IMCIVREE®
(setmelanotide) injection

What to expect when starting a patient on IMCIVREE

The **FIRST** and **ONLY** treatment to target impairment in the MC4R pathway, a root cause of hyperphagia and obesity in POMC, PCSK1, or LEPR deficiency[1,2]

LEPR=leptin receptor; MC4R=melanocortin-4 receptor; PCSK1=proprotein convertase subtilisin/kexin type 1; POMC=pro-opiomelanocortin.

Indication

IMCIVREE is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with monogenic or syndromic obesity due to pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

Limitations of Use

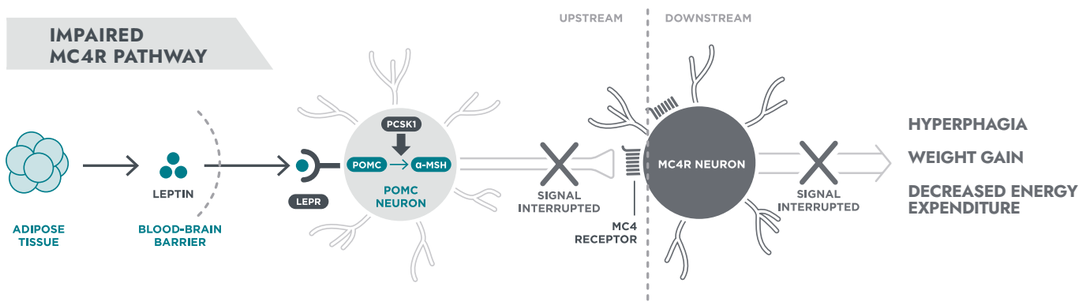
IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:

- Obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC, PCSK1*, or *LEPR* variants classified as benign or likely benign
- Other types of obesity not related to POMC, PCSK1, or LEPR deficiency, or other FDA-approved indications for IMCIVREE, including obesity associated with other genetic syndromes and general (polygenic) obesity

Please see Important Safety Information on page 15 and full Prescribing Information.

Impairment in the MC4R pathway is a root cause of obesity and hyperphagia in patients with obesity due to POMC, PCSK1, or LEPR deficiency[2-5]

The MC4R pathway is a key signaling pathway that regulates hunger, satiety, and energy expenditure[2-5]



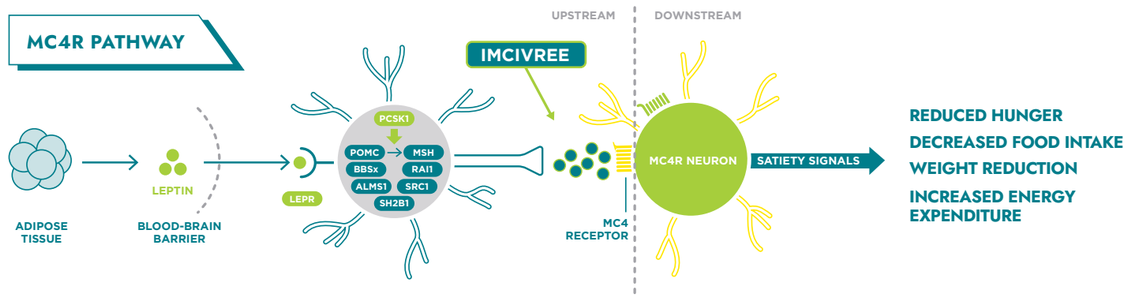
Genetic variants in this pathway can lead to insatiable hunger and early-onset severe obesity[2]

MSH=melanocyte-stimulating hormone.

In patients with obesity due to POMC, PCSK1, or LEPR deficiency

IMCIVREE is the first and only treatment to target impairment in the MC4R pathway, a root cause of obesity and hyperphagia[1,2]

IMCIVREE may restore function in the signaling cascade responsible for regulating hunger, caloric intake, energy expenditure, and, consequently, body weight



IMCIVREE, an MC4R agonist, is designed to re-establish MC4R pathway activity

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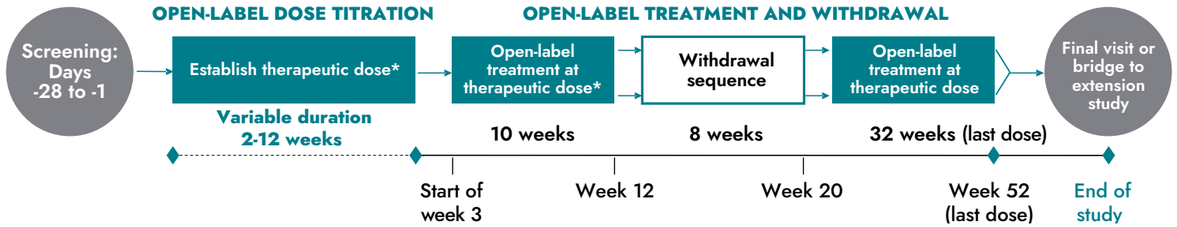
Important Safety Information

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

IMCIVREE was studied in 2 identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period[1,6]



Primary endpoint:

- Proportion of participants who achieved ≥10% weight loss at 1 year of treatment (POMC or PCSK1, N=10; LEPR, N=11)

*Only participants who lost ≥5 kg weight (or ≥5% of body weight if baseline weight was <100 kg) in the first open-label active treatment phase entered an 8-week, double-blind withdrawal period.

Baseline characteristics in the IMCIVREE trials[1,6]

	Study 1 POMC or PCSK1 (N=10)	Study 2 LEPR (N=11)
Male, n (%)	5 (50)	3 (27)
Age (mean), years	18.4	23.7
Range	11.0-30.0	13.0-37.0
Race, n (%)		
White	7 (70)	10 (91)
Other	3 (30)	1 (9)
Weight (mean), kg	118.7	133.3
SD	37.5	26.0
Range, kg	55.9-186.7	89.4-170.4
BMI (median), kg/m^2	40.0	46.6
Range, kg/m^2	26.6-53.3	35.8-64.6

SD=standard deviation.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Depression and Suicidal Ideation: Depression and suicidal ideation have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Skin Pigmentation and Darkening of Pre-existing Nevi: Generalized increased skin pigmentation and darkening of pre-existing nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmentary lesions.

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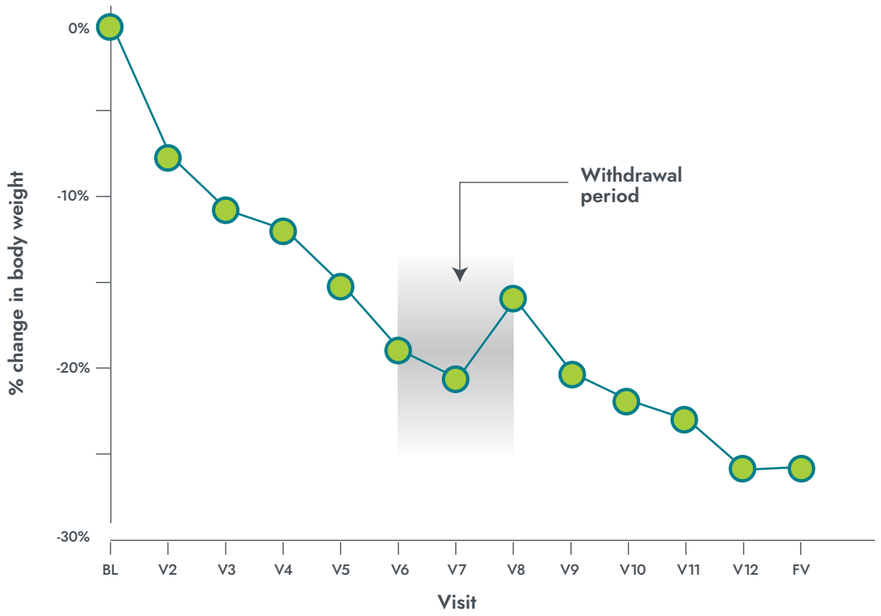
In patients with obesity due to POMC, PCSK1, or LEPR deficiency

IMCIVREE delivered significant, clinically meaningful weight loss over 1 year[1]

Mean % change in body weight over 1 year

POMC or PCSK1 deficiency (n=9)*



-23.1% mean percentage change in weight at 1 year

(95% CI: -31.9%, -14.4%); *P*=0.0003; N=10

80% of patients achieved ≥10% weight loss at 1 year (primary endpoint)

(95% CI: 44.4%, 97.5%); *P*<0.0001; N=10

*Participants who achieved weight loss threshold (≥5 kg or 5% if baseline body weight was <100 kg) during the 10-week open-label period.
†The withdrawal period lasted 8 weeks, which included 4 weeks of IMCIVREE followed by 4 weeks of placebo.
BL=baseline; CI=confidence interval; FV=final visit; V=visit.

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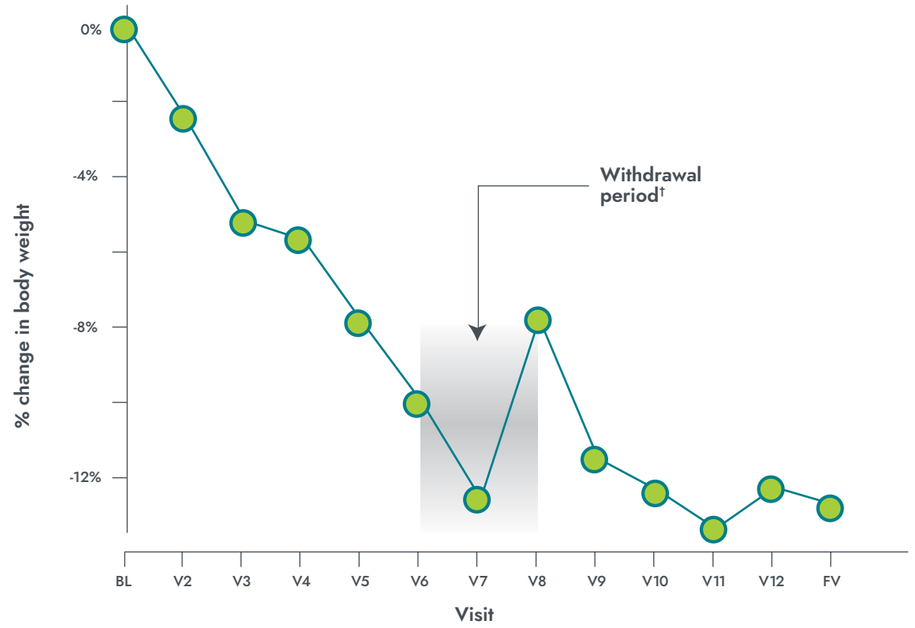
Mean % change in body weight over 1 year

LEPR deficiency (n=7)*



-9.7% mean percentage change in weight at 1 year

(95% CI: -16%, -3.3%); *P*=0.0074; N=11

45.5% of patients achieved ≥10% weight loss at 1 year (primary endpoint)

(95% CI: 16.8%, 76.6%); *P*=0.0002; N=11

In both studies, weight increased during the withdrawal period, then decreased once treatment was reinitiated

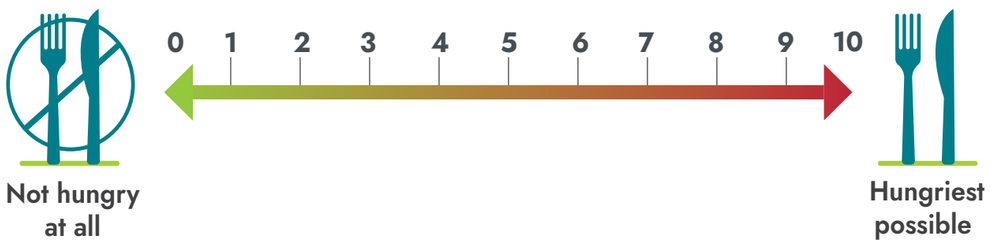
Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs.

Measuring hunger[1]

Hunger scale in the POMC, PCSK1, or LEPR deficiency clinical trials



- Patients ≥12 years of age who were able to self-report their hunger (n=16) recorded their daily maximal hunger in a diary, which was then assessed by the Daily Hunger Questionnaire Item 2
- Hunger was scored on an 11-point scale from 0 (“not hungry at all”) to 10 (“hungriest possible”)

Important Safety Information (cont’d)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection

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In patients with obesity due to POMC, PCSK1, or LEPR deficiency

IMCIVREE decreased hunger scores over 1 year[1]

Median change in maximal hunger score over 1 year

POMC or PCSK1 (n=8)*

2-POINT REDUCTION in median hunger score

- In patients with obesity due to POMC or PCSK1 deficiency, IMCIVREE demonstrated **a median 2-point reduction in maximal hunger score** at 1 year
(Range: -6.5, -0.1)

LEPR (n=8)*†

3.4-POINT REDUCTION in median hunger score

- In patients with obesity due to LEPR deficiency, IMCIVREE demonstrated a **median 3.4-point reduction in maximal hunger score** at 1 year
(Range: -4.7, -1.0)

When treatment was withdrawn, hunger scores generally worsened and then improved when IMCIVREE was reinitiated

*The median score at baseline (and week 52) was determined by calculating the average week 1 score (and average week 52 score) for each patient and determining for the median for the group.
†Three patients had missing hunger data at 1 year.

Please see additional Important Safety Information on page 15 and full Prescribing Information.

IMCIVREE has a well-established safety and tolerability profile[1,7]

Adverse reactions occurring in ≥23% of patients treated with IMCIVREE in open-label clinical studies of 1-year duration for POMC, PCSK1, or LEPR deficiency[1]

Adverse reaction	N=27 (%)	Adverse reaction	N=27 (%)
Injection site reaction*	96%	Back pain	33%
Skin hyperpigmentation†	78%	Fatigue	30%
Nausea	56%	Vomiting	30%
Headache	41%	Depression§	26%
Diarrhea	37%	Upper respiratory tract infection	26%
Abdominal pain‡	33%	Spontaneous penile erection‖	23%

- Reported incidences of nausea and vomiting primarily occurred within the first month of treatment, then decreased over time[7]
- Reported incidences of nausea and vomiting typically resolved within a few days in patients with a rare genetic disease of obesity in IMCIVREE clinical trials[7]
- Nausea and vomiting should be managed by dose titration and standard care[1]

*Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discoloration.[1]
†Includes skin hyperpigmentation, pigmentation disorders, and skin discoloration.[1]
‡Includes abdominal pain and upper abdominal pain.[1]
§Includes depressed mood.[1]
‖n=13 male patients.[1]

An extension study evaluating long-term outcomes for patients on IMCIVREE is ongoing[8]

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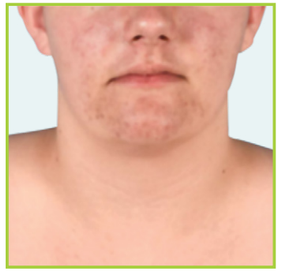
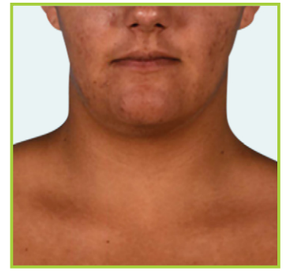
Hyperpigmentation was common and rarely led to discontinuation[1,6]

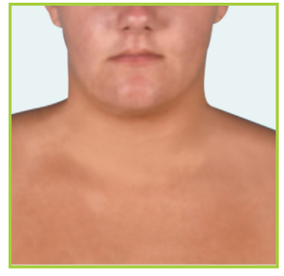
Example of hyperpigmentation[9]



Baseline



After treatment



Following study

- Changes in skin pigmentation or hair color typically presented 2-3 weeks after initiation of IMCIVREE, with most events occurring within the first month of treatment[10]
  - Skin darkening plateaued within the initial months of treatment[10]
  - Hyperpigmentation is variable[9]
  - This effect is reversible upon discontinuation of treatment[1]
  - Perform a full body skin examination prior to initiation and periodically during treatment with IMCIVREE to monitor pre-existing and new skin pigmentary lesions[1]
- **There were no reports of melanoma related to the observed hyperpigmentation in clinical trials of IMCIVREE[10]**
  - Hyperpigmentation is not unexpected given that IMCIVREE activates the melanocortin-1 receptor, which results in melanin production[1]

Once-daily, subcutaneous injection that can be administered at home[1]

Titrate IMCIVREE to the target dose

	Starting dose (weeks 0-2)	Uptitration dose	Target dose
Adult and pediatric (≥12 years of age)	**2 mg** once daily		**3 mg** once daily
Pediatric (6 to <12 years of age)	**1 mg** once daily	**2 mg** once daily	**3 mg** once daily

- IMCIVREE should be administered once daily, at the beginning of the day, without regard to meals
  - There is no food requirement for administration
- No dose adjustments are needed for patients with mild to moderate renal impairment
  - Refer to the Prescribing Information for dose adjustments for patients with severe renal impairment
- Periodically assess response to IMCIVREE therapy. In pediatric patients, evaluate the impact of weight loss on growth and maturation
- Evaluate weight loss after 12 to 16 weeks of treatment
- If a patient has not lost at least 5% of baseline body weight, or 5% of baseline BMI for patients with continued growth potential, discontinue IMCIVREE as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment

Dose should be titrated to optimize tolerability and response

References: 1. IMCIVREE [prescribing information]. Boston, MA. Rhythm Pharmaceuticals, Inc. **2.** Eneli I et al. *Appl Clin Genet.* 2019;12:87-93. **3.** Yazdi FT et al. *PeerJ.* 2015;3:e856. **4.** Shen W-J et al. *Biochim Biophys Acta Mol Basis Dis.* 2017;1863:2477-2485. **5.** Farooqi IS et al. *J Endocrinol.* 2014;223(1):T63-T70. **6.** Clément K et al. *Lancet Diabetes Endocrinol.* 2020;8(12):960-970. **7.** Argente J et al. The Pediatric Endocrine Society Annual Meeting. Poster 155. April 28-May 1, 2022. **8.** Long Term Extension Trial of Setmelanotide. ClinicalTrials.gov. August 29, 2018. Updated September 17, 2021. Accessed August 8, 2022. https://clinicaltrials.gov/ct2/show/NCT03651765. **9.** Clément K et al. *Lancet Diabetes Endocrinol.* [Supplementary appendix] 2020;8(12):960-970. **10.** Data on file. Rhythm Pharmaceuticals, Inc. Boston, MA.

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Getting your patients started on IMCIVREE

3 simple steps to initiate treatment

1. Download the IMCIVREE Start Form at IMCIVREE.com/start*
2. Follow the instructions to complete the form
3. Submit all pages of the completed form via fax to **1-877-805-0130** or email **patientsupport@rhythmtx.com**

*The preferred method of starting IMCIVREE is via our Start Form. If you would prefer to e-prescribe, please contact PANTHERx Rare Pharmacy.

IMCIVREE is only available through our specialty pharmacy†

†PANTHERx Rare Pharmacy.

Financial support may be available to eligible patients for whom IMCIVREE treatment is indicated. For questions on IMCIVREE or how to start a patient, call Rhythm® InTune at **1-855-206-0815**, Monday–Friday, 8 AM to 8 PM ET.

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at 833-789-6337 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Rhythm InTune
Support made personal

A support program designed for caregivers and people living with POMC, PCSK1, or LEPR deficiency

A Rhythm InTune Patient Education Manager is a single point of contact who can help patients and caregivers:

Access educational resources, such as information about POMC, PCSK1, or LEPR deficiency or treatment with IMCIVREE® (setmelanotide) injection.

Connect to a community where they can learn from the experiences of others.

Access treatment by helping with understanding drug coverage, prior authorizations, appeals support, and, for eligible patients, copay support and financial assistance.

Get started on treatment by coordinating IMCIVREE deliveries and injection support with the specialty pharmacy.

Rhythm InTune is committed to helping your patients access treatment with IMCIVREE

For more information about the services Rhythm InTune provides, contact us at:

patientsupport@rhythmtx.com

1-855-206-0815

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ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection

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In patients with obesity due to POMC, PCSK1, or LEPR deficiency

IMCIVREE is the first and only treatment to target impairment in the MC4R pathway, a root cause of hyperphagia and obesity[1,2]

IMCIVREE delivered significant, clinically meaningful weight loss over 1 year[1]

- **23.1% mean reduction in weight** from baseline after 1 year in patients with obesity due to POMC or PCSK1 deficiency (95% CI: -31.9%, -14.4%); *P*=0.0003; N=10
- **9.7% mean reduction in weight** from baseline after 1 year in patients with obesity due to LEPR deficiency (95% CI: -16%, -3.3%); *P*=0.0074; N=11

IMCIVREE decreased maximal hunger scores over 1 year[1]

- **Median 2-point reduction** in maximal hunger score at 1 year in patients with POMC or PCSK1 deficiency (range: -6.5, -0.1)
- **Median 3.4-point reduction** in maximal hunger score at 1 year in patients with LEPR deficiency (range: -4.7, 1.0)

Well-established safety and tolerability profile[1,7]

- The most common adverse reactions (incidence ≥23%) were injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection

Rhythm InTune provides your patients with personalized support

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patientsupport@rhythmtx.com 1-855-206-0815

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Rhythm® PHARMACEUTICALS

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