Unit: Technical Assessment Unit

Public assessment report for biological products

Yesintek

Administrative information:

Trade name of the medicinal product:	**Yesintek 45 mg** **Yesintek 45 mg** **Yesintek 90 mg** **Yesintek 130 mg**
INN (or common name) of the active substance(s):	**Yesintek 45 mg Vial:** Ustekinumab 45 mg/ 0.5 mL **Yesintek 45 mg PFS:** Ustekinumab 45 mg/0.5 mL. **Yesintek 90 mg PFS:** Ustekinumab 90 mg/1 mL. **Yesintek 130 mg Vial:** Ustekinumab 130 mg / 26 ml (5 mg/mL).
Manufacturer of the finished product	Biocon Biologics Limited, Block No. B1, B2, B3, B5, Q13 of Q1 and W20 and Unit S18, 1st Floor, Block B4, Special Economic Zone, Plot No. 2, 3, 4 and 5, Phase IV, Bommasandra-Jigani Link Road, Bommasandra Post, Bengaluru - 560 099, INDIA.
Marketing Authorization holder	**Biosimilar Collaborations Ireland Limited, Unit 35/36 Grange Parade, Baldoyle Industrial Estate, Dublin 13, DUBLIN, Ireland, D13 R20R**
Applied Indication(s):	– **Plaque psoriasis** – **Paediatric plaque psoriasis** – **Psoriatic arthritis** - **Crohn' s Disease** - **Pediatric Crohn' s Disease**
Pharmaceutical form(s) and strength(s):	**Yesintek 45 mg Vial:** Solution for S.C injection **Yesintek 45 mg PFS:** Solution for S.C injection in prefilled syringe **Yesintek 90 mg PFS:** Solution for S.C injection in prefilled syringe **Yesintek 130 mg Vial:** Concentrate for solution

(Yesintek 45 & 90 & 130 mg)

	for I.V infusion
Route of administration	**Yesintek 45 mg Vial:** S.C injection **Yesintek 45 mg PFS:** S.C injection **Yesintek 90 mg PFS:** S.C injection **Yesintek 130 mg Vial:** I.V infusion
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

ADA: anti-drug antibody
AEs: adverse events
AESI: adverse events of special interest
CI: confidence interval
EU: European Union
FAS: full analysis set
NAb: neutralizing antibody
PASI: Psoriasis Area and Severity Index improvement
PK: pharmacokinetic
PPS: per protocol set
RMP: Reference Medicinal Product
SAEs: serious adverse events
SC: subcutaneous
SOC: system organ class
TEAEs: treatment-emergent adverse events
US: United States

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications…….…….…….2
2. Quality aspects……...…….....2
2.2 Drug Substance (Active ingredient) …… ……...……..... 2
2.3 Drug product……..….2
3. Non-clinical aspects…….……...…..3
4. Clinical aspect…….…….…….....6
5. General Conclusion and Recommendations if any……...8

1. Introduction

The file evaluated according to EDA Reliance Model & the company submitted data which are the following:

1. Quality module-3 from the CTD file.
2. EMA Unredacted Assessment.

2. **Quality aspects:**

Manufacturer (s):

• **Drug Substance:** Biocon Biologics Limited, Block No, B1, B2, B3, B5, Q13 of Q1 and W20 and Unit S18,1st Floor, Block B4, Special Economic Zone, Plot No. 2,3,4 and 5, Phase IV, Bommasandra-Jigani Link Road, Bommasandra Post, Bengaluru - 560 099, - INDIA ;

• **Drug product:** Biocon Biologics Limited, Block No, B1, B2, B3, B5, Q13 of Q1 and W20 and Unit S18,1st Floor, Block B4, Special Economic Zone, Plot No. 2,3,4 and 5, Phase IV, Bommasandra-Jigani Link Road, Bommasandra Post, Bengaluru - 560 099, - INDIA ;

Stability of:

Drug substance

For Yesintek 45mg. & 130mg. Vial:

For Yesintek 45mg. & 90mg. PFS:

Approved Storage Conditions: -40˚C ± 5°C
Approved Shelf Life: 36 months

Drug product

For Yesintek 45mg. & 130mg. Vial:

Approved Storage Conditions:

- Store in a refrigerator (2 – 8 °C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light

Approved Shelf Life: 24 months

For Yesintek 45mg. & 90mg. PFS:

Approved Storage Conditions:

-Store in a refrigerator (2 – 8 °C).
-Do not freeze.
-Keep the pre-filled syringe in the outer carton in order to protect from light.

Approved Shelf Life: 36 months

For Yesentik 45mg. Vial:

3. **Non–clinical aspect**

Yesintek has the same amino acid sequence, formulations, dosage forms, presentations, and product strengths as Reference Medicinal Product (RMP) Stelara. The results from the *in vitro* pharmacodynamic characterization studies demonstrated functional similarity between Yesintek and RMP Stelara (EU/US), which also provides support for the claimed therapeutic indications of Yesintek. The analytical methods used were scientifically valid and fit for purpose.

Comparative *in vivo* pharmacology, secondary pharmacodynamics, safety pharmacology, and pharmacodynamic drug interaction studies as well as *in vivo* pharmacokinetics and toxicology (or toxicokinetic) studies were not conducted. The absence of these studies is considered justified because (i) animal models are not considered sensitive enough to determine pharmacological differences and (ii) comparability exercise revealed no uncertainties, which could be addressed in non-clinical *in vivo* pharmacokinetics and toxicology studies. The waiving of such studies is in line with relevant guidelines.

Overall conclusion: From the non-clinical point of view, no issues for concern regarding the data submitted for Yesintek.

4. **Clinical aspect:**

The clinical development program of the product included two clinical studies, one completed phase I study (BM12H-NHV-01-G-01) to assess PK equivalence of Bmab 1200 compared to EU-Stelara, and US-Stelara as reference products in healthy volunteers using a therapeutic dose of 45 mg, which is within the linear range of the doses tested by Stelara. Phase 1 study was followed by a completed comparative Phase 3 (BM12H-PSO-03- G-02) for assessment of the similarity between the proposed biosimilar Bmab 1200 and EU-Stelara in patients with moderate to severe plaque psoriasis with regard to efficacy, PK, safety, and immunogenicity.

❖ **Clinical Efficacy & Immunogenicity**

Clinical Efficacy

- The 52-week analysis in study (BM12H-PSO-03- G-02) demonstrated equivalent efficacy between Bmab 1200 and Stelara in patients with moderate to severe chronic plaque psoriasis for the primary efficacy endpoint (percentage change from baseline in the PASI score at Week 12).
- The efficacy of Bmab 1200 was comparable with that of Stelara for the secondary efficacy endpoints throughout the study up to Week 52.
- There was no difference between the treatment arms post switching from Stelara to Bmab 1200 with respect to efficacy parameters.
- Equivalence of Bmab 1200 and Stelara was established for the primary, secondary, and tertiary estimands for the FAS, PPS, and subset of patients who received 45 mg of Bmab 1200 or Stelara based on the predefined equivalence margins of ±10% for the 90% CI and ±13% for the 95% CI.

Clinical Immunogenicity

- Immunogenicity did not seem to have an effect on efficacy, or on hypersensitivity reactions which were independent of ADA titres and NAb status with no injection site reactions being reported.
- Overall, the ADA incidence and nAb-reactive rate were generally comparable between the Bmab 1200 and Stelara groups and the Stelara-Stelara and Stelara-Bmab 1200 groups throughout the study, with no apparent impact of switching from Stelara to Bmab 1200.
- Although the nAb reactive rate was higher in the Stelara group versus the Bmab 1200 group and in the Stelara-Stelara group versus the Stelara-Bmab 1200 group post-switching, these differences were not clinically meaningful as the clinical response rates were comparable.
- Both ADA+ and nAb reactivity rates decreased over time despite the switch. The AEs as recorded (overall AEs, SAEs, TEAEs, AESI) and particularly hypersensitivity reactions were independent of ADA titers and nAb status, with no injection site reactions being reported.

❖ **Clinical Safety**

- Across the clinical development program that included 2 studies (BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02), the safety profile of Bmab 1200 was similar to that of Stelara.
- The most common TEAEs were reported in the SOC of infections and infestations (like nasopharyngitis), which are expected with ustekinumab. The majority of the reported TEAEs were mild or moderate in severity, and most of these events were considered not related to the study drug.
- The number of severe/Grade 3 TEAEs was generally low and was comparable between the treatment groups in both the studies. No deaths were reported in both the studies.
- The incidence of serious TEAEs was low in both studies, with a treatment-related serious TEAE reported only in the Phase 3 study. There were no (Phase 1) or only few (Phase 3) TEAEs leading to either study or treatment discontinuation, and the incidence was similar across the treatment groups.

- Also, the incidence of TEAEs of special interest was similar across the treatment groups and consistent with Stelara.
- No significant increase in the hypersensitivity reactions was observed post single switch from Stelara to Bmab 1200. There were no clinically meaningful differences among the treatment groups linked to immunogenicity in the clinical studies upon evaluation of the incidence or titer of ADA and incidence of NAb, hypersensitivity reactions were independent of ADA titers and NAb status with no injection site reactions being reported.
- **Overall, no new significant safety concerns were reported that would change the risk benefit assessment of ustekinumab treatment.**

❖ **Overall Conclusion**

- The clinical package consisting of Study BM12H-NHV-01-G-01 and Study BM12H-PSO-03-G-02 (the 2 clinical studies) confirms the high similarity established at the biological levels and demonstrates no clinically meaningful differences between Bmab 1200, US-Stelara, and EU-Stelara, thus supporting biosimilarity.

❖ **Benefit–Risk Conclusion**

- The overall benefit/risk of of Yesintek (45mg/0.5ml) Solution for injection (Vial) (SC), is favorable in treatment of Plaque Psoriasis, Pediatric plaque psoriasis, Psoriatic Arthritis and Crohn's Disease (CD**).**

For Yesentik 130mg. Vial:

3. Non–clinical aspect

Yesintek has the same amino acid sequence, formulations, dosage forms, presentations, and product strengths as Reference Medicinal Product (RMP) Stelara. The results from the *in vitro* pharmacodynamic characterization studies demonstrated functional similarity between Yesintek and RMP Stelara (EU/US), which also provides support for the claimed therapeutic indications of Yesintek. The analytical methods used were scientifically valid and fit for purpose.

Comparative *in vivo* pharmacology, secondary pharmacodynamics, safety pharmacology, and pharmacodynamic drug interaction studies as well as *in vivo* pharmacokinetics and toxicology (or toxicokinetic) studies were not conducted. The absence of these studies is considered justified because (i) animal models are not considered sensitive enough to determine pharmacological differences and (ii) comparability exercise revealed no uncertainties, which could be addressed in non-clinical *in vivo* pharmacokinetics and toxicology studies. The waiving of such studies is in line with relevant guidelines.

Overall conclusion: From the non-clinical point of view, no issues for concern regarding the data submitted for Yesintek.

4. Clinical aspect:

The clinical development program of the product included two clinical studies, one completed phase I study (BM12H-NHV-01-G-01) to assess PK equivalence of Bmab 1200 compared to EU-Stelara, and US-Stelara as reference products in healthy volunteers using a therapeutic dose of 45 mg, which is within the linear range of the doses tested by Stelara. Phase 1 study was followed by a completed comparative Phase 3 (BM12H-PSO-03- G-02) for assessment of the similarity between the proposed biosimilar Bmab 1200 and EU-Stelara in patients with moderate to severe plaque psoriasis with regard to efficacy, PK, safety, and immunogenicity.

❖ **Clinical Efficacy & Immunogenicity**

Clinical Efficacy

-The 52-week analysis in study (BM12H-PSO-03- G-02) demonstrated equivalent efficacy between Bmab 1200 and Stelara in patients with moderate to severe chronic plaque psoriasis for the primary efficacy endpoint (percentage change from baseline in the PASI score at Week 12).

- The efficacy of Bmab 1200 was comparable with that of Stelara for the secondary efficacy endpoints throughout the study up to Week 52.
- There was no difference between the treatment arms post switching from Stelara to Bmab 1200 with respect to efficacy parameters.
- Equivalence of Bmab 1200 and Stelara was established for the primary, secondary, and tertiary estimands for the FAS, PPS, and subset of patients who received 45 mg of Bmab 1200 or Stelara based on the predefined equivalence margins of ±10% for the 90% CI and ±13% for the 95% CI.

Clinical Immunogenicity

- Immunogenicity did not seem to have an effect on efficacy, or on hypersensitivity reactions which were independent of ADA titres and NAb status with no injection site reactions being reported.
- Overall, the ADA incidence and nAb-reactive rate were generally comparable between the Bmab 1200 and Stelara groups and the Stelara-Stelara and Stelara-Bmab 1200 groups throughout the study, with no apparent impact of switching from Stelara to Bmab 1200.
- Although the nAb reactive rate was higher in the Stelara group versus the Bmab 1200 group and in the Stelara-Stelara group versus the Stelara-Bmab 1200 group post-switching, these differences were not clinically meaningful as the clinical response rates were comparable.
- Both ADA+ and nAb reactivity rates decreased over time despite the switch. The AEs as recorded (overall AEs, SAEs, TEAEs, AESI) and particularly hypersensitivity reactions were independent of ADA titers and nAb status, with no injection site reactions being reported.

❖ **Clinical Safety**

- Across the clinical development program that included 2 studies (BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02), the safety profile of Bmab 1200 was similar to that of Stelara.

- The most common TEAEs were reported in the SOC of infections and infestations (like nasopharyngitis), which are expected with ustekinumab. The majority of the reported TEAEs were mild or moderate in severity, and most of these events were considered not related to the study drug.
- The number of severe/Grade 3 TEAEs was generally low and was comparable between the treatment groups in both the studies. No deaths were reported in both the studies.
- The incidence of serious TEAEs was low in both studies, with a treatment-related serious TEAE reported only in the Phase 3 study. There were no (Phase 1) or only few (Phase 3) TEAEs leading to either study or treatment discontinuation, and the incidence was similar across the treatment groups.
- Also, the incidence of TEAEs of special interest was similar across the treatment groups and consistent with Stelara.
- No significant increase in the hypersensitivity reactions was observed post single switch from Stelara to Bmab 1200. There were no clinically meaningful differences among the treatment groups linked to immunogenicity in the clinical studies upon evaluation of the incidence or titer of ADA and incidence of nAb, hypersensitivity reactions were independent of ADA titers and NAb status with no injection site reactions being reported.
- **Overall, no new significant safety concerns were reported that would change the risk benefit assessment of ustekinumab treatment.**

❖ **Overall Conclusion**

- The clinical package consisting of Study BM12H-NHV-01-G-01 and Study BM12H-PSO-03-G-02 (the 2 clinical studies) confirms the high similarity established at the biological levels and demonstrates no clinically meaningful differences between Bmab 1200, US-Stelara, and EU-Stelara, thus supporting biosimilarity.
- Since the reference product is approved for both IV and SC administration (dosage form and route of administration for Bmab1200 is identical to Stelara (EU)) and the selected route for the clinical studies is the SC route only, the applicant supported the assessed PK primary endpoints for proving biosimilarity with co-primary (AUC0-inf and Cmax), in addition to partial AUCs to ensure comparability of absorption and elimination and to support extrapolation of SC data to IV administration.

❖ **Benefit–Risk Conclusion**

- The overall benefit/risk of of Yesintek Concentrate for solution for Infusion in vial (130mg/26ml) (IV), is favorable in treatment of Crohn's Disease (CD**).**

Yesintek 45&90 mg. PFS:

3. Non–clinical aspect

Yesintek has the same amino acid sequence, formulations, dosage forms, presentations, and product strengths as Reference Medicinal Product (RMP) Stelara. The results from the *in vitro* pharmacodynamic characterization studies demonstrated functional similarity between Yesintek and RMP Stelara (EU/US), which also provides support for the claimed therapeutic indications of Yesintek. The analytical methods used were scientifically valid and fit for purpose.

Comparative *in vivo* pharmacology, secondary pharmacodynamics, safety pharmacology, and pharmacodynamic drug interaction studies as well as *in vivo* pharmacokinetics and toxicology (or toxicokinetic) studies were not conducted. The absence of these studies is considered justified because (i) animal models are not considered sensitive enough to determine pharmacological differences and (ii) comparability exercise revealed no uncertainties, which could be addressed in non-clinical *in vivo* pharmacokinetics and toxicology studies. The waiving of such studies is in line with relevant guidelines.

Overall conclusion: From the non-clinical point of view, no issues for concern regarding the data submitted for Yesintek.

4. Clinical aspect:

The clinical development program of the product included two clinical studies, one completed phase I study (BM12H-NHV-01-G-01) to assess PK equivalence of Bmab 1200 compared to EU-Stelara, and US-Stelara as reference products in healthy volunteers using a therapeutic dose of 45 mg, which is within the linear range of the doses tested by Stelara. Phase 1 study was followed by a completed comparative Phase 3 (BM12H-PSO-03- G-02) for assessment of the similarity between the proposed biosimilar Bmab 1200 and EU-Stelara in patients with moderate to severe plaque psoriasis with regard to efficacy, PK, safety, and immunogenicity.

- **Clinical Efficacy & Immunogenicity**

Clinical Efficacy

- The 52-week analysis in study (BM12H-PSO-03- G-02) demonstrated equivalent efficacy between Bmab 1200 and Stelara in patients with moderate to severe chronic plaque psoriasis for the primary efficacy endpoint (percentage change from baseline in the PASI score at Week 12).
- The efficacy of Bmab 1200 was comparable with that of Stelara for the secondary efficacy endpoints throughout the study up to Week 52.

- There was no difference between the treatment arms post switching from Stelara to Bmab 1200 with respect to efficacy parameters.
- Equivalence of Bmab 1200 and Stelara was established for the primary, secondary, and tertiary estimands for the FAS, PPS, and subset of patients who received 45 mg of Bmab 1200 or Stelara based on the predefined equivalence margins of ±10% for the 90% CI and ±13% for the 95% CI.

Clinical Immunogenicity

- Immunogenicity did not seem to have an effect on efficacy, or on hypersensitivity reactions which were independent of ADA titres and NAb status with no injection site reactions being reported.
- Overall, the ADA incidence and nAb-reactive rate were generally comparable between the Bmab 1200 and Stelara groups and the Stelara-Stelara and Stelara-Bmab 1200 groups throughout the study, with no apparent impact of switching from Stelara to Bmab 1200.
- Although the nAb reactive rate was higher in the Stelara group versus the Bmab 1200 group and in the Stelara-Stelara group versus the Stelara-Bmab 1200 group post-switching, these differences were not clinically meaningful as the clinical response rates were comparable.
- Both ADA+ and nAb reactivity rates decreased over time despite the switch. The AEs as recorded (overall AEs, SAEs, TEAEs, AESI) and particularly hypersensitivity reactions were independent of ADA titers and nAb status, with no injection site reactions being reported.

❖ **Clinical Safety**

- Across the clinical development program that included 2 studies (BM12H-NHV-01-G-01 and BM12H-PSO-03-G-02), the safety profile of Bmab 1200 was similar to that of Stelara.
- The most common TEAEs were reported in the SOC of infections and infestations (like nasopharyngitis), which are expected with ustekinumab. The majority of the reported TEAEs were mild or moderate in severity, and most of these events were considered not related to the study drug.
- The number of severe/Grade 3 TEAEs was generally low and was comparable between the treatment groups in both the studies. No deaths were reported in both the studies.
- The incidence of serious TEAEs was low in both studies, with a treatment-related serious TEAE reported only in the Phase 3 study. There were no (Phase 1) or only few (Phase 3) TEAEs leading to either study or treatment discontinuation, and the incidence was similar across the treatment groups.
- Also, the incidence of TEAEs of special interest was similar across the treatment groups and consistent with Stelara.
- No significant increase in the hypersensitivity reactions was observed post single switch from Stelara to Bmab 1200. There were no clinically meaningful differences among the treatment groups linked to immunogenicity in the clinical studies upon evaluation of the incidence or titer of ADA and incidence of nAb, hypersensitivity reactions were independent of ADA titers and NAb status with no injection site reactions being reported.

- **Overall, no new significant safety concerns were reported that would change the risk benefit assessment of ustekinumab treatment.**

❖ **Overall Conclusion**

- The clinical package consisting of Study BM12H-NHV-01-G-01 and Study BM12H-PSO-03-G-02 (the 2 clinical studies) confirms the high similarity established at the biological levels and demonstrates no clinically meaningful differences between Bmab 1200, US-Stelara, and EU-Stelara, thus supporting biosimilarity.

❖ **Benefit–Risk Conclusion**

- The overall benefit/risk of Yesintek (45mg/0.5ml & 90mg/1ml) Solution for injection in PFS (SC), is favorable in treatment of Plaque Psoriasis, Pediatric plaque psoriasis, Psoriatic Arthritis and Crohn's Disease (CD**).**

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.

https://www.ema.europa.eu/en/documents/product-information/yesintek-epar-product-information_en.pdf