CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761434Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary (CIS)

Date	10/27/2025
From	John Lee, M.D., Primary Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Austin Hu, Medical Officer Rekha Kambhampati, Clinical Team Leader Aliza Thompson, Division Director Anna Park, Regulatory Project Manager Division of Cardiology and Nephrology (DCN)
Application	BLA 761434
Applicant	Otsuka Pharmaceutical Development & Commercialization, Inc.
Drug	Sibeprenlimab (Voyxact™)
Original Application	Yes (New Molecular Entity)
Proposed Indication	Treatment of Primary Immunoglobulin A Nephropathy
Consult Date	05/21/2025
CIS Goal Date	10/28/2025
Review Clock	Priority Review
Action Goal Date	11/28/2025
PDUFA Due Date	11/28/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For this BLA 761434, two BIMO review-based Good Clinical Practice (**GCP**) inspections (clinical investigator and sponsor) were conducted in auditing Study 41720100007-MAIN:

- Seokwoo Park, M.D. (Seongnam, South Korea; Site 110)
- Otsuka Pharmaceutical Development & Commercialization, Inc. (Rockville, MD; sponsor)

Based on the inspection findings, the study appears to have been conducted in observance of GCP principles and in compliance with FDA regulations. The data reported by the clinical investigator (**CI**) and submitted by the sponsor appear to be acceptable in support of this BLA.

II. BACKGROUND

This original BLA 761434 from Otsuka Pharmaceutical Development & Commercialization, Inc. (**Otsuka**) supports the US marketing approval of sibeprenlimab (pending, Voyxact™) for treating primary IgA nephropathy in adults.

Globally, IgA nephropathy is the most common cause of primary glomerulonephritis, a serious disorder with limited treatment options. In the US, the annual incidence of IgA nephropathy is about 13 per million.

- The progression of glomerular disease in adults with IgA nephropathy is variable, with 25% - 40% of patients progressing to a 50% decline in the estimated glomerular filtration rate (**eGFR**) or reaching end-stage kidney disease (**ESKD**) over 10-20 years.
- Proteinuria over 50 gram-percent is predictive of increased ESKD risk (lifetime). Current treatment options are limited by inadequate efficacy/safety profile. Sibeprenlimab inactivates the B cell growth factor involved in the progression of IgA nephropathy.

The clinical safety and efficacy of sibeprenlimab in treating IgA nephropathy was demonstrated in the currently on-going pivotal study (interim analysis), identified at preliminary BLA review for on-site audit at GCP inspection of one CI and the sponsor. No review concerns were identified for these otherwise routine pre-approval inspections.

Protocol 417-201-00007-MAIN: *A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects with Immunoglobulin A Nephropathy*

This randomized, placebo-controlled, double-blinded study was initiated (under IND 158899) in March 2022 and is currently on-going; as of the interim analysis (data cut-off 4 September 2024, over 30 months), 510 subjects had been enrolled at 240 clinical investigator (CI) sites in 31 countries worldwide.

The primary study objective was to compare the change from baseline in urine protein/creatinine weight (gram) ratio (**uPCR**) with sibeprenlimab or placebo (in conjunction with standard of care) after 9 months of subcutaneous (SC) administration.

Subject Selection

- Biopsy-confirmed IgA nephropathy on maximal standard-of-care therapy (angiotensin converting enzyme inhibitor or angiotensin receptor blocker) for at least 3 months

- uPCR ≥ 0.75 or urine protein ≥ 1.0 g/day (24-hour urine, mean of 2 collections up to 2 weeks apart) and eGFR of 30-44 mL/min/1.73 m^2 (main cohort)

Exclusion (after initial selection)

- Secondary IgA nephropathy or any coexisting chronic kidney disease and body mass index < 16 kg/m^2 or serum IgG < 600 mg/dL
- Kidney biopsy with mesangial cellularity, endocapillary proliferation, segmental glomerulosclerosis, or significant tubular atrophy (with or without crescents)
- Recently initiated sodium-glucose transporter inhibitor therapy for IgA nephropathy (within 3 months prior to screening urine collections)

Treatment Groups and Regimen

- Randomization 1/1 to sibeprenlimab/placebo, stratified by uPCR (≤ or > 2.0), eGFR (30-44 or ≥ 45 mL/min/1.73 m^2), sodium-glucose transporter-2 inhibitor (**SGLT2i**) use (yes/no)
- 26 doses (sibeprenlimab or placebo) given once every 4 weeks: Dose 1 on Day 1, Dose 26 in Week 100 (SC into abdomen, thigh, or upper arm), post-treatment follow-up at Week 104 and end-of-trial assessment at Week 112

Study Evaluations

- *Primary endpoint:* Ratio of uPCR at 9 months and baseline (24-hour urine)
- *Key secondary endpoint:* eGFR over two years

III. INSPECTION RESULTS

1. Seokwoo Park, M.D.
82 Gumi-Ro, 173 Beon-Gil
Bundang, Gyeonggido 13620
Seongnam, South Korea

Inspection Dates: August 11 – 14, 2025

Protocol 41720100007-MAIN, Site 110: 11 subjects were screened, 9 were enrolled, and 9 completed the study through September 4, 2024 (data cut-off for interim analysis, study on-going at inspection). Case records were completely reviewed for all subjects.

- Study conduct at this CI site was audited for: adherence to the study protocol, institutional review board (**IRB**) oversight, site monitoring, staff training, study medication disposition and accountability, and CI financial disclosure.
- Case records review covered: informed consent, subject eligibility, subject enrollment and randomization, efficacy endpoint assessment, and adverse event monitoring.
- Data verification (against source data) covered: treatment assignment, major efficacy endpoints, adverse events, protocol deviations, and concomitant medication use.

No significant GCP deficiencies or regulatory violations were observed. The sponsor's monitoring appeared adequate. The study records showed complete CI financial disclosure, adequate reporting of adverse events and protocol deviations, and acceptable drug accountability. The major efficacy and adverse event data were verifiable.

2. Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, Maryland 20850

Inspection Dates: July 14 – 18, 2025

Protocol 41720100007-MAIN: This BIMO review-based sponsor inspection consisted of a general records review, to evaluate compliance with the GCP principles and regulations applicable to the sponsor, including oversight of all CI sites (emphasis on inspected Site 110).

The records reviewed included: product accountability records, monitoring correspondence, vendor contracts, documentation of data management procedures, safety reporting records, staff qualification and training, and clearance records for electronic data systems.

No significant regulatory violations were observed. The findings at this sponsor inspection were consistent with those observed at the CI inspection (Site 110). The sponsor's oversight of the study including CI site monitoring appears to have been adequate to assure subject safety and study data quality.

{See appended electronic signature page}

John Lee, M.D., Primary Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D., Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DCN / Division Director / Aliza Thompson
DCN / Team Leader / Rekha Kambhampati
DCN / Medical Officer / Austin Hu
DCN / Regulatory Project Manager / Anna Park

OSI / Office Director / David Burrow
OSI / Deputy Office Director / Laurie Muldowney
OSI / DCCE / Division Director / Kassa Ayalew
OSI / DCCE / GCPAB / Branch Chief / Jenn Sellers
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Primary Reviewer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / DCCE / GCPAB / Program Analyst / Loreto-Corazon Lim

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JONG HOON LEE
10/27/2025 12:34:06 PM

PHILLIP D KRONSTEIN
10/27/2025 12:42:12 PM

JENN W SELLERS
10/27/2025 12:53:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 10/6/2025 **Date consulted:** 8/21/2025

From: Katherine Kratz, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: CDR Miriam Dinatale, DO, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Cardiology and Nephrology (DCN)

Drug: Voyxact (sibeprenlimab-szsi) solution for injection

BLA: 761434

Applicant: Otsuka Pharmaceutical Development and Commercialization, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: (b) (4) in adults with primary immunoglobulin A nephropathy (IgAN)[1]

Materials Reviewed:

- DPMH consult request dated 8/21/2025. DARRTS Reference ID:5647080
- Applicant's submitted background package and proposed labeling for BLA 761434, Sequence Number (SN) 0001, dated 3/28/2025.

Consult Request: "Please assist with labeling [Pregnancy and Lactation Labeling Rule] (PLLR), provide comments, and attend relevant meetings for this BLA."

[1] BLA 761434, SN 0001, Module 1.14.1, Annotated Draft Labeling, under review by DCN.

I. INTRODUCTION AND BACKGROUND

On March 28, 2025, the Applicant, Otsuka Pharmaceutical Development and Commercialization, Inc., submitted a new Biologics License Application (BLA) pursuant to 351(a) for sibeprenlimab for the treatment of IgAN in adults. Sibeprenlimab is a humanized immunoglobulin G2 (IgG2) monoclonal antibody (mAb) that binds to a B-cell growth factor called A Proliferation Inducing Ligand (APRIL) and prevents it from binding to its receptors. APRIL is implicated in the pathogenesis of IgAN. In February 2024, sibeprenlimab was granted Breakthrough Therapy Designation. Currently, there are no other approved therapies that target APRIL. On August 21, 2025, DCN consulted the DPMH MHT to assist with the Pregnancy and Lactation subsections of labeling. In this review, DPMH will also provide recommendations regarding postmarketing requirements (PMRs) related to pregnancy and lactation.

II. LABELING RECOMMENDATIONS

DPMH recommendations for subsections 8.1 and 8.2 and section 17 of labeling for compliance with the PLLR are below. DPMH's rationale for these labeling recommendations appears within each section of the labeling below. The text in black is proposed by the Applicant. The text in blue is recommended by DPMH. The text in orange is recommended by the Pharmacology/Toxicology (P/T) team. The text with a strikethrough is recommended for deletion. DPMH defers to the BLA action for final labeling.

DPMH does not recommend including subsection 8.3 of labeling because there are no data to convey to prescribers related to fertility, contraception, or pregnancy testing. In animal studies, there were no effects of sibeprenlimab on fertility;[2] sibeprenlimab is not expected to be genotoxic;[3] and sibeprenlimab does not have any drug-drug interactions with hormonal contraceptives. There are no clinical data related to fertility available from clinical trials or published literature.

[2] BLA 763414, SN 0001, Module 2.4, Nonclinical Overview, p. 46: "There were no sibeprenlimab-related effects on fertility parameters in male and female adult cynomolgus monkeys following biweekly IV administration up to 100 mg/kg for 6 months."

[3] BLA 763414, SN 0001, Module 2.4, Nonclinical Overview, p. 11:"The genotoxicity potential of sibeprenlimab was not assessed. As sibeprenlimab is a monoclonal antibody (mAb), it is not expected to interact directly with DNA or chromosomes, and the antibody contains no synthetic components, such as linkers or conjugates, that might cause genotoxicity. Therefore, in accordance with ICH S6(R1), no genotoxicity studies have been performed and none are planned."

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on VOYXACT use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. [redacted (b) (4)] Monoclonal antibodies, such as sibeprenlimab-szsi, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy *(see Clinical Considerations)*. [redacted (b) (4)] In an enhanced prenatal and postnatal development (ePPND) toxicity study, administration of sibeprenlimab-szsi subcutaneously to pregnant monkeys did not result in any adverse effects on embryofetal or postnatal development at exposures approximately 10-times the clinical exposure at the maximum recommended human dose (MRHD) based on area under the curve (AUC) (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Pregnant women exposed to VOYXACT, or their healthcare providers, should report VOYXACT exposure by calling [1-XXX-XXX-XXXX] or visiting [insert webpage].

Reviewer comment:
The first sentence of the Risk Summary is recommended because there are no clinical data from trials or in the published literature to inform the safety of sibeprenlimab use during pregnancy. DPMH searched PubMed and Embase using the search terms "sibeprenlimab" or "IgG2 monoclonal antibodies" and "pregnancy," "pregnancy outcomes," "birth defects," "malformations," "stillbirth," and "spontaneous abortion." No relevant publications were found.

DPMH recommends deletion of the second sentence because it suggests [redacted (b) (4)] *The third sentence is recommended because monoclonal antibodies are actively transported across the placenta with most transfer occurring during the third trimester. This sentence appears in labeling for many other mAbs. A reference is included to the Clinical Considerations (CC) section, where more information about the placental transfer of mAbs is included in labeling.*

The text in orange is recommended by the Pharmacology/Toxicology (P/T) team based on the Good Laboratory Practice (GLP) enhanced pre- and postnatal development (ePPND) study that the Applicant conducted in pregnant cynomolgus monkeys. In the ePPND study, pregnant cynomolgus monkeys received sibeprenlimab 100.65 mg/kg via

subcutaneous (SC) injection biweekly from gestation day 20 ± 2 (GD20) until delivery. There were no adverse outcomes seen in the pregnant adult females, the fetuses or the infants.[4]

This second paragraph about the background risk of birth defects and miscarriage is included based on the PLLR.

The last statement in the Risk Summary is based on DPMH's recommendation to issue a PMR for a descriptive pregnancy safety study (DPSS). According to the PLLR, this sentence appears at the end of the Risk Summary when a DPSS is issued. See the PMR Recommendations section below for more information about the DPSS.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

(b) (4) IgA nephropathy may be ~~is~~ associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, preeclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including ~~stillbirth and~~ low birth weight.

Reviewer comment:
The following text appears in under Clinical Considerations (CC), Disease-Associated Maternal and/or Embryo/Fetal Risk, in the labeling for budesonide and iptacopan, indicated to treat IgAN:[5,6]

> *IgA nephropathy [IgAN in iptacopan labeling] is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, preeclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.*

This CC section does not appear in labeling for sparsentan or atrasentan, which are also indicated to treat IgAN. Given that sparsentan and atrasentan labelings contain a boxed warning for embryofetal toxicity, a CC section was not included. Inclusion of a CC in a labeling for a drug product that is not recommended for use during pregnancy may confuse prescribers into thinking that it could be used during pregnancy.

DPMH has previously reviewed IgAN and pregnancy.[7,8,9] *For this review, DPMH again conducted a literature search in Pubmed, using the search terms "IgAN" and "pregnancy" or "pregnancy outcomes" or "spontaneous abortion" or "stillbirth" or*

[4] BLA 763414, SN 0001, Module 2.4, Nonclinical Overview, p. 42.
[5] United States Prescribing Information (USPI) for Tarpeyo (budesonide)
[6] United States Prescribing Information (USPI) for Fabhalta (iptacopan)
[7] DPMH review of Filspari (sparsentan), NDA 216403, by Katherine Kratz, MD, dated August 24, 2022. DARRTS Reference ID: 5035058
[8] DPMH review of Vanrafia (atrasentan), NDA 219208, by Katherine Kratz, MD, dated December 20, 2024. DARRTS Reference ID: 5500009
[9] DPMH review of Tarpeyo (budesonide) NDA 213976, by Jane Liedtka, MD, dated August 20, 2021. DARRTS Reference ID: 4841589

"pregnancy induced hypertension" or "pre-eclampsia." See Appendix A for detailed information about the publications that were identified. Overall, publications report associations between IgAN and adverse maternal and fetal outcomes as follows:

- *Cesarean Section (CS):*
  - *Liu et al.[10] conducted a retrospective cohort study in patients with IgAN. CS occurred more frequently in patients with IgAN than in the general Chinese population (61% versus 42%, respectively).*
  - *Jarrick et al.[11] conducted a retrospective cohort study using data from the Swedish Medical Birth Register and reported a significant increased risk of CS in patients with IgAN compared to pregnancies in a matched reference population (adjusted odds ratio (aOR) 1.74 (95% Confidence Interval (CI): 1.14-2.65)); however, when compared to their sisters, patients with IgAN were not at an increased risk of CS (aOR 0.74 (95% CI: 0.35-1.59)).*
- *Pregnancy induced hypertension (PIH):*
  - *Piccoli et al.[12] conducted a systematic review of case reports and case series. When pregnancies in patients with IgAN were compared with low-risk pregnancies in patients without IgAN, there was a significant increased risk of PIH (OR 10.39 (95% CI: 5.45-19.80).*
- *Pre-Eclampsia (PEC):*
  - *Piccoli et al.[13] reported a significant increased risk of PEC (OR 11.80 (95% CI: 7.53-18.48).*
  - *O'Shaunghnessy et al.[14] reported that PEC occurred in 33% of patients with IgAN.*
  - *Jarrick et al.[15] reported a significant increased risk of PEC in patients with IgAN compared to pregnancies in a matched reference population (aOR 4.29 (95% CI: 2.42–7.62); however, when compared to their sisters,*

[10] Liu Y, Ma X, Lv J, Shi S, Liu L, Chen Y, Zhang H. Risk factors for pregnancy outcomes in patients with IgA nephropathy: a matched cohort study. Am J Kidney Dis. 2014 Nov;64(5):730-6. doi: 10.1053/j.ajkd.2014.06.021. Epub 2014 Aug 16. PMID: 25134778.

[11] Jarrick S, Lundberg S, Stephansson O, Symreng A, Bottai M, Höijer J, Ludvigsson JF. Pregnancy outcomes in women with immunoglobulin A nephropathy: a nationwide population-based cohort study. J Nephrol. 2021 Oct;34(5):1591-1598. doi: 10.1007/s40620-021-00979-2. Epub 2021 Mar 8. PMID: 33683676; PMCID: PMC8494659.

[12] Piccoli GB, Kooij IA, Attini R, Montersino B, Fassio F, Gerbino M, Biolcati M, Cabiddu G, Versino E, Todros T. A Systematic Review on Materno-Foetal Outcomes in Pregnant Women with IgA Nephropathy: A Case of "Late-Maternal" Preeclampsia? J Clin Med. 2018 Aug 11;7(8):212. doi: 10.3390/jcm7080212. PMID: 30103519; PMCID: PMC6111833.

[13] See ref 12 (Piccoli).

[14] O'Shaughnessy MM et al. Pregnancy Outcomes in Patients with Glomerular Disease Attending a Single Academic Center in North Carolina. Am J Nephrol 2017;45:442–451.

[15] See ref 11 (Jarrick).

patients with IgAN had a nonsignificant increased risk of PEC (aOR 2.46 (0.49-12.43).

- *Liu et al.[16] (2016) reported a higher rate of PEC in patients with IgAN than the rate found in the general Chinese population (7.3% versus 1.9%, respectively).*

- *Stillbirth:*
  - *Chen et al. [17] published a case report about a 36-year-old woman with one year of untreated mild high blood pressure who was admitted with renal insufficiency and stillbirth at 28 weeks gestational age. She was subsequently diagnosed with IgAN.*
- *Preterm Birth (PTB):*
  - *Liu et al.[18] reported that PTB occurred more frequently in patients with IgAN than in the general Chinese population (10% versus 7%, respectively).*
  - *Piccoli et al.[19] reported a siignificant increased risk of PTB in patients with IgAN compared with low-risk pregnancies in patients without IgAN (OR 3.37 (95% CI: 1.91-5.95).*
  - *O'Shaughnessy et al.[20] reported that PTB occurred in 48% of patients with IgAN.*
  - *Jarrick et al.[21] reported a significant increased risk of PTB in patients with IgAN in patients compared to pregnancies in a matched reference population (aOR 2.69 (95% CI: 1.52-4.77); however, when compared to their sisters, patients with IgAN had a nonsignificant increased risk of PTB (aOR 1.37 (95% CI: 0.24-7.73).*
- *Low Birth Weight (LBW):*
  - *Liu et al.[22] reported that LBW occurred more frequently in patients with IgAN than in the general Chinese population (14% versus 6%, respectively).*
  - *Piccoli et al.[23] reported a significant increased risk of LBW in patients with IgAN compared with low-risk pregnancies in patients without IgAN (OR 2.36 (95% CI: 1.52-3.66).*
- *Small for Gestational Age (SGA):*
  - *Jarrick et al.[24] reported a significant increased risk of SGA in patients with IgAN in patients compared to pregnancies in a matched reference population (aOR 1.84 (95% CI: 1.17-2.88); however, when compared to*

[16] Liu Y, Ma X, Zheng J, Liu X, Yan T. A Systematic Review and Meta-Analysis of Kidney and Pregnancy Outcomes in IgA Nephropathy. Am J Nephrol. 2016;44(3):187-93. doi: 10.1159/000446354. Epub 2016 Aug 27. PMID: 27578454.
[17] Chen H et al. Pregnancy-induced complications in IgA nephropathy A case report. Medicine. 2018; 97:15 (e0470).
[18] See ref 10 (Liu, 2014).
[19] See ref 12 (Piccoli).
[20] See ref 14 (O'Shauhgnessy).
[21] See ref 11 (Jarrick).
[22] See ref 10 (Liu, 2014).
[23] See ref 12 (Piccoli).
[24] See ref 11 (Jarrick).

their sisters, patients with IgAN had a nonsignificant increased risk of SGA (aOR 1.73 (95% CI: 0.84-3.58).

Available data do not suggest an impact of pregnancy on IgAN disease progression.[25] Available data suggest an association between IgAN and CS, PIH, PEC and PTB; however, there are limitations to the data. In the case of CS, the data are limited to the Chinese population (Liu et al.), and the association was nonsignificant when sisters were compared (Jarrick et al.), which suggests possible residual confounding in the comparison with the reference population. In the case of PIH and PEC, the findings by Piccoli et al. involve large confidence intervals due to small sample size, making the associations less certain. O'Shaughnessy et al. observed a higher rate of PEC (i.e., 33%) in a U.S. population than was reported in the U.S. during the years evaluated in the study (i.e., 1996-2015); the rate of PEC in the U.S. was reported at <10% between 1980-2010.[26] However, the O'Shaughnessy et al. data are limited by a small sample size of patients with IgAN (n=17). Although the studies demonstrating an association between IgAN and PTB had the limitations explained above and in Appendix A, multiple studies suggested an association with PTB. The association between IgAN and stillbirth is not strong as it appears to be based on a single case report. Data suggest an association between IgAN and LBW across two different populations (i.e., Chinese and Italian). The association between IgAN and SGA is less clear, as this finding was reported in one study limited by a small sample size and residual confounding. Overall, DPMH recommends revising the CC to state that available data suggest that IgAN may be associated with adverse maternal and fetal/neonatal outcomes as shown in the edited text above.

DPMH discussed the suggested revisions to the CC section with the DCN team on 10/6/25. DCN prefers to use the text for CC that appears in the labeling for budesonide and iptacopan. DPMH defers to DCN for the final labeling.

Fetal/Neonatal Adverse Reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Therefore, it is expected that VOYXACT may be present in infants exposed *in utero*. The potential clinical impact of VOYXACT exposure in infants exposed *in utero* should be considered.

Reviewer comment:

DPMH recommends including a CC section for fetal/neonatal adverse reactions because sibeprenlimab is an mAb. Given that sibeprenlimab has an inhibitory action on immune response, the potential for immunosuppression in infants exposed to monoclonal antibodies in utero should be considered and conveyed to prescribers. Labelings for other humanized IgG mAbs[27] contain this CC section.

[25] See ref 10 and 16 (Liu 2014 and Liu 2016).

[26] Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013 Nov 7;347:f6564. doi: 10.1136/bmj.f6564. PMID: 24201165; PMCID: PMC3898425.

[27] USPIs for Dupixent (dupilumab); Tremfya (guselkumab); Nemluvio (nemolizumab-ilto); Stelara (ustekinumab)

Data

Animal Data

In an ePPND toxicity study, subcutaneous administration of sibeprenlimab-szsi once every two weeks to pregnant cynomolgus monkeys from gestation Day 20 through delivery (includes the period of organogenesis) did not result in any adverse effect on embryofetal or postnatal development at the single tested dose of 101 mg/kg, which provided an approximately 10-fold exposure margin to the clinical exposure at the MRHD based on AUC.

(b) (4)

Reviewer comment:

The P/T team recommends including the text in orange under the Animal Data section and deleting the text with the strikethrough.

8.2 Lactation

Risk Summary

(b) (4) There are no data on the presence of sibeprenlimab-szsi in human milk, the effects of sibeprenlimab-szsi on the breastfed infant, or the effects of sibeprenlimab-szsi on milk production. (b) (4) (b) (4) Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure on sibeprenlimab-szsi in the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VOYXACT and any potential adverse effects on the breastfed child from VOYXACT or from the underlying maternal condition.

Reviewer comment:

The Applicant did not provide any nonclinical information pertaining to lactation. In terms of clinical data, the Applicant stated, " (b) (4) *the presence of sibeprenlimab in human milk, the effects of sibeprenlimab on the breastfed infant, or the effects of sibeprenlimab on milk production.* (b) (4) (b) (4) *[28]" The Applicant did not provide a literature review related to IgG2 monoclonal antibodies that target APRIL and lactation. DPMH searched for published human studies in PubMed and Embase, using the search terms: "IgG2 monoclonal antibodies" and "lactation" and "breastfeeding." No relevant publications were found.*

[28] BLA (b) (4) SN 0001, Module 2.7.4, Summary of Clinical Safety, p. 118.

Since there are no nonclinical or clinical lactation data on the presence of sibeprenlimab in human milk, its effects on the brestfed infant or its effects on milk production, this information needs to be included in the first sentence of the Risk Summary according to the PLLR. DPMH recommends including information about what is known about endogenous IgG and mAbs being present in human milk in the second sentence of the Risk Summary. Gastrointestinal (GI) exposure is likely to degrade mAbs and may result in decreased systemic exposure in breastfed infants; however, the exact effects of GI exposure in the infant are unknown. This information should be conveyed to prescribers in this Risk Summary. Finally, according to the PLLR, for drugs absorbed systemically for which no risks have been identified that would preclude breastfeeding, a risk and benefit statement must appear at the end of the Risk Summary. Therefore, DPMH agrees with the Applicant's proposed risk and benefit statement that appears as the last sentence in the Risk Summary of subsection 8.2.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients who are exposed to VOYXACT during pregnancy to contact Otsuka Pharmaceutical Development and Commercialization, Inc. at [1-XXX-XXX-XXXX] or [insert webpage].

Reviewer comment:

This sentence is recommended in section 17 when a PMR for a DPSS is issued. See the PMR Recommendations section below for more information.

III. PMR RECOMMENDATIONS

Pregnancy

DPMH recommends issuing a PMR for a DPSS for the following reasons:

1) The animal data show transfer of sibeprenlimab to the fetus. Sibeprenlimab concentrations were quantifiable in all dams and infants on postpartum day 28, with concentration ratios approximately 3.7-fold higher in infants compared to their mothers. Because sibeprenlimab is systemically absorbed, it is likely that the drug will transfer to the human fetus.
2) There is a potential risk to a fetus due to exposure to a drug that is not indicated for fetal treatment.
3) There are no clinical data from trials or in the published literature to inform the safety of sibeprenlimab use during pregnancy.
4) The use of sibeprenlimab is anticipated in females of reproductive potential.

A DPSS is recommended over a pregnancy exposure registry study when a drug is expected to be used in a small population. Given that IgAN is a rare disease, the available study population is likely to be small. With a DPSS, there will be a systematic approach to collect pregnancy outcome data that may be used to evaluate the safety of the drug when used during pregnancy.

Lactation

DPMH recommends issuing a PMR for a Clinical Lactation Study for the following reasons:

1) Endogenous maternal IgG and monoclonal antibodies are transferred into human milk, so it is likely that sibeprenlimab will be present in human milk.
2) There is anticipated use of sibeprenlimab in females of reproductive potential including lactating women.

DPMH recommends issuing a PMR for a clinical lactation study (milk-only or mother-infant pair study) to assess the degree to which sibeprenlimab is transferred into human milk and to assess the potential effects on the breastfed infant.

APPENDIX A – REVEIWER-GENERATED TABLE OF PUBLICATIONS RELATED TO IgAN AND PREGNANCY

Author Publication Date Study Design Country	Study Population	Results	Author's conclusions	Strengths/Limitations (S/L)
Liu Y et al.[29] 2014 Retrospective cohort study China	69 pregnancies in IgAN patients 62 matched nonpregnant patients with IgAN	C-section: 42/69 (61%) Vaginal delivery: 17/69 (25%) Pre-eclampsia (PEC): 6/69 (9%) Intrauterine demise: 2/69 (3%) Spontaneous abortion: 1/69 (2%) Malformation: 3/69 (4%) Pre-term delivery: 7/59 (10%) Low birth weight (<2500 g): 8/59 (14%) There was no significant difference in the median rate of eGFR decline in the 2 groups (22.5 vs 22.4 mL/min/1.73 m2 per year; p=0.7).	Frequencies of caesarean delivery (61% vs 42%), preterm delivery (10% vs 7%), and low birth weight (14% vs 6%) in patients with IgAN in this study were all higher than those in the general Chinese population. Proteinuria during pregnancy was a borderline statistically significant risk factor for adverse pregnancy outcomes.	S: Focused on pregnancy and fetal outcomes, which other studies had not at the time of publication L: Small sample size
Piccoli et al.[30] 2018 Systematic Review Italy	729 pregnancies in IgAN patients 1,418 low-risk pregnancies without IgAN from the TOCOS (Torino Cagliari Observational Study) cohort	The incidence of adverse pregnancy-related outcomes was increased compared to low-risk controls for PEC Odds Ratio (OR) 11.80; CI 7.53–18.48 Pregnancy Induced Hypertension OR 10.39; CI 5.45–19.80 Preterm birth OR 3.37; CI 1.91–5.95 Low birth weight OR 2.36; CI 1.52–3.66	Pregnancy in women with IgAN was not associated with a higher risk of progression of kidney disease, possibly due to the overall preserved kidney function at baseline. The incidence of PE and PIH was increased in women with IgAN compared to low-risk controls.	S: Large review L: Heterogeneous studies Comparison was made to a low-risk population from one Italian study
Chen et al.[31] 2018 Case Report China	1 pregnant patient with IgAN	36-year-old woman with one year of untreated mild high blood pressure who was admitted with renal insufficiency and stillbirth at 28 weeks gestational	Not applicable	S: Novel report L: Single case

[29] See ref 10 (Liu 2014).
[30] See ref 12 (Piccoli).
[31] See ref 17 (Chen).

		age. She was subsequently diagnosed with IgAN.		
O'Shaughnessy et al.[32] 2017 Retrospective cohort study U.S.	48 pregnancies in biopsy-proven glomerular disease patients without end-stage kidney disease from a single center 17 patients had IgAN	Adverse pregnancy outcomes included perinatal death (13%) prematurity (48%) preeclampsia (33%)	Adverse pregnancy outcomes are frequently observed in women with glomerular disease.	S: Provided data on observed pregnancy outcomes L: Small sample size of patients with IgAN; Single center observations; no comparison group
Liu Y et al.[33] Systematic Review 2016 China	376 pregnancies in IgAN patients 241 non-pregnant IgAN patients	Pregnancy in patients with IgAN did not increase the risk of kidney outcomes (OR 0.97, 95% CI 0.55–1.70; p = 0.90) with no evidence of heterogeneity ((I 2 = 0.0%, p = 0.79) across studies. The rates of low birth weight (9.5%) and preeclampsia (7.3%) in patients with IgAN were higher than the rates found among the general Chinese population (6 and 1.9%, respectively).	Studies found no significant difference in the change of eGFR at the end of follow-up between the pregnant and non-pregnant groups. IgA nephropathy, even when kidney function is relatively well preserved, may increase the risk of unfavorable pregnancy outcomes.	S: Accounted for heterogeneity of studies; assessed disease activity during pregnancy L: Small sample size
Jarrick et al.[34] 2021 Retrospective cohort study based on Swedish Medical Birth Register Sweden	327 pregnancies in IgAN patients 1060 pregnancies in matched reference population 167 pregnancies in sisters of patients with IgAN (for the comparison with the sisters,	Compared to the reference population, IgAN was associated with an increased risk of preterm birth (13.1% vs 5.6%; aOR = 2.69; 95% confidence interval [CI] = 1.52–4.77); preeclampsia (13.8% vs 4.2%; aOR = 4.29; 95% CI = 2.42–7.62) SGA birth (16.0% vs 11.1%; aOR = 1.84; 95% CI = 1.17–2.88); cesarean section (23.9% vs 16.2%; aOR = 1.74, 95% CI = 1.14–2.65)		S: Large sample size Reference group Biopsy-confirmed IgAN L: Retrospective study design; IgAN not stratified by disease activity because GFR and proteinuria were not included in the database

[32] See ref 14 (O'Shauhgnessy).
[33] See ref 16 (Liu 2016).
[34] See ref 11 (Jarrick).

	125 pregnancies in IgAN patients were used)	Compared to sisters, IgAN was not associated with an increased risk of any adverse outcomes. adjusted for calendar year of conception, maternal age, BMI, educational level, smoking status, pre-pregnancy diabetes type 1 or 2 (except in the analysis of gestational diabetes), other autoimmune diseases (see publication), and multiple gestation pregnancies		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHERINE G KRATZ
10/06/2025 01:42:55 PM

MIRIAM C DINATALE
10/06/2025 02:01:41 PM

LEYLA SAHIN on behalf of LYNNE P YAO
10/06/2025 02:05:10 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 24, 2025

To: Anna Park, Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for VOYXACT® (sibeprenlimab-szsi) injection, for subcutaneous use

BLA: 761434

Background: In response to DCN's consult request dated April 3, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for VOYXACT® (sibeprenlimab-szsi) injection, for subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 16, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI and IFU, and comments were sent under separate cover on September 23, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on September 24, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240)-402-8686 or Koung.lee@fda.hhs.gov.

12 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOUNG U LEE
09/24/2025 09:09:14 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 23, 2025
To:	Anna Park Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung U. Lee, RPh, MSHS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	VOYXACT (sibeprenlimab-szsi)
Dosage Form and Route:	injection, for subcutaneous
Application Type/Number:	BLA 761434
Applicant:	Otsuka Pharmaceutical Company, Ltd.

1 INTRODUCTION

On March 28, 2025, Otsuka Pharmaceutical Company, Ltd. submitted for the Agency's review an original Biologics License Application (BLA) 761434 for VOYXACT (sibeprenlimab-szsi) injection, for subcutaneous use. With this submission, the Applicant seeks approval for the proposed indication for the treatment of Immunoglobulin A Nephropathy (IgAN) in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on April 3, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for VOYXACT (sibeprenlimab-szsi) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on August 27, 2025.

2 MATERIAL REVIEWED

- Draft VOYXACT (sibeprenlimab-szsi) injection PPI received on March 28, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 16, 2025.
- Draft VOYXACT (sibeprenlimab-szsi) injection IFU received on March 28, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 16, 2025.
- Draft VOYXACT (sibeprenlimab-szsi) injection Prescribing Information (PI) received on March 28, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 16, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

20 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN W REDWOOD
09/23/2025 10:31:14 AM

KOUNG U LEE
09/23/2025 11:49:37 AM

BARBARA A FULLER
09/23/2025 11:51:47 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 17, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	BLA 761434
Product Name, Dosage Form, and Strength:	Voyxact (sibeprenlimab-szsi) injection, 400 mg/2 mL
Applicant Name:	Otsuka Pharmaceutical Development & Commercialization (Otsuka)
FDA Received Date:	September 15, 2025
TTT ID #:	2025-14015-1
DMEPA 2 Safety Evaluator:	Ila Srivastava, PharmD
DMEPA 2 Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Otsuka Pharmaceutical Development & Commercialization (Otsuka) submitted revised container label and carton labeling received on September 15, 2025 for Voyxact. The Division of Cardiology and Nephrology (DCN) requested that we review the revised container label and carton labeling for Voyxact (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

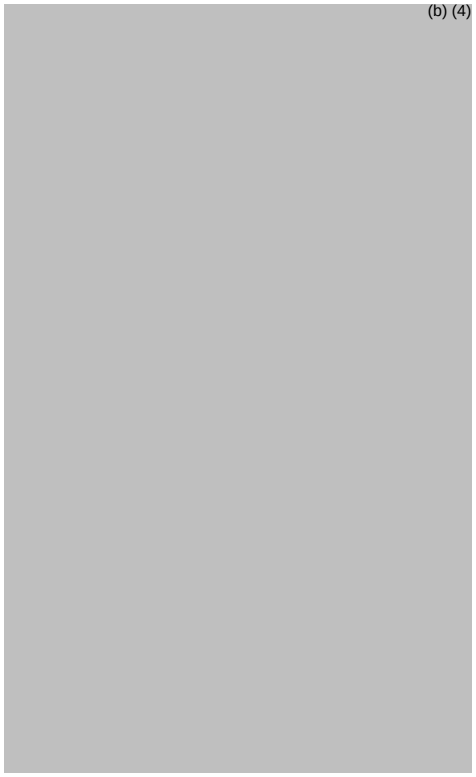
2 CONCLUSION

Otsuka Pharmaceutical Development & Commercialization (Otsuka) implemented all of our recommendations and we have no additional recommendations at this time.

[a] Srivastava, I. Label and Labeling Review for Voyxact (BLA 761434). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 AUG 27. TTT ID: 2025-14015; 2025-13928.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON SEPTEMBER 15, 2025

Container Label:



Carton Labeling:

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ILA SRIVASTAVA
09/17/2025 08:29:25 AM

MILLIE B SHAH
09/17/2025 09:47:07 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 27, 2025
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	BLA 761434
Product Name, Dosage Form, and Strength:	Voyxact[a] (sibeprenlimab-szsi[b]) injection, 400 mg/2 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Device Constituent:	Prefilled Syringe (PFS)
Applicant Name:	Otsuka Pharmaceutical Development & Commercialization (Otsuka)
FDA Received Date:	March 28, 2025
TTT ID #:	2025-14015; 2025-13928
DMEPA 2 Safety Evaluator:	Ila Srivastava, PharmD
DMEPA 2 Team Leader:	Millie Shah, PharmD, BCPS
DMEPA 2 Associate Director for Human Factors	Lolita Sterrett, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling:	Hina Mehta, PharmD

[a] The proprietary name Voyxact was found to be conditionally acceptable under BLA 761434 on 06/06/25. PNR_2025-1044726365.

[b] The proposed nonproprietary name “sibeprenlimab-szsi” was found conditionally acceptable on July 25, 2025.

1 REASON FOR REVIEW

As part of the approval process for Voyxact (sibeprenlimab-szsi) injection, the Division of Cardiology and Nephrology (DCN) requested that we review the proposed Voyxact Prescribing Information (PI), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors. In addition, we re-evaluated the human factors (HF) information to support the licensure of a 351(a) BLA for sibeprenlimab-szsi.

1.1 REGULATORY HISTORY

On May 8, 2023, Otsuka submitted a use-related risk analysis (URRA) and additional HF information under IND 158899 for the sibeprenlimab-szsi 400 mg/2 mL prefilled syringe (PFS) to determine whether additional human factors data are needed to support the future licensure of a 351(a) BLA for sibeprenlimab-szsi. In our October 5, 2023 review, we determined that Otsuka did not need to submit additional HF data to support the PFS for sibeprenlimab-szsi.[c]

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Human Factors (HF) Related Supporting Documents	C

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

3.1 INJECTION DELIVERY DEVICE DESIGN CONSIDERATIONS

In addition to the data and analyses reviewed previously, we reviewed the design characteristics of the proposed injection delivery device to determine suitability for the intended use and intended users. Numerous device design options exist on the marketplace to deliver subcutaneous injections, including syringe and needle (drug withdrawn from vial), prefilled syringes, autoinjectors, pen injectors, infusion pumps and needle-free injectors. Otsuka is proposing a single dose disposable prefilled syringe (i.e., (b) (4) syringe with (b) (4) Needle Safety Device platform) with non-novel design features common across the broad landscape of existing PFS platforms available in the marketplace, including automatic safety features. The steps required to deliver a dose include remove the cap, position the PFS at an appropriate injection site, and pushing the plunger until it stops, which indicates the injection is complete. The PFS has an attached needle with a passive needle safety device (NSD). Once the thumb is removed from the plunger the NSD automatically activates covering the needle, thus, there are no steps to obtain, select,

[c] Topper, C. Use-Related Risk Analysis and Comparative Analyses Review for sibeprenlimab (IND 158899). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US): 2023 OCT 5. TTT #: 2023-4748.

attach/detach, or recap the needle. Additionally, the PFS is pre-assembled, and one PFS contains the full proposed dose for the intended use, thus, there are no steps to calculate a dose, or to manipulate the device (e.g., assemble, expel contents to achieve the prescribed dose). Furthermore, the PFS is disposable, thus, there are no steps to re-use, store or clean/maintain the device.

We find the proposed PFS design is suitable for the proposed intended use (chronic, non-urgent/non-emergent delivery of a fixed monthly dose) and incorporates design controls that mitigate certain use-related risks common to other subcutaneous injection delivery devices. However, we anticipate the PFS will be vulnerable to known use problems that exist with similarly designed PFS devices, for example, local or systemic infection due to the needle coming in contact with a nonsterile surface after the needle cap is removed or potential needlestick injury in an attempt to recap the needle by the user, systemic or chronic infection in another person from a needle stick due to the needle shield not being activated and the syringe not being discarded immediately after injection. We further considered the PFS design, critical tasks, and residual risks in the context of the intended users and intended uses and provide our discussion below in section 3.2.

3.2 INTENDED USER AND INTENDED USE CONSIDERATIONS

The proposed PFS is intended for the chronic, non-urgent/non-emergency treatment of adult IgAN patients, administered by subcutaneous injection every 4 weeks at home (by patients or caregivers) or in clinical settings (by HCPs). According to the submission, IgAN disease characteristics include hematuria, proteinuria, and progressive decline in kidney function. We assessed the disease characteristics and do not anticipate adult patients with IgAN to have distinct manual dexterity, vision, or cognitive impairments or user needs that may negatively impact the ability to use the PFS as intended. Specifically, we do not anticipate adult IgAN patients to exhibit disease-specific symptoms that would impact their cognitive ability to comprehend the critical tasks or their physical ability to perform them under the intended use conditions.

3.3 HUMAN FACTORS DATA

We also reviewed Otsuka's Formative Usability Study Report resubmitted with this submission. While iterative formative studies typically lack sufficient methodology to satisfy HF data needs to support a BLA, in this case, we find the study was sufficiently designed to evaluate the safe and effective simulated use of the proposed user interface in 18 representative untrained adult lay users to inform our evaluation of the proposed product[d].

[d] Iterative formative HF studies generally do not employ methodology to produce sufficient data representative of real-life use. Additionally, formative studies rarely evaluate a sufficient quantity of representative users and generally do not provide robust and/or reviewable analyses of the study results. In this case, we find the methodology employed was acceptable, the results report is sufficiently comprehensive to review, and, based on our determination that adult IgAN patients do not have distinct or unique user needs that distinguish them from

The use errors, close calls and use difficulties that occurred in the formative study are in alignment with the known use problems for similarly designed PFS delivery devices. The report provides sufficient root cause information and subjective feedback to inform our comprehensive review. We confirmed that the use errors, close calls and use difficulties were mitigated to an acceptable level. We determined that the mitigations implemented as a result of the human factors data findings do not require additional validation. We provide additional best practice labeling recommendations to promote safe use of this product from a medication error perspective in Section 5 and Section 6 below.

3.4 COMPARATIVE ANALYSES

We acknowledge Otsuka submitted a comparative analyses (CA) using US-licensed Dupixent (dupilumab) (300 mg/2 mL) prefilled syringe with needle shield (BLA 761055) as a comparator to the proposed sibeprenlimab-szsi prefilled syringe. However, because Otsuka did not submit a right of reference to US-licensed Dupixent HF validation data with its BLA, the CA was not used to inform our review.

4 CONCLUSION

The proposed Voyxact Prescribing Information (PI), Instructions for Use (IFU), container label, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Cardiology and Nephrology (DCN) in Section 5 and for Otsuka Pharmaceutical Development & Commercialization in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

Table 2. Identified Issues and Recommendations for the Division of Cardiology and Nephrology (DCN)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information and Full Prescribing Information – Section 2 Dosage and Administration			
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16 includes the following statement, [redacted] (b) (4)	As currently presented, the statement is incomplete and does not align with the storage instructions in the IFU.	Update the statement so it includes the following: “Discard the VOYXACT prefilled syringe if it has not been used right away after warming to room temperature”.

other lay users, we found the participant user group sufficiently representative of the intended users. Thus, in this case, the HF data provided is sufficient to evaluate the proposed product.

Table 2. Identified Issues and Recommendations for the Division of Cardiology and Nephrology (DCN)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) [redacted]		
Patient Information			
1.	As currently presented, the patient information leaflet is attached to the end of the Prescribing Information (PI).	The PI is intended for healthcare professionals. Therefore, we are concerned the intended product users (e.g., lay patients and caregivers) may not locate the patient information leaflet at the end of the PI.	Include the patient information leaflet as a separate document from the PI.
Instructions for Use (IFU)			
1.	The image showing the insertion of the prefilled syringe at a 45-degree angle in Figure H of the IFU is unclear and may be missed.	As currently presented, Figure H of the IFU can be improved to increase clarity and decrease confusion.	Relocate the 45-degree graphic in Figure H so it is in between the hand and the skin.

6 RECOMMENDATIONS FOR OTSUKA PHARMACEUTICAL DEVELOPMENT & COMMERCIALIZATION

Table 3. Identified Issues and Recommendations for Otsuka Pharmaceutical Development & Commercialization (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			

Table 3. Identified Issues and Recommendations for Otsuka Pharmaceutical Development & Commercialization (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The product strength is not expressed as a total quantity per total volume followed by the concentration per mL.	The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling.	Express the product strength as total quantity per total volume followed by the concentration per mL in accordance with USP General Chapter <7> [(i.e., 400 mg/2 mL (200 mg/mL)].
2.	The route of administration statement, "For Subcutaneous Use" does not include the word "only".	Ensure consistency with the carton labeling, Prescribing Information, and Instructions for Use.	Update the statement so it reads, "For Subcutaneous Use Only".
Carton Labeling			
1.	The terminology within the statement of dosage (i.e., (b) (4)) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, "Recommended Dosage: see Prescribing Information".
2.	The carton includes the statement (b) (4)	Given the entire contents of the prefilled syringe will be administered and no partial doses are possible, we find this statement can be revised for clarity.	Revise the statement to, "Discard after use" and consider relocating the statement to follow the statement, "Contains one single-dose prefilled syringe" on the principal display panel.
3.	The statement , (b) (4) is present on the principal display panel (PDP).	The (b) (4) statement is not required (b) (4) and may contribute to clutter on the PDP.	We recommend you remove the statement from the carton.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Voyxact received on March 28, 2025 from Otsuka Pharmaceutical Development & Commercialization.

Table 4. Relevant Product Information for Voyxact	
Initial Approval Date	N/A
Nonproprietary Name	sibeprenlimab
Indication	(b) (4) in adults with primary immunoglobulin A nephropathy (IgAN)
Dosage Form	injection
Strength	400 mg/2 mL
Route of Administration	Subcutaneous
Dose and Frequency	400 mg once every 4 weeks
How Supplied	Carton with a single-dose prefilled syringe with a 27 gauge, ½ inch needle and (b) (4) needle safety device
Storage	• Refrigerator at 36°F to 46°F (2°C to 8°C) • Keep the prefilled syringe in its original box to protect it from light. • Do not freeze (b) (4) (b) (4) • (b) (4)
Container Closure/Device Constituent	(b) (4) Device Platform: (b) (4) syringe with (b) (4) Needle Safety Device

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error experiences with similar products, we reviewed the following Voyxact labels and labeling submitted by Otsuka Pharmaceutical Development & Commercialization received on March 28, 2025.

- Prescribing Information available from \\CDSESUB1\EVSPROD\bla761434\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean.pdf
- Instructions for Use available from \\CDSESUB1\EVSPROD\bla761434\0001\m1\us\114-labeling\draft\labeling\voyxact-pfs-ifu-clean-10mar2025.pdf
- Container label(s) available from: \\CDSESUB1\EVSPROD\bla761434\0001\m1\us\114-labeling\draft\carton-and-container\voyxact-5000020aa-us-lbl-art3.pdf
- Carton labeling available from: \\CDSESUB1\EVSPROD\bla761434\0001\m1\us\114-labeling\draft\carton-and-container\draft-carton-container-labels.pdf

B.2 Container Label and Carton Labeling Images

Container Label:

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ILA SRIVASTAVA
08/27/2025 07:32:33 AM

MILLIE B SHAH
08/27/2025 07:36:04 AM

LOLITA G STERRETT
08/27/2025 12:44:59 PM

HINA S MEHTA
08/27/2025 03:44:34 PM