Collaborative Clinical, Cross-Discipline Team Leader, and Division Summary Review

Date	See Electronic Stamp Date
From	Juwaria Waheed, MD, Clinical Reviewer Anil Rajpal, MD, MPH, CDTL Nikolay Nikolov, MD, DIvision Director
Subject	Cross-Discipline Team Leader & Collaborative Clinical Review
sBLA # and Supplement#	761059/S-004
Applicant	Samsung
Date of Submission	August 17, 2021
BsUFA Goal Date	June 17, 2022
Proprietary Name (Proper Name)	Hadlima (adalimumab-bwwd)
Product Code Name	SB5
Reference Product Proprietary Name (Proper Name)	Humira (adalimumab)
Applicant Proposed Dosage Form(s)	Single-dose glass vial for institutional use only: 40 mg/0.8 mL
Applicant Proposed Indication(s)/Population(s)	Polyarticular Juvenile Idiopathic Arthritis (pJIA) 2 years of age Pediatric Crohn's disease (CD) 6 years of age and older
Applicant Proposed Dosing Regimen(s)	Same as US-Humira dosing for the respective indications
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Polyarticular Juvenile Idiopathic Arthritis (pJIA) 2 years of age and older Pediatric Crohn's disease (CD) 6 years of age and older
Recommended Dosing Regimen(s) (if applicable)	Same as US-Humira dosing for the respective indications

1. Introduction

The Applicant submitted this supplement 004 to expand the indications of Juvenile Idiopathic Arthritis (JIA) and Crohn's Disease (CD) that were previously under orphan exclusivity and to provide the pediatric assessment for Ulcerative Colitis (UC). In doing so, the Applicant also proposes to fulfill the PREA PMR commitments that were issued with the original approval of Hadlima on July 23, 2019 (See Section 9, Pediatrics). No new clinical information is included or is required for this submission. Rather, the Applicant cross-references the original application submission under BLA 761059 and has now provided supporting justification of extrapolation for each of the indications currently being sought for licensure.

Additionally, in the same supplement 004, the Applicant proposes to add a new presentation - 40 mg/0.8 mL vial presentation for single-dose subcutaneous (SC) injection for institutional use only. In doing so, the Applicant proposes to fulfill PMR 3671-4 (See Section 3, Product Quality and Section 9, Pediatrics).

2. Background

Adalimumab-bwwd (Hadlima) is a biosimilar to US-licensed Humira (US-Humira) approved on July 23, 2019 under section 351(k) of the Public Health Service Act (PHS Act) for the treatment of:

1) Rheumatoid Arthritis (RA)
2) Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older
3) Psoriatic Arthritis (PsA)
4) Ankylosing Spondylitis (AS)
5) Adult Crohn's Disease (adult CD)
6) Ulcerative Colitis (UC)
7) Plaque Psoriasis (PsO)

The Applicant originally submitted a BLA under section 351(k) of the Public Health Service Act (PHS Act) for adalimumab-bwwd on July 23, 2018.

The original application included the following:

- A comprehensive comparative analytical assessment of adalimumab-bwwd, US-Humira, and EU-approved Humira (EU-Humira). These included comparative characterization of physicochemical attributes and comparative functional assessments.
- Nonclinical studies including a 7-week pharmacology study in Tg197 mice and a 4-week repeat-dose toxicology study in monkeys to compare the effects of adalimumab-bwwd to those of EU-Humira.
- A PK similarity study (SB5-G11-NHV) in healthy subjects following a single SC 40 mg dose of adalimumab-bwwd, EU-Humira, or US-Humira.
- A comparative clinical study (SB5-G31-RA) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-bwwd and EU-Humira in combination with methotrexate in patients with moderately to severely active RA who have had an inadequate response to methotrexate.
- A scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) for extrapolation of data and information submitted in the application to support licensure of adalimumab-bwwd for each of the additional indications for which Samsung was seeking licensure and for which US-Humira had been previously licensed.

In considering the totality of the evidence for the original BLA submission, review of the data submitted by the Applicant showed that adalimumab-bwwd is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no

clinically meaningful differences between adalimumab-bwwd and US-Humira in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of adalimumab-bwwd for the non-studied indications being sought. Review of the information submitted by the Applicant demonstrated that adalimumab-bwwd is biosimilar to US-Humira for each of the following indications for which US-Humira has been previously approved and the Applicant was seeking licensure for adalimumab-bwwd: RA, JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and Adult UC. See DPARP BMER in collaboration with DDDP and DGIEP, dated July 23, 2019.[1]

3. Product Quality

With this supplement, 004, the Applicant proposes to add a new presentation - 40 mg/0.8 mL vial presentation for single-dose subcutaneous (SC) injection for institutional use only. In doing so, the Applicant proposes to fulfill PMR 3671-4.

> PMR 3671-4: Develop a presentation that can be used to accurately administer (adalimumab-bwwd) to pediatric patients who weigh less than 30 kg.

Please see Office of Biotechnology Products (OBP) and Office of Pharmaceutical Manufacturing Assessment (OPMA) reviews for details of their assessment of the proposed presentation.

The Office of Pharmaceutical Quality (OPQ), CDER completed the assessment of sBLA 761059/4 for the addition of a SB5 40 mg/0.8 mL institutional use vial presentation. From a product quality, product quality microbiology, and sterility assurance perspective, OPQ does not note any product quality deficiencies that would preclude approval of sBLA 761059/4.

In the original BLA, extensive comparative analytical analyses (CAA) were conducted for SB5 40 mg/0.8 mL and US-licensed Humira 40 mg/0.8 mL prefilled syringe (PFS) presentations to support that SB5 is highly similar to US-licensed Humira not notwithstanding minor differences in clinically inactive components. The addition of the 40 mg/0.8 mL institutional use vial presentation leverages this CAA data through analytical comparability between the approved SB5 40 mg/0.8 mL PFS and the proposed SB5 40 mg/0.8 mL institutional use vial presentation, all of which are manufactured using the same drug substance. Therefore, the totality of these analytical data supports the conclusion that the SB5 40 mg/0.8 mL institutional use vial presentation is highly similar to the US-licensed Humira 40 mg/0.8 mL institutional use vial presentation, notwithstanding minor differences in clinically inactive components.

The SB5 40 mg/0.8 mL glass vial presentation is manufactured to have the same strength, dosage form, and route of administration as the US-licensed Humira 40 mg/0.8 mL institutional use vial presentation. The SB5 40 mg/0.8 mL institutional use vial presentation

[1] DPARP: Division of Pulmonary, Allergy and Rheumatology Products; BMER: Biosimilar Multi-disciplinary Evaluation and Review; DDDP: Division of Dermatology and Dental Products; DGIEP: Division of Gastroenterology and Inborn Errors Products

(b) (4)

The strength of the SB5 40 mg/0.8 mL institutional use vial presentation is the same as that of 40 mg/0.8 mL US-licensed Humira.

Regarding assessment of PMR 3671-4, see Section 9 – Pediatrics.

There are no CMC or product quality issues that would preclude approval of the indications sought for licensure.

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indications sought for licensure.

5. Clinical Pharmacology

There are no clinical pharmacology issues that would preclude approval of the indications sought for licensure.

6. Clinical/Statistical- Efficacy

Adalimumab-bwwd was previously studied in patients with RA in the comparative clinical study (SB5-G31-RA). The data were previously reviewed and summarized in the BMER dated July 23, 2019 for the original application. There are no clinical/statistical efficacy issues that would preclude approval of the indications sought for licensure.

7. Safety

Adalimumab-bwwd was previously studied in patients with RA in the comparative clinical study (SB5-G31-RA) and in healthy subjects in the PK similarity study (SB5-G11-NHV). The data were previously reviewed and summarized in the BMER dated July 23, 2019 for the original application. There are no clinical safety issues that would preclude approval of the indications sought for licensure.

8. Considerations for Extrapolation of Biosimilarity in Other Conditions of Use

The Guidance for Industry Questions and Answers on Biosimilar Development and the Biologics Price Competition and Innovation (BPCI) Act[2] (September 2021), notes that in the context of the potential biosimilar product under the Act, the biosimilar applicant may fulfill

[2] https://www.fda.gov/media/119258/download

the Pediatric Research Equity Act (PREA) requirements by satisfying the statutory requirements for demonstrating biosimilarity and providing an adequate scientific justification under the Biologics Price Competition and Innovation (BPCI) Act for extrapolating data and information to support a licensure for each condition of use for which licensure is sought.[3]

Adalimumab-bwwd is an approved biosimilar for the treatment of RA, PsA, AS, adult CD, adult UC, JIA in patients 4 years of age and older, and PsO. The Applicant has now submitted justification for extrapolation of the data and information in support of licensure of adalimumab-bwwd for the treatment of pJIA in patients 2 years to less than 4 years of age, pediatric CD in patients 6 years to 17 years of age, and pediatric UC in patients 5 years to 17 years of age (see also Section 9 Pediatrics).

Scientific considerations for the extrapolation of biosimilarity to the pediatric populations - JIA (2-4 years), Pediatric CD (6-17 years), and Pediatric UC (5-17 years), are outlined below:

1. Biosimilarity has previously been established between adalimumab-bwwd and the reference product, US-Humira based on extensive analytical characterization, comparative PK study, comparative clinical study, safety and immunogenicity data.
2. Adequate scientific justification supporting extrapolation of scientific information and data (based on mechanism of action, PK and immunogenicity, safety and toxicities) from the original BLA submission (761059) allowed licensure of non-studied indications for which the reference product has been approved.
3. Similar extrapolation of scientific information and data from the original application applies to the indications that are subject of this supplement. Therefore, in pJIA in patients 2 years to less than 4 years of age, pediatric CD in patients 6 years to 17 years of age, and pediatric UC in patients 5 years to 17 years of age:
    a. a similar PK profile would be expected between adalimumab-bwwd and US-Humira
    b. similar immunogenicity would be expected between adalimumab-bwwd and US-Humira
    c. similar safety profile would be expected between adalimumab-bwwd and US-Humira
    d. Samsung addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that adalimumab-bwwd and US-Humira have the same mechanisms for each of the discussed indications, to the extent that the mechanisms of action are known or can reasonably be determined

Additional considerations include:

Regarding MOA, the shared importance of TNF in the pathophysiology of disease, and clinical response, in adult RA and JIA support extrapolation to the existing JIA data for the reference product. There are no data or scientific evidence that the MOA differs in pJIA in patients

[3] For more information on extrapolation in this context, see FDA's guidance for industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (May 2015)

between 2 years to less than 4 years of age such that the same justification for extrapolation could not apply to this younger subgroup of pJIA patients.

In terms of MOAs for the IBD indications, including pediatric CD in patients 6 years of age and older and pediatric UC in patients 5 years of age and older, in addition to the neutralization of a soluble form of tumor necrosis factor alpha (sTNF), transmembrane tumor necrosis factor alpha (mTNF, also tmTNF) binding and subsequent reverse signaling and/or Fc-related effects are also relevant. However, there are no data or scientific evidence that the MOA differs in adult CD and adult UC such that the same justification for extrapolation could not apply to pediatric CD patients 6 years of age and older and to pediatric UC patients 5 years of age and older, respectively.

Regarding immunogenicity and PK, data supported extrapolation in the original application for pJIA in patients 4 years of age and older, adult CD, and adult UC. There is no data or scientific evidence that PK and immunogenicity differ in pJIA in patients between 2 years to less than 4 years of age such that the same justification for extrapolation could not apply. Similarly, there is no data or scientific evidence that PK and immunogenicity differ in pediatric CD patients 6 years of age and older, and pediatric UC patients 5 years of age and older such that the same justification for extrapolation could not apply.

In terms of safety and toxicity, the same safety data which supported approval of the extrapolated indications, including pJIA in patients 4 years of age and older, adult CD and adult UC, is applicable and relevant to support safety in patients with pJIA between 2 years to less than 4 years of age, pediatric CD in patients 6 years of age and older, and pediatric UC in patients 5 years of age and older.

Also see Division of Gastroenterology memo for BLA 761059 S-004 in the Appendix for further discussion of the pediatric CD and pediatric UC indications.

In conclusion, the totality of evidence as discussed above is adequate to justify extrapolating the data and information submitted to the BLA to support licensure of adalimumab-bwwd for the indication of “reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older” and for the indication of “Crohn’s disease in pediatric patients 6 years of age and older.”

Note that while the Applicant has also submitted acceptable extrapolation justification for pediatric UC patients 5 years of age and older, FDA has determined that US-Humira is eligible for orphan drug exclusivity for pediatric UC, ages 5-17 years. FDA therefore cannot license adalimumab-bwwd for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028.

This information is sufficient to also fulfill the requirements of PMR 3671-1, PMR 3671-2 and PMR 3671-3 from the approval of original BLA. To address the PREA-PMR requirements for these indications and age-groups, the Applicant has satisfied the statutory requirements by demonstrating biosimilarity and also provided an adequate scientific justification under the BPCI Act for extrapolating the findings of biosimilarity to the non-studied conditions of use

for which the Applicant is seeking licensure and for which US-Humira has been previously approved.

9. Pediatrics

On November July 23, 2019, adalimumab-bwwd was approved by FDA as a biosimilar to US-Humira. It was considered to have a new active ingredient and triggered PREA. At that time, the PREA-required pediatric assessments for pediatric JIA patients 2 years to less than 4 years of age, pediatric CD patients 6 years to 17 years of age and pediatric UC in pediatric patients 5 years to 17 years of age were deferred.

At the time of initial BLA, Samsung did not seek approval for indications of US- Humira that are subject to remaining orphan exclusivity. At the time of BLA approval, post-marketing requirements (PMRs) were required for Hadlima, as deferred pediatric assessment by section 505B(a) of the Federal Food, Drug, and Cosmetic Act.

The following PMRs were issued:

PMR #	PMR Details	Final Report Due Date
3671-1	Assessment of Hadlima (adalimumab-bwwd) for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 to less than 4 years of age	September 2021
3671-2	Assessment of Hadlima (adalimumab-bwwd) for the treatment of Pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age.	September 2021
3671-3	Assessment of Hadlima (adalimumab-bwwd) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age	September 2021
3671-4	Develop a presentation that can be used to accurately administer Hadlima (adalimumab-bwwd) to pediatric patients who weigh less than 30 kg	September 2021

In the current submission, the Applicant provided final reports to fulfill PMRs 3671-1, 3671-2, 3671-3 and 3671-4.

PMR's 3671-1, 3671-2, and 3671-3

The current supplement includes the pediatric assessments with justification for extrapolation proposing to fulfill the PREA PMRs 3671-1, 3671-2, and 3671-3. The Applicant has provided adequate information to fulfill the requirements of PMR 3671-1, PMR 3671-2 and PMR 3671-3 from the approval of the original BLA. Refer to Section 8 Extrapolation for the review of the scientific assessment of these requirements.

PMR 3671-4

To fulfill PMR 3671-4, the Applicant proposed the following presentation:

"Single-Dose Institutional Use Vial
Injection: 40 mg/0.8 mL in a single-dose, glass vial for institutional use only."

The Review Team questioned the appropriateness of the single-dose, glass vial for institutional use only as an age-appropriate presentation.

The Division of Pediatric and Maternal Health (DPMH) was consulted. DPMH concluded the following: "The proposed Hadlima Single Dose Institutional Use Vial is similar to Humira's Single Dose Institutional Use Vial. However, Humira has several other presentations including 20 mg and 10 mg presentations which can be used by pediatric patients weighing less than 30 kg in an outpatient setting. Pediatric dosing is administered every other week. It is not reasonable to expect pediatric patients to visit an institution including a physician's office every two weeks for administration of the drug. While the PMR does not expressly state that the Applicant is required to develop a presentation that can be used as an outpatient, DPMH believes that was the intent of the PMR."

A Pediatric Review Committee (PeRC) meeting occurred on May 10, 2022. Taking the above DPMH concerns into consideration, as well as the language of the PMR and the statutory language in PREA, PeRC recommended the following: "Consider the PREA PMR 3671-4 fulfilled with the proposed presentation of the 40 mg/0.8 mL glass vial for institutional use only. PeRC noted that the Agreed iPSP included a plan from Samsung Bioepis for a 40 mg glass vial for pediatric use."

The Applicant has provided adequate information to fulfill the requirements of PMR 3671-4.

10. Other Relevant Regulatory Issues

None.

11. Labeling

The proposed Hadlima prescribing information incorporated relevant data and information from the US-Humira prescribing information, with appropriate modifications. It was determined that the proposed labeling is consistent with the current FDA labeling practice.

12. Postmarketing Recommendations

There are no potential or new safety or efficacy issues determined from this review that warrant further assessment with a postmarketing requirements or commitments.

13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS) to ensure the safe use of adalimumab-bwwd.

14. Recommended Regulatory Action

Approval.

15. Division Director Comments

I concur with the team's assessment of the data and information submitted in this supplemental BLA.

The information submitted fulfills PREA-required assessments for JIA in patients 2 to <4 years of age, pediatric Crohn's disease, and pediatric ulcerative colitis (PMR 3671-1, PMR 3671-2, and PMR 3671-3, respectively, from the approval of original BLA 761059, July 23, 2019). Also, the information submitted fulfills PREA PMR 3671-4 for a pediatric presentation. No additional data, new PMRs, PMC, or REMS are required for this supplement.

16. Appendix

Division of Gastroenterology Memo

Hadlima (SB5) is currently approved for the treatment of inflammatory bowel disease (IBD) indications of Crohn's disease (CD) and ulcerative colitis (UC) in adults, in addition to other indications.[4] While the IBD indications were not directly studied in the SB5 clinical program, as noted in the DG extrapolation review of the original BLA[5] dated 06/07/2019, consistent with the principles of the FDA Guidance For Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product[6], the Applicant had provided sufficient scientific justification based on the mechanism of action, PK, immunogenicity and toxicity profile, and sufficient information, including clinical data from the studied populations (healthy subjects and patients with rheumatoid arthritis, RA), to support licensure of SB5 for UC and CD in adults. At the time of the original BLA application, the Applicant did not seek the licensure of the pediatric CD indication due to pending orphan drug exclusivity. In addition, US-Humira was not licensed for the pediatric UC indication at the time. Thus, the approval letter for BLA 761059, dated 07/23/2019 included the following PREA PMRs to address the pediatric IBD indications[2]:

- 3671-2 Assessment of Hadlima (adalimumab-bwwd) for the treatment of Pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age.

[4] Hadlima USPI accessed on 02/25/2022: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761059s000lbl.pdf
[5] Hadlima, Original BLA Division of Gastroenterology Review (06/07/2019)
[6] Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)

Final Report Submission: September 2021

- 3671-3 Assessment of Hadlima (adalimumab-bwwd) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age.
  Final Report Submission: September 2021 (updated as per the deferral extension letter issued by the DG on 08/18/2020)

The orphan drug exclusivity of US-Humira for pediatric CD had since expired on September 23, 2021. Furthermore, on February 24, 2021, US-Humira was licensed for the treatment of moderately to severely active UC in pediatric patients 5 years and older, and eligible for an orphan drug exclusivity until February 24, 2028. With the submission of BLA 761059/S-004, the Applicant intends to address the pending PREA PMRs for pediatric CD (3671-2) and pediatric UC (3671-3) for Hadlima and is seeking the licensure for the pediatric CD indication.

The Applicant has provided justification for extrapolating data and information submitted in the application and supplement to support licensure of SB5 as a biosimilar for each of the pediatric IBD indications for which licensure is sought and for which US-Humira has been previously approved. The Applicant's justification was evaluated and considered adequate, as summarized below:

- Mechanism of Action (MOA)- Similar to the studied indication (RA), TNF-α plays a central role in the pathogenesis of IBD, as evidenced by the efficacy of approved TNF-α inhibitors in the treatment of UC and/or CD. In addition to the binding and neutralization of sTNFα, the efficacy of adalimumab in the treatment of IBD is thought to also involve reverse signaling via binding to tmTNF-α, and other plausible mechanisms of action involving the Fc region of the antibody[7,8,9]. The mechanisms by which adalimumab exerts its therapeutic effect are expected to be the same in adults *vs*. pediatric CD and pediatric UC patients. Together with demonstrated structural and functional similarity between SB5 and US-Humira, the mechanisms of action of SB5 are not expected to be different from that of US-Humira in pediatric CD and pediatric UC patients, to the extent that the mechanisms are known or can be reasonably determined.
- Pharmacokinetics (PK)- There are no significant differences in the PK characteristics of US-Humira in healthy subjects or across its various approved indications. Adalimumab concentrations are similar in adult vs. pediatric CD and UC patients (Humira USPI, 2021). Together with the data from the original BLA that demonstrated a 3-way PK similarity between SB5 vs. US-Humira vs. EU-Humira in healthy volunteers (Study SB5-G11-NHV), and between SB5 vs. EU-Humira in patients with RA (Study SB5-G31-RA), the PK following SB5 are not expected to be different to that of US-Humira in pediatric CD and pediatric UC patients.
- Immunogenicity- There is no scientific data or evidence to assume that the mechanisms involved in the development of ADAs would differ across indications to preclude extrapolation of immunogenicity data. Immunogenicity rates of US-Humira are comparable between adult *vs.* pediatric CD and UC patients (Humira USPI, 2021). Together with the comparable immunogenicity in healthy volunteers (SB5 vs. US-Humira vs. EU-Humira, in SB5-G11-NHV) and in RA patients (SB5 vs. EU-Humira, in SB5-G31-

[7] Oikonomopoulos A, et al., Current Drug Targets 2013; 14:1421-32.
[8] Tracey D, et al., Pharmacology & Therapeutics 2008; 117:244–79.
[9] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

RA), the immunogenicity of SB5 is not expected to be different from that of US-Humira in pediatric CD and UC patients.
- Safety- The safety profile of US-Humira was comparable in adult vs. pediatric CD and pediatric UC patients (Humira USPI, 2021). Together with the data submitted to the original BLA that demonstrated comparable safety profile of SB5 vs. EU-Humira in adult RA patients, combined with establishment of an adequate scientific bridge to justify the relevance of clinical data using EU-Humira as the comparator, the safety of SB5 is not expected to be different from that of US-Humira in pediatric CD and pediatric UC patients.

Note that while the applicant has submitted acceptable extrapolation justification for pediatric UC patients 5 years of age and older, FDA has determined that US-Humira is eligible for orphan drug exclusivity for pediatric UC, ages 5-17 years. FDA therefore cannot license SB5 for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028.

Regulatory Recommendations: The Division of Gastroenterology concludes that the totality of evidence provided by the Applicant supports licensure of SB5 for the following indication for which the Applicant is seeking licensure for:
- the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

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/s/

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Signed also for the primary clinical reviewer, Dr. Juwaria Waheed, as she is on extended leave.

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