# Supplementary Material on

# Consensus-based recommendations for the use of biosimilars to treat rheumatologic diseases

*including Supplementary Tables S1, S2, S3, S4, S5, and S6.*

Supplementary Table S1. Biosimilars approved for rheumatologic indications by the European Medicines Agency (EMA) and/or the US Food Drug Administration (FDA), as of August 2017.

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| --- | --- | --- |
| Reference Product | EMA | FDA |
| adalimumab (Humira®) | Amgevita™/Solymbic™ (adalimumab)  Imraldi® (adalimumab) | Amjevita™ (adalimumab-atto) Cyltezo® (adalimumab-adbm) |
| etanercept (Enbrel®) | Benepali® (etanercept)  Erelzi™ (etanercept) | Erelzi™ (etanercept-szzs) |
| infliximab (Remicade®) | Flixabi® (infliximab)  Inflectra®/Remsima® (infliximab) | Inflectra® (infliximab-dyyb)  Renflexis™ (infliximab-abda) |
| rituximab (MabThera®, Rituxan®) | Ritemvia®/Truxima® (rituximab)  Rixathon®/Riximyo® (rituximab) | − |

## Supplementary Table S2. Search Terms used in the Medline database.

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| ((adalimumab[Title/Abstract] AND biosimilar)[Title/Abstract] OR (etanercept[Title/Abstract] AND biosimilar)[Title/Abstract] OR (infliximab[Title/Abstract] AND biosimilar)[Title/Abstract] OR (abatacept[Title/Abstract] AND biosimilar)[Title/Abstract] OR (rituximab[Title/Abstract] AND biosimilar)[Title/Abstract] OR amjevita[Title/Abstract] OR Adalimumab-atto[Title/Abstract] OR benepali[Title/Abstract] OR SB4[Title/Abstract] OR erelzi[Title/Abstract] OR etanercept-szzs[Title/Abstract] OR flixabi[Title/Abstract]) OR SB2[Title/Abstract]) OR inflectra[Title/Abstract] OR infliximab-dyyb[Title/Abstract] OR CT-P13[Title/Abstract] OR remsima[Title/Abstract]) |

## Supplementary Table S3. Research questions for the systematic literature search that were formulated by the task force.

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| 1. At the time of publication of phase III trials, how frequently is information on phase I trials (PK/PD data) available and which assays were used in PK/PD studies? |
| 1. Is there evidence for any risk of extrapolation of indication? Is the success of extrapolation related to immunogenicity? |
| 1. Immunogenicity: What types of assays have been used to assess anti-drug antibodies (ADAbs)? Is there a correlation with adverse events and clinical efficacy? What levels of ADAbs have been shown to be neutralising and non-neutralising? What other mechanisms apart from lowering drug concentrations have been described for lowering efficacy? What similarity or differences of immunogenicity are there between BS and originators? Are there differences between diseases with regard to immunogenicity? |
| 1. What equivalence margins (EM) have been used in trials? |
| 1. Is there (i) loss of efficacy and/or (ii) increase in immunogenicity and/or (iii) change in AE/safety if pts are switched from one drug to another? What is known about multiple switches? |
| 1. What has been the trial design of switching trials? What is the level of harmonisation of (i) efficacy-, (ii) toxicity-, and (iii) immunogenicity- data in current registries? |

*PK/PD= pharmacokinetic/pharmacodynamic; ADAb=anti-drug-antibodies; EM=equivalence margins; AE=adverse events.*

## Supplementary Table S4. Assays used in PK / PD studies.

|  |  |
| --- | --- |
| **ABP 501 (adalimumab-atto; Amjevita®) ADA** | |
| **Phase I / healthy** Kaur[1] | **ECL** |
| **SB4 (Benepali®) ETA** | |
| **Phase I / healthy** Lee[2] | **ELISA** |
| **GP2015 (etanercept-szzs, Erelzi®) ETA** | |
| **Phase I / healthy** von Richter[3] | **ELISA** |
| **SB2 (Flixabi®) IFX** | |
| **Phase I / healthy** Shin[4] | **ELISA** |
| **CT-P13 (Inflectra® / Remsima®) IFX** | |
| **Phase I / RA** Yoo[5,6] PLANETRA | **ELISA; flow-through immunoassay platform** (GyrolabxP; Gyros AB, Sweden) |
| **Phase I / RA** [Takeuchi](https://www.ncbi.nlm.nih.gov/pubmed/?term=Takeuchi%20T%5BAuthor%5D&cauthor=true&cauthor_uid=25736355)[7] | **sandwich ELISA with fluorescence detection**. Gyrolab system (flow-through format) |
| **Phase I / AS** Park[8,9] PLANETAS  **Phase I / healthy** [Park](https://www.ncbi.nlm.nih.gov/pubmed/?term=Park%20W%5BAuthor%5D&cauthor=true&cauthor_uid=26395834)[10] | **ELISA; flow-through immunoassay** platform (GyrolabxP; Gyros AB, Sweden). |

*ECL=electrochemiluminescence; ELISA=Enzyme-linked Immunosorbent Assay.*

## Supplementary Table S5. Assays used to assess anti-drug antibodies.

|  |  |
| --- | --- |
| **ABP 501** |  |
| **Kaur**[1] | binding ADAbs: ECL  NAbs: cell-based bioassay to detect all classes of antibodies that inhibit the biological activity of the drug |
| **EUDRA-CT-Nr** [**2013-000525-31**](https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-000525-31) | ECL-based bridging immunoassay to detect ADAbs against ABP 501 and adalimumab (binding antibody assay). If positive for binding ADAbs, subsequent NAb-assay in a non-cell based bioassay to determine neutralizing activity |
| **Cohen**[11] | not stated (AB) |
| **SB4** |  |
| [**Emery**](https://www.ncbi.nlm.nih.gov/pubmed/?term=Emery%20P%5BAuthor%5D&cauthor=true&cauthor_uid=26150601)[12] | ECL bridging assay (Meso Scale Discovery, Rockville, MD, USA) for screening and confirmatory assay for ADAb determination |
| **Lee**[2] | ECL; screen for presence of ADAbs and cell-based assay to determine whether ADAb positive samples had neutralizing activity |
| **GP2015** |  |
| **EUDRA-CT Nr 2012-002009-23** | ECL for ADAb development evaluation and competitive ligand binding neutralising assay for neutralising capacity |
| **von Richter**[3] | ECL screening for ADAb and ECL confirmatory assay and competitive ligand binding neutralising (NAb) assay to evaluate neutralising capacity of ADAbs |
| **SB2** |  |
| **Choe**[13] | ECL screening; if ADAb pos., additional assessment for NAb: competitive ligand-binding assay (MesoScale Discovery platform, Meso Scale Discovery, Rockville, Maryland, USA) |
| **Shin**[4] | ECL for ADAb detection; functional cell-based assay for NAb |
| **Smolen**[14] | not stated (AB) |
| **CT-P13** |  |
| [**Yoo**](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yoo%20DH%5BAuthor%5D&cauthor=true&cauthor_uid=23687260)[5,6,15] **PLANETRA;**  [**Park**](https://www.ncbi.nlm.nih.gov/pubmed/?term=Park%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23687259)[8,9,16] **PLANETAS** | ECL; neutralising activity of ADAbs: flow-through immunoassay method (Gyros AB Immunoassay platform). |
| **Braun** AB[17] | ECL (MSD, Rockville, Maryland, USA) |
| **Takeuchi**[7] | ADAbs: ECL (Meso Scale Discovery platform; MSD, Rockville, Maryland, USA); neutralizing activity of ADAbs: Gyros assay |
| **Nikiphorou**[18] | ELISA |
| **NOR-SWITCH**[19] | not stated (AB) |
| Glintborg AB **DANBIO**[20] | automated in-house assays at OUS-Radiumhospitalet |
| **Benucci**[21] | ECL; neutralising capability of the detected ADAbs: flow-through immunoassay (Gyros Immunoassay, Gyros AB, Sweden) |

*ADAbs=anti-drug antibodies; ECL=electrochemiluminescence; ELISA=Enzyme-linked Immunosorbent Assay, NAbs=neutralizing antibodies; AB=abstract*

## Supplementary Table S6. Equivalence margins.

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| **PK / Phase I** |  | **Primary PK parameter** | **90% CI within** |
| ABP 501 / healthy | Kaur[1] | 90% CI of GMRs of Cmax, AUC | **80–125%** |
| SB4 / healthy | Lee[2] | 90% CI ratios of geometric LSMeans of pairwise comparison | **80–125%** |
| GP2015 / healthy | von Richter[3] | 90% CI ratios of geometric mean of GP2015/ETN for Cmax, AUC | **80–125%** |
| SB2 / healthy | Shin[4] | 90 % CI of ratio of geometric least squares means (LSMeans) | **80–125%** |
| CT-P13 / AS | Park[8, 9] PLANETAS | 90% CI of geometric mean ratios of AUC and Cmax assessed between weeks 22 and 30 | **80-125%** |
| CT-P13 / RA | Takeuchi[7] | AUC (weeks 6-14) and Cmax / week 6 | **80-125%** |
| **Phase III** |  | **Primary efficacy endpoint** |  |
| ABP 501 / RA | EUDRA-CT-Nr [2013-000525-31](https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-000525-31); 24w results; AB | risk ratio of ACR20 at week 24 | Not reported (AB) |
| SB4 / RA | [Emery](https://www.ncbi.nlm.nih.gov/pubmed/?term=Emery%20P%5BAuthor%5D&cauthor=true&cauthor_uid=26150601)[12] | ACR20 at week 24 | **85-115%** |
| GP2015 / RA | EUDRA-CT Nr 2012-002009-23 / no results |  | Not reported (unpublished) |
| SB2 / RA | Choe[13] | ACR20 at week 30  **95% CI** of ACR20 rate **±15%** | **85-115%** |
| CT-P13 / RA | Yoo[5] PLANETRA | ACR20 at week 30  if the **95% CIs** for treatment difference were within **±15%** at week 30. | **85-115%** |
| CT-P13 / AS | Park[8,9] PLANETAS | ASAS20, ASAS40 at weeks 14 and 30 | **80-125%** |
| CT-P13 / RA | NOR-SWITCH[19] | disease worsening | **non-inferiority margin:** -**15%** |

*EM=equivalence margin; AB=abstract; CI=confidence interval; GMR=geometric mean ratio; AUC=area under the curve; LSMeans= least squares means; C=concentration; ACR=American College of Rheumatology response criteria; ASAS= Assessment of SpondyloArthritis International Society response criteria.*

## Legend for Supplementary Figure S1.

**Figure S1.** Flow Chart Illustrating the Selection Process.

*AB=abstract; BS=biosimilar.*

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