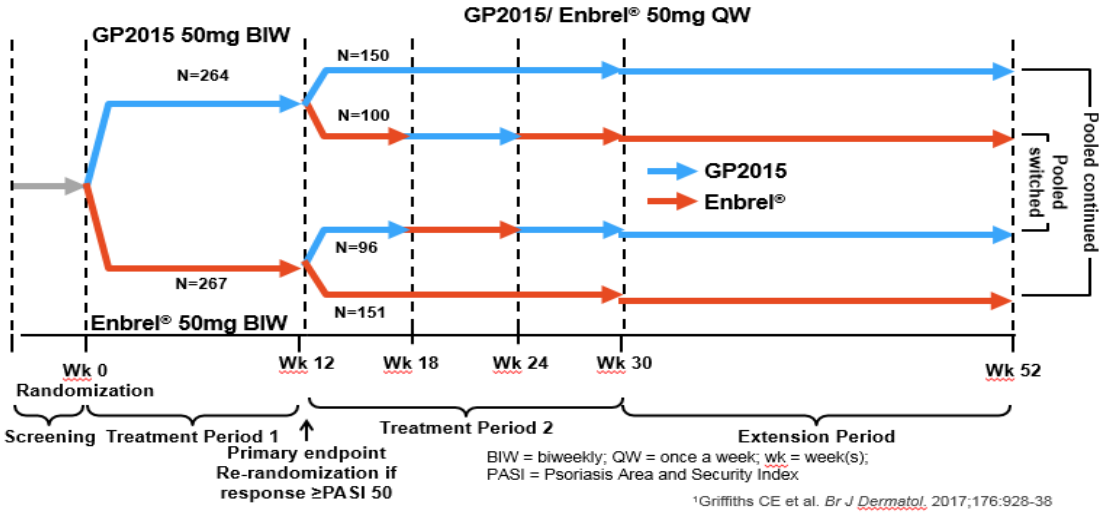
GP2015 (Erelzi®) is the second approved biosimilar of the reference p75 TNF receptor-Fc fusion protein etanercept

- Demonstrated analytical similarity, bioequivalence and biosimilarity with reference etanercept (ETN)[1-3]
- An approved biosimilar in the United States[4] and European Union[5]:
  - rheumatoid arthritis
  - polyarticular juvenile idiopathic arthritis
  - psoriatic arthritis
  - ankylosing spondylitis
  - plaque psoriasis
- Because an increase of TNF-α is the common pathophysiology of all etanercept indications blocking the binding of soluble TNF-α to its receptor is the common mechanism of action (MoA) for all indications

[1]Hofmann HP et al. *Expert Opin Biol Ther*. 2016;16:1185-95; [2]von Richter et al. *Br J Clin Pharmacol*. 2017;83:732-41; [3]Griffiths CE et al. *Br J Dermatol*. 2017;176:928-38. [4]https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761042lbl.pdf, Accessed on 11 Sep, however, Sandoz biosimilar etanercept will not be available for psoriatic indicatons in the US till August 13, 2019; [5]http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004192/WC500230144.pdf Accessed on 11 Sep

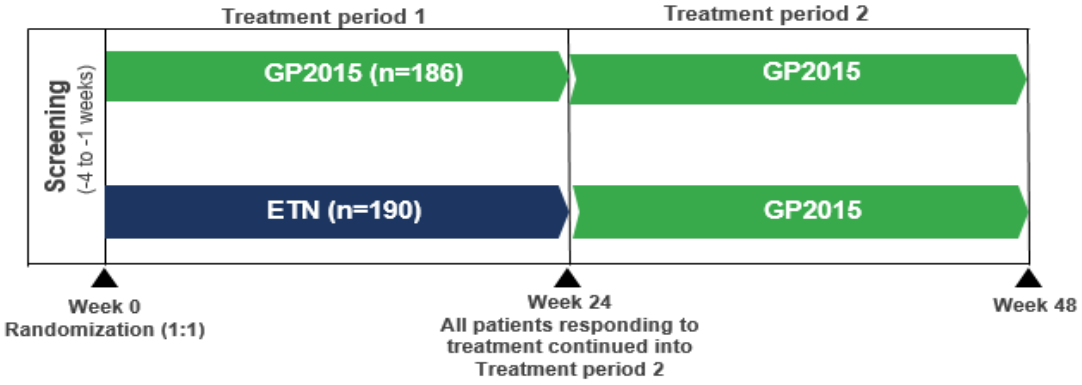
GP2015: Clinical Phase III studies

- **Phase III clinical study in psoriasis (EGALITY)**



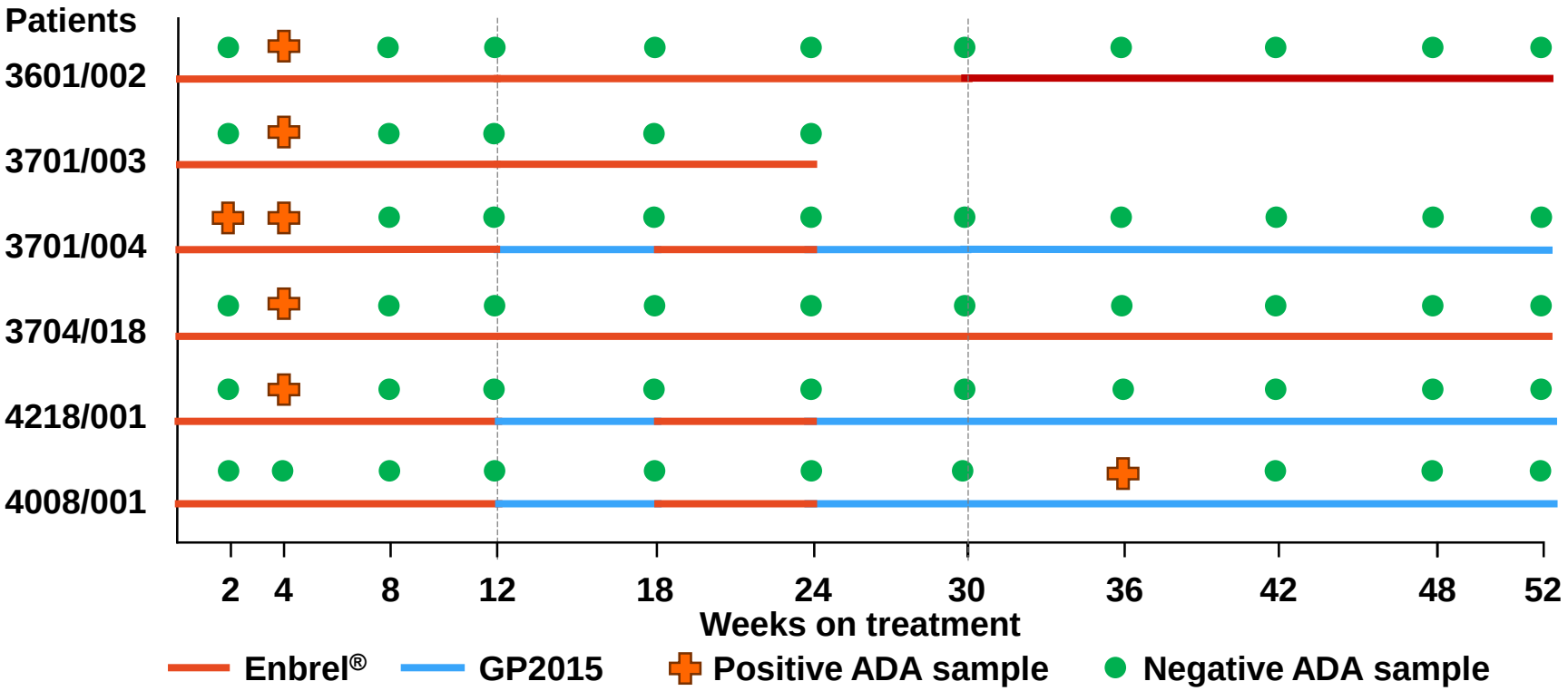
Griffiths CEM, Reich K, Thaçi D, Gerdes S, Arenberger P, Kingo K, Weglowska J, Woehling H. Switching treatments of etanercept biosimilar GP2015 with originator product does not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis. J Invest Dermatol 2017; 137(10): S193

- **Phase III clinical studv in rheumatoid arthritis (EQUIRA)**



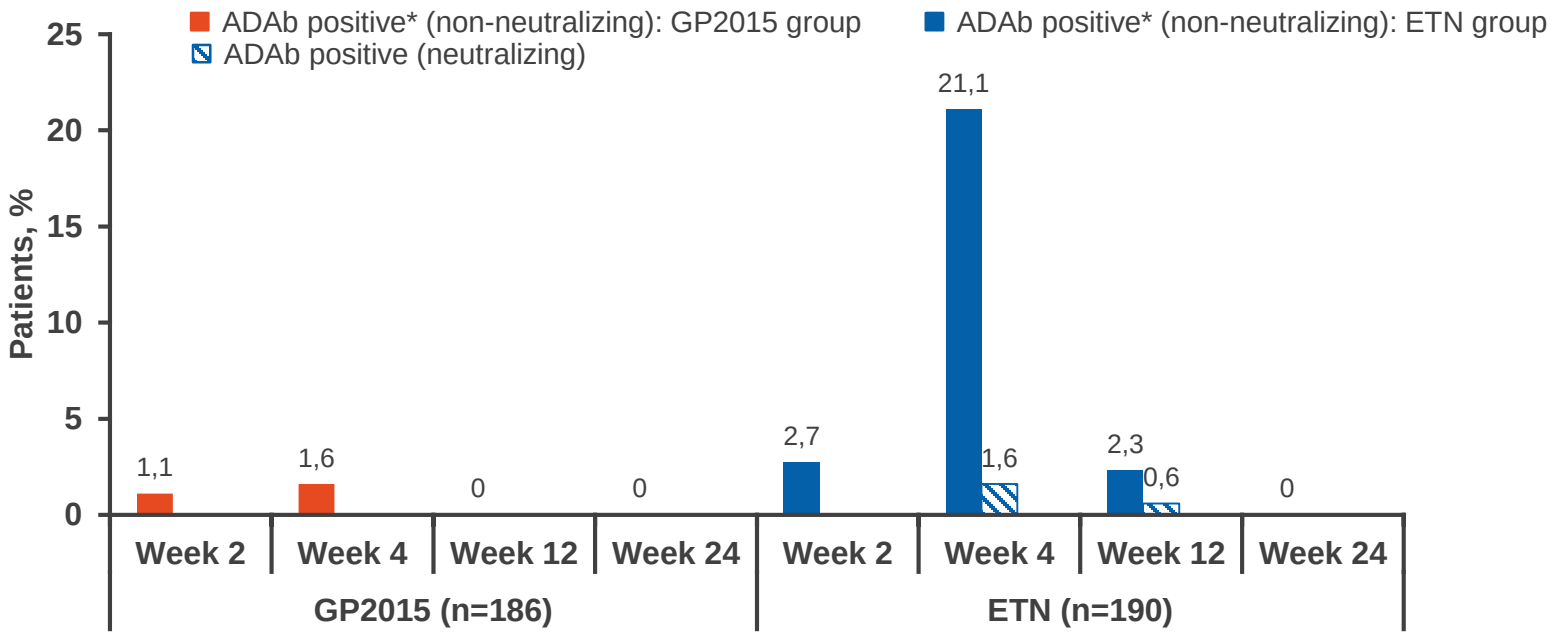
Matucci-Cerinic M, Allanore Y, Kavanaugh A, Buch MH, Schulze-Koops H, Kucharz EJ, Woehling H, Babic G, Poetzl J, Davis A, Schwebig A. Efficacy, safety, and immunogenicity of GP2015, an etanercept biosimilar, compared to the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative Phase III, randomised, double-blind,EQUIRA study. RMD Open 2018; accepted manuscript

EGALITY: immunogenicity outcome as expected



- **5 patients, all in the Enbrel group, had confirmed ADA-positive samples up to Week 12 and 30, respectively** (*corresponds to a rate of 1.8% for Enbrel → in line with published data)*
- **1 patient in the switched Enbrel group had a confirmed ADA-positive sample at Week 36** (receiving GP2015 for 12 weeks at the time of the finding)
- **All ADA were non-neutralizing**, transient, and low titer

EQUIRA: immunogenicity outcome for Enbrel® higher than expected



- Only transient immune response against GP2015/ETN were detected with no detectable ADA levels at week 24
- ADA levels reported as titer were consistently very low
- No hints for any impact of ADA formation on safety or efficacy outcomes

ADA, anti-drug antibodies

Immunogenicity of the originator Enbrel® according to EPAR

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. ***There appears to be no correlation between antibody development and clinical response or adverse events.***

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were

- approx 6% of subjects with rheumatoid arthritis,
- 7.5% of subjects with psoriatic arthritis,
- 2% of subjects with ankylosing spondylitis,
- 7% of subjects with psoriasis,
- 9.7% of subjects with paediatric psoriasis,
- 4.8% of subjects with juvenile idiopathic arthritis.

[1] ANNEX I of the EMA Public Assessment Reports (EPARs) : SUMMARY OF PRODUCT CHARACTERISTICS

Overview of Immunogenicity in Enbrel® Trials

- Higher ADA rate with rheumatoid arthritis than psoriasis[a-l]

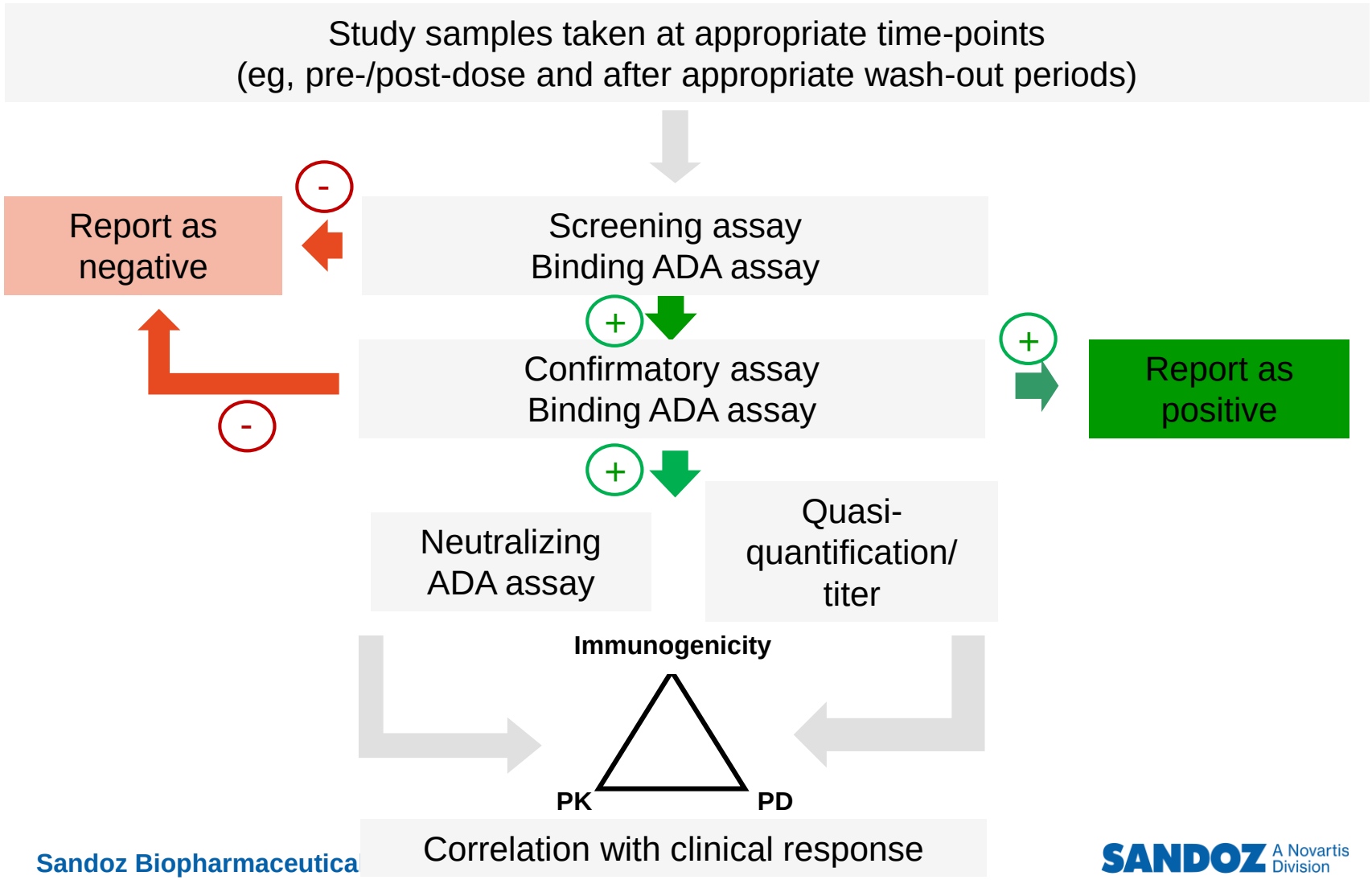
Disease	Patients, n	ETN dosage	Period, wk	ADA, %	Reference
Rheumatoid arthritis	549	2 × 25 mg /w	193	5.0	Klareskog et al
	292	50 mg /w or 25 mg × 2/w	26	0.0	Jamnitski et al
	40	2 × 25 mg/w	32	0.0	Hoshino et al
	420	50 mg/w	16	3.0	Keystone et al
	214	50 mg/w	28	5.6	Dore et al
Ankylosing spondylitis	53	25 mg × 2/w	26	0.0	de Vries et al
Psoriatic arthritis	205	2 × 25 mg/w	24	0.0	Mease et al
Psoriasis	618	2 × 50 mg/w	12	1.5	Tyring et al
	583	2 × 25 or 2 × 50 mg/w followed by 2 × 25 mg/w	12	1.1	Papp et al
			24	1.6	
	652	25mg/w ; 2 × 25mg/w, or 2 × 50 mg/w	24	1.6	Leonardi et al

[a] Griffiths et al. [b] Emery et al, [c] 2015; Klareskog et al; [d] Jamnitski et al; [e] Hoshino et al; [f] Keystone et al; [g] Dore et al; [h] de Vries et al; i Mease et al; [j] Tyring et al; [k] Papp et al; [l] Leonardi et al.

Source:

Root cause analysis for identified differences

Tiered approach of immunogenicity testing



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Source:

EGALITY: Immunogenicity Assessment Bioanalytical Strategy and Methodology

Bioanalytical strategy for immunogenicity assessment

- Tiered analysis approach: validated screening, confirmatory, titer and neutralization antibody assay
- Conservative 1 assay-approach for the detection of ADA using GP2015 as capture and detection reagent
- False positive rate: Screening assay 5% and confirmatory assay 0.1%

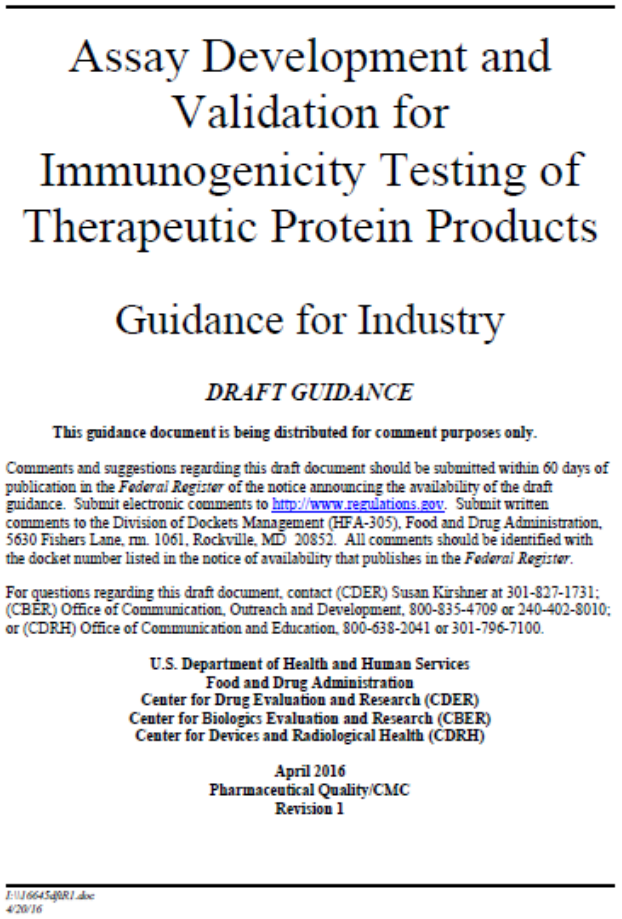
Immunogenicity testing

- Electrochemoluminescence (ECL) bridging immunogenicity assay for screening, confirmatory and titer step
  - High assay sensitivity (~100 ng/mL)
  - High and same drug tolerance level for GP2015 and Enbrel: at least 20,000 ng/mL (all measured drug levels below drug tolerance of ADA assay)
- Determination of neutralizing capacity using a competitive ligand binding assay of confirmed ADA positive samples

ADA=anti-drug antibodies

Determination of Cut-points according to revised FDA guideline

- The draft guidance from 2016 revises the draft Guidance for Industry *Assay Development for Immunogenicity Testing of Therapeutic Proteins* issued in December 2009.
- ***Confirmatory assay cut point:*** Because the purpose of this assay is to eliminate false-positive samples arising as a result of non-specific binding, it is adequate to use a 1% false positive rate for the calculation of the confirmatory cut point. The use of tighter false-positive rates such as 0.1% is not recommended because it will lead to an increased risk of false-negative results.



Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Susan Kirshner at 301-827-1731; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Office of Communication and Education, 800-638-2041 or 301-796-7100.

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EQUIRA: Immunogenicity Assessment Bioanalytical Strategy and Methodology

Bioanalytical strategy for immunogenicity assessment

- Tiered analysis approach: validated screening, confirmatory, titer and neutralization antibody assay
- Conservative 1 assay-approach for the detection of ADA using GP2015 as capture and detection reagent
- False positive rate: Screening assay 5% and confirmatory assay 1%

Immunogenicity testing

- Electrochemoluminescence (ECL) bridging immunogenicity assay for screening, confirmatory and titer step
  - High assay sensitivity (< 100 ng/mL)
  - High and same drug tolerance level for GP2015 and Enbrel: at least 50,000 ng/mL (all measured drug levels below drug tolerance of ADA assay)
- Determination of neutralizing capacity using a competitive ligand binding assay of confirmed ADA positive samples

Source:

EQUIRA: Incidence of ADAs highly depend on false positive rate for cut-point calculation

Visit	GP2015 N = 186				Enbrel N = 190			
	Assessed Samples	ADA positive (1% false positive) n (%)	ADA positive (0.1% false positive) n (%)	Neutra-lizing n (%)	Assessed Samples	ADA positive (1% false positive) n (%)	ADA positive (0.1% false positive) n (%)	Neutra-lizing n (%)
Baseline	186	2 (1.1)	1 (0.5)	0	190	0	0	0
Week 2	183	2 (1.1)	1 (0.5)	0	185	5 (2.7)	2 (1.1)	0
Week 4	183	3 (1.6)	0	0	185	42 (22.7)	31 (16.8)	3 (1.6)
Week 12	179	0	0	0	176	5 (2.8)	4 (2.3)	1 (0.6)
Week 24	179	0	0	0	172	0	0	0
Week 30	171	2 (1.2)	0	0	161	0	0	0
Week 36	169	0	0	0	159	0	0	0
Week 48	166	2 (1.2)	1 (0.6)	0	154	0	0	0
Overall	184	9 (4.9)	2 (1.1)	0	188	50 (26.6)	36 (19.1)	4 (2.1)

- Highly sensitive and drug tolerant ADA assays were applied
- GP2015: All ADA measured were of low titer, non-neutralizing and non-persistent
- Enbrel: Few neutralizing ADA of transient nature

Reference to Samsung‘s SB4

Differences in immunogenicity also identified for Samsung's SB4

Benepali EPAR[1]:

- Three (1.0%) of Benepali (SB4) treated patients tested positive for ADAs at least once in Study SB4-G31-RA, compared to 39 (13.1%) patients in the EU Enbrel group, one of which also tested positive for neutralizing antibodies.
- However, this finding is uncertain because of the low drug tolerance of the ADA assay that led to a low sensitivity and a potential bias.

Emery et al (2016)[2] response to Shah et al (2016)[3]:

- Additional data from the PK population on immunogenicity with a more sensitive assay with regard to drug tolerance have been reported in the response to Marshall et al[4]: 2.4% in SB4 and 21.1% in ETN (results to be published).
- Already the SB4 phase I immunogenicity results showed that ADA incidence was lower in SB4 (0.0%) compared with European-sourced ETN (15.6%) or US-sourced ETN (22.7%) without the concern of drug interference.

1 EMA Public Assessment Reports (EPARs) Beneplai https://www.ema.europa.eu/en/medicines/human/EPAR/benepali
2 Emery P, Vencovský J, Ghil J, et al. Response to: 'Lower anti-drug antibodies with etanercept biosimilar: Can Ctrough explain the differences' by ShahAnn Rheum Dis 2016;75:e61.
3 Shah C. Lower anti-drug antibodies with etanercept biosimilar: can Ctrough explain the differences? Ann of Rhuem Dis 2016;75:e60.
4 Emery P, Vencovský J, Ghil J, et al. Response to: 'Comparing the immunogenicity of the etanercept biosimilar SB4 with the innovator etanercept: another consideration' by Marshall et al. Ann Rheum Dis 2016;75:e38.

Source:

Consequences and points of discussion

Erelzi® has been approved as an etanercept biosimilar

Although GP2015 demonstrated numerically lower immunogenicity than the originator this does not preclude classification as a biosimilar because

- ADAs were generally transient, which is in accordance with the established immunogenicity profile for etanercept in previous studies
- detected immunogenicity in our studies considered being of no clinical relevance
- originator product also concluded that no correlation between antibody development and clinical response or adverse events exists
- high analytical similarity as well as equivalent efficacy and comparable safety between the originator product and GP2015 (Erelzi®) has been demonstrated

Points of discussion

The incidence of ADA shown in the Enbrel® group of some Phase III studies with etanercept biosimilars was numerically higher compared with what has been reported in previous studies and in the EPAR although there is no evidence that the immunogenic potential of Enbrel® has changed.

The identified differences can at least partially be explained by

- higher sensitivity of the used assays
- higher drug tolerance of the assays compared to methods used in the past.

Given that immunogenicity assay validation and performance characteristics are different from assay to assay, at least the most relevant immunogenicity assay parameters have to be published to allow comparing study results with historical data[1].

[1] Poetzl et al. State-of-the-art immunogenicity evaluation in phase 3 confirmatory study (EGALITY) with etanercept biosimilar GP2015. JEADV 2017


THANK
YOU!