|  |  |  |
| --- | --- | --- |
| **Specific domains for switching studies** | **Criteria to identify bias** | **Judgment** |
| **Domain 1 – The randomized and blinded design with appropriate control arm** | There was a randomization step before the switch? | 1. Yes 2. No 3. Unclear |
| Did they keep the switching period blinded? | 1. Yes 2. No 3. Unclear |
| The study population was selected for a positive response or less disease severity? | 1. Yes 2. No 3. Unclear |
| What is your judgment about the randomized and blinded design with appropriate control arms? | **Low risk of bias:** There was a randomization step before the switch; They kept the switching period blinded; The study population was not selected for a positive response or less disease severity.  **High risk of bias:** There is no randomization step before the switch; It was an open-label period; The study population was selected for a positive response or less disease severity.  **Unclear risk of bias:** Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. |
| **Domain 2 – The number and way of switching** | The study had at least 1 arm incorporating switching between the proposed interchangeable product and the reference? | 1. Yes 2. No 3. Unclear |
| What is your judgment about the number and way of switching? | **Low risk of bias:** At least 1 arm incorporating switching between the proposed interchangeable product and the reference product, whereas the other arm remains on the reference product.  **High risk of bias:** It is not available 1 arm incorporating switching between the proposed interchangeable product and the reference product, whereas the other arm remains on the reference product.  **Unclear risk of bias:** Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. |
| **Domain 3 – The assessment of immunogenicity** | Immunogenicity was adequately measured in both switching and nonswitching arms? | 1. Yes 2. No 3. Unclear |
| Immunogenicity was measured for enough time (more than 12 months)? | 1. Yes 2. No 3. Unclear |
| What is your judgment about the assessment of immunogenicity? | **Low risk of bias:** Immunogenicity was adequately measured in both switching and nonswitching arms; Immunogenicity was measured for sufficient time (more than 12 months).  **High risk of bias:** Immunogenicity was not measured in both switching and nonswitching arms; Immunogenicity was not measured for sufficient time (less than 12 months).  **Unclear risk of bias:** Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. |
| **Domain 4 – The washout period between treatment** | Had the study a wash-period before the switch? \* | 1. Yes 2. No 3. Unclear |
| If yes, the washout was done for enough time? \*\* | 1. Yes 2. No 3. Unclear |
| What is your judgment about the washout period between treatment (multiple switching)? | **Low risk of bias:** There is an enough and appropriate wash-out period before switching  **High risk of bias:** There is no wash-out period before switching  **Unclear risk of bias:** Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. |
| **Domain 5 – Enough power to assess efficacy and safety (equivalence studies)** | Had the study a small number (<50) of patients in the switch groups? | 1. Yes 2. No 3. Unclear |
| Was there a high rate of differential loss of participants before switching? | 1. Yes 2. No 3. Unclear |
| Was the study powered to assess efficacy in individual diseases? | 1. Yes 2. No 3. Unclear |
| What is your judgment about enough power to assess efficacy and safety (equivalence studies)? | **Low risk of bias:** Statistical power was enough, i.e. There are many patients in the switch groups.  There was a low or similar rate of loss of participants before switching;  The study was powered to assess efficacy in individual diseases.  **High risk of bias:** Statistical power was limited because of small patient numbers in the switch groups;  There was a high or differential loss of participants before switching; The study was NOT powered to assess efficacy in individual diseases.  **Unclear risk of bias:** Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. |
| **Domain 6 – An enough follow-up period** | The follow-up period after a switch was sufficiently long to allow detection of clinically relevant differences (equal or less than 24 weeks)? | 1. Yes 2. No 3. Unclear |
| What is your judgment about enough follow-up period? | **Low risk of bias:** The follow-up period after a switch was sufficiently long to allow the detection of clinically relevant differences ( More than 24 weeks)  **High risk of bias:** The follow-up period after a switch was not sufficiently long to allow detection of clinically relevant differences (equal or less than 24 weeks)  **Unclear risk of bias:** Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. |