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APPLICATION NUMBER:

216185Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Clinical Pharmacology Review

NDA/BLA Number	NDA 216185
Link to EDR	\\CDSESUB1\evsprod\NDA216185\0001
Submission Date	7/7/2022
Submission Type	505(b)(2)
Brand Name	MOTPOLY XR
Generic Name	Lacosamide
Dosage form (Strength)	Extended-Release Capsules: 100 mg, 150 mg and 200 mg
Proposed Indication	Treatment of partial-onset seizures in patients 17 years of age and older
Applicant	Aucta Pharmaceuticals
OCP Review Team	Dawei Li, Ph.D., Gopichand Gottipati, Ph.D.

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Executive Summary

In this current New Drug Application (NDA) 216185 for Lacosamide Extended-Release Capsules (MOTPOLY XR) the Applicant (Aucta Pharmaceuticals) is seeking approval for the treatment of partial-onset seizures in patients 17 years of age and older. The applicant filed this application under the 505(b)(2) pathway and used VIMPAT® (lacosamide IR tablet) as the listed drug (LD) (NDA 022253), originally approved in 2008. MOTPOLY XR capsules (100 mg, 150 mg and 200 mg) are developed for once-daily (QD) dosing. Since MOTPOLY XR is intended to be taken as an intact capsule, the Applicant is seeking a monotherapy and adjunctive therapy for partial-onset seizures in patients 17 years and older instead of 1 month of age and older indicated for the LD. The Applicant is not seeking the indication for primary generalized tonic-clonic seizures.

The clinical pharmacology program consists of 4 Phase 1 studies in healthy adult volunteers assessing the single dose relative bioavailability (Study 20-VIN-0088), the steady-state relative bioavailability (Study 20-VIN-0095) between MOTPOLY XR capsules and the reference VIMPAT® IR tablets, dose linearity/proportionality (Study 22-VIN-0340) and food effect (Study 21-VIN-0184).

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study 20-VIN-0095. OSIS determined that inspections are not needed at this time (please refer to OSIS review in DARRTS dated 10-11-2022 for additional details).

The primary focus of this review is to evaluate the adequacy of scientific bridge between MOTPOLY XR capsules and the reference VIMPAT® IR tablets.

Recommendation

The Office of Clinical Pharmacology reviewed the information submitted under this NDA and recommends approval of MOTPOLY XR capsules provided that an agreement is reached between the Applicant and the Agency regarding the revised labeling language. This recommendation is based on an adequate PK bridge demonstrated between MOTPOLY XR capsules and the LD, VIMPAT® IR tablets, allowing the applicant to rely upon FDA's previous findings of LD for efficacy and safety from LD's label.

Summary of Key Clinical Pharmacology Findings

Pharmacokinetics

- Linear pharmacokinetics (PK) of lacosamide were observed following single oral doses of MOTPOLY XR capsules over the range of 100 to 400 mg.
- Tmax was reported to be approximately 8 hours following a single 400 mg oral dose of MOTPOLY XR, and approximately 7 hours after repeat dosing.

Scientific bridge between MOTPOLY XR capsules and VIMPAT® tablets

Results from a pilot comparative PK study (Study 20-VIN-0088) showed that MOTPOLY XR was bioequivalent to the reference VIMPAT® IR tablet with respect to the overall exposure (AUC0-inf and Cmax).

In the pivotal comparative PK study (study 20-VIN-0095), bioequivalence was established between MOTPOLY XR and the LD VIMPAT® IR tablet at steady state with respect to AUC0-24hr,ss, Cmax,ss, and Cmin,ss. Additional analyses showed that the point-to-point comparisons for lacosamide partial AUC (AUC0-t), plasma concentrations and the partial AUC between time-points (AUCt1-t2) are bioequivalent at steady-state for majority of the time points throughout the day based on conventional BE criteria.

Food effect

High fat food and sprinkle of MOTPOLY XR with applesauce had no clinically meaningful impact on the PK of MOTPOLY XR capsules. The 90% confidence intervals of the geometric least square mean ratio (Tfast/Tfed and Tfast/TSprinkle) for Cmax, AUC0-t, and AUC0-inf were within 80-125%. The median (min - max) Tmax under fasting, fed and sprinkle conditions were 9.00 (6.00 - 12.00) hr, 10.00 (8.00 - 14.00) hr and 8.00 (7.00 - 11.00) hr, respectively.

Overview of the Product and Regulatory Background

Lacosamide is a white to light yellow powder. It is sparingly soluble in water and slightly soluble in acetonitrile and ethanol. Lacosamide Extended-Release Capsules for oral administration contain lacosamide and the following inactive ingredients: microcrystalline cellulose, povidone (b) (4) ethylcellulose, triethyl citrate, hypromellose titanium dioxide and dye pigments.

In a Type B meeting WRO in October 2018, the Agency advised on the proposed clinical development program for lacosamide ER capsules to compare AUCss; Cmax,ss; and Cmin,ss of lacosamide ER capsules to establish the bioequivalence (BE) between lacosamide ER capsules and LD, immediate release (IR) tablets. In the pre-NDA meeting WRO in August 2021, the Agency noted that the sponsor needed to demonstrate bioequivalence (BE) for the relevant PK parameters using the standard BE criteria (i.e., 90% confidence intervals of geometric mean ratios lying within 0.80 and 1.25) between the final to-be-marketed product and VIMPAT® Tablets (LD), to support reliance on the Agency's previous findings of efficacy and safety information from the LD.

Summary of Relative Bioavailability at Steady State

Study 20-VIN-0095

Study design: This was a phase 1, an open label, balanced, randomized, multiple-dose, two-treatment, two-sequence, two-period, oral comparative bioavailability study in healthy, adult, human subjects under fasting condition.

Number of Subjects (Planned and Analyzed): 35 subjects were enrolled into the study. 27 subjects who completed both the periods of the study were included in pharmacokinetic and statistical analysis.

Treatments:

The subjects were fasted overnight for at least 10.00 hours before schedule time of dosing - except second dosing of reference formulation.

For Test Product: Two capsule of Test product (2 x 200mg dose) were administered orally once daily (i.e., in morning) on day 1, 2, 3, 4, 5, 6 and 7 at scheduled dosing time in sitting posture with 240 ± 2 mL of drinking water at ambient temperature as per randomization schedule. Subjects were instructed not to chew, open, or crush the Investigational product but to consume it as a whole.

For Reference Product: One tablet (1 x 200mg dose) was administered orally twice daily (i.e., at an interval of 12.0 hours after morning dose) on day 01, 02, 03, 04, 05, 06 and 07 at scheduled dosing time in sitting posture with 240 ± 2 mL of drinking water at ambient temperature as per randomization schedule. Subjects were instructed not to chew or crush the Investigational product but to consume it as a whole.

There was a washout period of 11 days between last dose of period 01 (on day 07) and first dose of period 02 (on day 01).

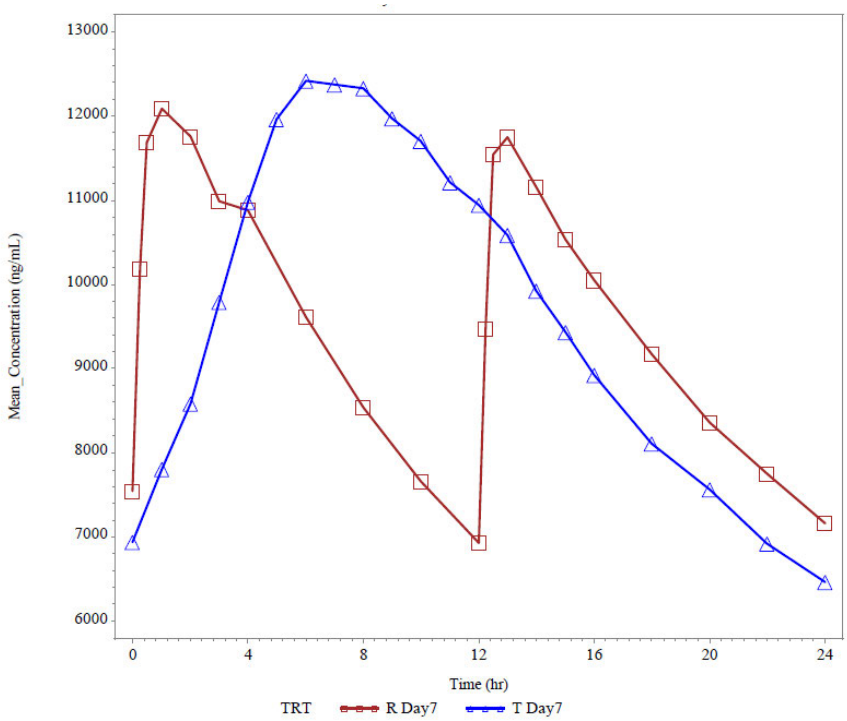
PK Sampling: Blood samples were collected at pre dose (0.00), post dose: 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 13.00, 14.00, 15.00, 16.00, 18.00, 20.00, 22.00 and 24.00 hours following drug administration.

Criteria for conclusion of bioequivalence: 90% confidence interval of the geometric least square mean ratio of Cmax,ss, Cmin,ss and AUC0-τ,ss of the test and reference products for lacosamide, are completely contained in the range of 80.00 to 125.00 % (limits inclusive) for ln-transformed data.

Results:

Data of 27 subjects were used for pharmacokinetic analysis and statistical analysis. Plot of the mean plasma levels for lacosamide is presented for linear data in Figure 1. Table 1 summarized the ratio of PK parameters and confidence intervals (C.I.).

Figure 1. Linear plot of mean plasma concentrations versus time.



Source: Clinical Study Report 20-VIN-0095, Appendix 16.2.6 Individual pharmacokinetic response data and graphs, figures on page 11 of 67.

Table 1. Ratio of the Least squares Geometric Means of PK parameters and 90% Confidence Intervals

PK Parameters (Units)	Geometric Least Squares Means and it's ratio				90% CI	Power (%)
	Test Product (T) (N=27)	Reference Product (R) (N=27)	(T/R)%	Intra-subject CV (%)		
$C_{max,ss}$ (ng/mL)	12584.623	13040.136	96.51	9.63	92.27% - 100.94%	98.49
$AUC_{0-\tau,ss}$ (hr*ng/mL)	226248.907	221131.272	102.31	3.55	100.63% - 104.03%	100.00
$C_{min,ss}$ (ng/mL)	6215.101	6660.061	93.32	6.18	90.66% - 96.05%	99.99

Source: Clinical Study Report 20-VIN-0095, Table on Page 65 of 81.

Reviewer's Comments:

The overall design of this pivotal BE study, including the dose selection, route of administration, study population, study sample size, PK sampling schedule, washout period and bioanalytical method validation data are appropriate. The applicant conducted PK analysis and applied statistical testing criteria are acceptable. The reviewer conducted independent analysis and verified the PK results concluding that the Cmax,ss, Cmin,ss and AUC0-τ,ss at steady state were within the acceptable limits of 80.00% to 125.00%.

Reviewer's Analysis

Independent NCA analysis was conducted by the reviewer using the raw PK data from study 20-VIN-0095. The descriptive statistics for PK parameters from the NCA analysis are shown in Table 2. Table 3 summarized the reviewer calculated ratio of the Least Squares Geometric Means for PK parameters and confidence intervals (C.I.).

Table 2. Summary of Pharmacokinetic Parameters for Lacosamide by Treatment (reviewer's analysis)

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV)	
	Reference Product (R) (N = 27)	Test Product (T) (N = 27)
Cmin,ss (ng/mL)	6681.7986 ± 1861.0226 (27.85%)	6440.752 ± 1884.2874 (29.26%)
Cmax,ss (ng/mL)	13052.1285± 2769.6150 (21.22%)	12730.784 ± 2267.4183 (17.81%)
Tmax,ss (hr)#	4.5 (0.25 - 10.00)	7.000 (5.00 - 10.00)
AUC0-τ,ss (hr*ng/mL)	227993.5655 ± 50006.6752 (21.9%)	230537.241 ± 51334.4716 (22.27%)

For Tmax,ss Median (min – max)

Table 3. Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals (reviewer's calculation)

PK Parameters (Units)	Geometric Least Squares Means and it's ratio			90% CI
	Test Product (%) (T) (N=27)	Reference Product (R) (N=27)	(T/R)%	
Cmax,ss (ng/mL)	12532.59	12794.89	97.95	93.54%-102.57%
AUC0-τ,ss (hr*ng/mL)	224814.98	219960.0	102.21	100.51%-103.93
Cmin,ss (ng/mL)	6150.90	6669.38	92.23	89.61%-94.91%

The reviewer's analysis confirmed that the Cmax,ss, Cmin,ss and AUC0-τ,ss results at steady state were within the acceptable limits of 80.00% to 125.00% for concluding the bioequivalence of the test product to the LD.

In addition to the BE analysis for overall exposure (i.e., AUC0-24hr,ss, Cmax,ss, and Cmin,ss) and partial AUC at steady state in the original submission, the applicant submitted additional BE analysis results per the OCP request for comparing the point-to-point lacosamide plasma concentrations and the partial AUC between two time-points (i.e., AUCt1-t2) to further examine and assure the plasma profile similarity.

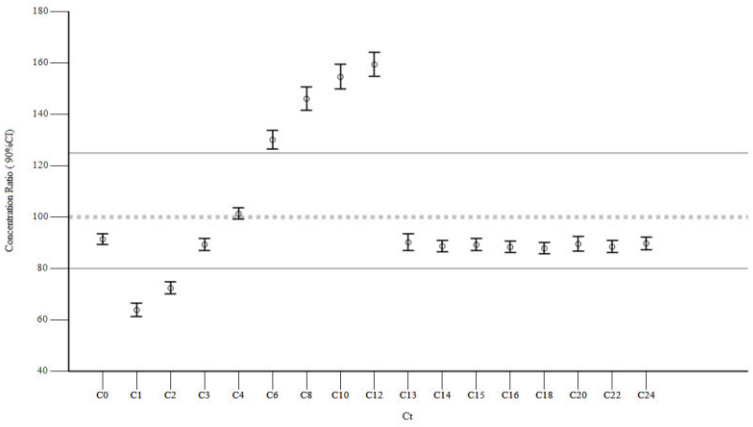
As shown in Table 4 below, point estimates and the 90% CIs for the ratios of steady state partial AUC (AUC0-p) between two formulations were mostly within the 80-125% BE limits, except for the initial time points before 4 hours. In addition, as shown in Figure 2 and Figure 3, the 90% CI for the ratios of point-to-point lacosamide plasma concentration and partial AUC between two time points (i.e., AUCt1-t2) of the 24-hour curves for the two formulations were mostly within the 80-125% BE limits, except for the initial time points before 2 hours postdose where the 90% CIs fell slightly outside the lower BE limit and few others between 6 hours and 12 hours postdose where the 90% CIs fell outside the higher BE limit.

Table 4. Partial AUC at multiple time points (study 20-VIN-0095)

AUC, ss (hr*ng/mL)	Geometric Least Square Means and Its Ratio			Calculated 90% confidence interval	Power (%)
	Test Product (N = 27)	Reference Product (N = 27)	(T/R) %		
AUC0 – 0.5, ss (hr*ng/mL)	3467.966	4751.964	72.98	68.07-78.24	80.53
AUC0 – 1, ss (hr*ng/mL)	7164.647	10616.180	67.49	63.98-71.19	94.53
AUC0 – 1.5, ss (hr*ng/mL)	11074.197	16563.339	66.86	64.00-69.85	98.81
AUC0 – 2, ss (hr*ng/mL)	15179.879	22413.359	67.73	65.17-70.39	99.67
AUC0 – 3, ss (hr*ng/mL)	24204.453	33626.558	71.98	69.84-74.19	99.99
AUC0 – 4, ss (hr*ng/mL)	34462.151	44392.522	77.63	75.78-79.52	100.00
AUC0 – 6, ss (hr*ng/mL)	57911.476	64558.920	89.70	87.99-91.45	100.00
AUC0 – 8, ss (hr*ng/mL)	82376.651	82360.178	100.02	98.21-101.86	100.00
AUC0 – 12, ss (hr*ng/mL)	128203.815	112395.895	114.06	111.91-116.26	100.00
AUC0 – 16, ss (hr*ng/mL)	167312.544	154856.085	108.04	106.18-109.94	100.00
AUC0 – 24, ss (hr*ng/mL)	226248.907	221131.272	102.31	100.63-104.03	100.00

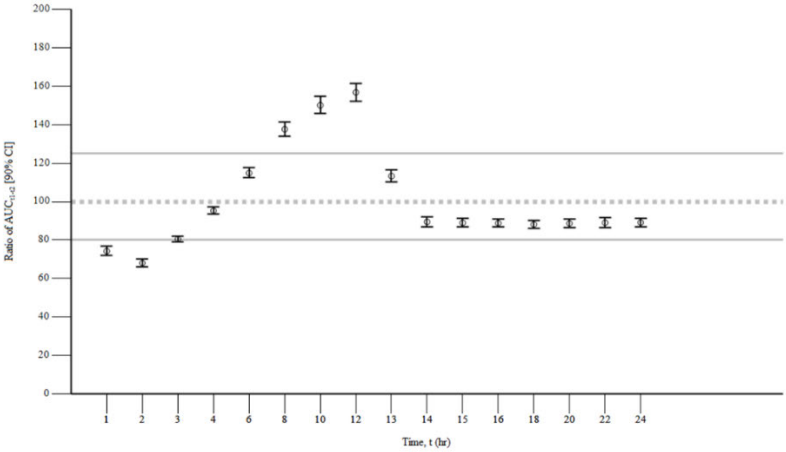
Source: Summary of Clinical Pharmacology, Table 7 on Page 8 of 18

Figure 2. Plot of Ratio of point-to-point lacosamide concentrations (90% CI) in relation of XR to IR Formulation



Source: Sponsor's response to clinical pharmacology information request dated 3/16/2023

Figure 3. Plot of Ratio of Partial AUC t1-t2 (90% CI) Vs. Time Points in relation of XR to IR Formulation



Source: Sponsor's response to clinical pharmacology information request dated 3/14/2023

Evidence to support indication for pediatric patients weighing 50 kg or more

In this current submission, the Applicant is seeking the approval for the treatment of partial-onset seizures in patients 17 years of age and older. According to the USPI of VIMPAT®, the approved dosing regimen for pediatric patients weighting 50 kg or more is same as that for adults, except for a lower initial dose of 100 mg/day for pediatrics and no alternate initial dosage (see table below). Because the proposed MOTPOLY XR capsules (100 mg, 150 mg and 200 mg) are appropriate for the dosing regimen for pediatric patients weighting 50 kg or more, the review team recommends including the indication for pediatric patients weighing 50 kg or more.

Food effect study 21-VIN-0184

Study 22-VIN-0340 was an open label, balanced, randomized, single dose, three-treatment condition, three-sequence, three-period, crossover oral bioavailability study of Lacosamide 200mg extended-release capsule of in 18 healthy adult subjects under fasting, fed, and fasting sprinkle condition. Results from this study showed that high fat food and sprinkle of the test product with applesauce had no clinically meaningful impact on the PK of MOTPOLY XR capsules. The 90% confidence intervals of the geometric least square mean ratio (Tfast/Tfed and Tfast/TSprinkle) for Cmax, AUC0-t, and AUC0-inf were within 80-125% (showed in tables below). The median (min – max) Tmax under fasting, fed and sprinkle conditions were 9.00 (6.00 – 12.00) hr, 10.00 (8.00 - 14.00) hr and 8.00 (7.00 - 11.00) hr, respectively.

Tfasting vs Tfed:

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (Tfa) (N = 18)	Test Product (Tfe) (N = 17)	(Tfa/Tfe) (%)			
C_{max} (ng/mL)	4315.818	3832.546	112.61	7.99	107.54% - 117.91%	100.00
AUC_{0-t} (hr*ng/mL)	126171.170	119931.199	105.20	5.65	101.83% - 108.69%	100.00
$AUC_{0-\infty}$ (hr*ng/mL)	132706.343	126288.418	105.08	5.76	101.64% - 108.64%	100.00

Tfasting vs TSprinkle:

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (Tfa) (N = 18)	Test Product (TSprinkle) (N = 18)	(Tfa/TSprinkle) (%)			
C_{max} (ng/mL)	4315.818	4349.126	99.23	7.99	94.86% - 103.81%	100.00
AUC_{0-t} (hr*ng/mL)	126171.170	123817.028	101.90	5.65	98.70% - 105.20%	100.00
$AUC_{0-\infty}$ (hr*ng/mL)	132706.343	130255.509	101.88	5.76	98.62% - 105.25%	100.00

Source: Tables on Page 57, Clinical Study Report 21-VIN-0184

Dose proportionality/linearity study 22-VIN-0340

Study 22-VIN-0340 was conducted to assess the dose proportionality of MOTPOLY XR capsules. This was a Phase 1, open-label, balanced, randomized, five-treatment, five-sequence, five - period cross-over, single-dose, proportionality/linearity and comparative bioavailability study of MOTPOLY XR capsules 100 mg, 200 mg, 300 mg, 400 mg with that of VIMPAT® 200mg Film coated tablet (Reference R) in 25 healthy adult subjects under fasting conditions.

Proportionality/linearity of Cmax, AUC0-t and AUC0-inf was assessed using a power model (Y=α*[Dose]β). A mixed effects model, allowing for random between-subject variability in the intercept and slope parameters, was used to estimate the proportionality/linearity constant, β and its 90% confidence interval. Based on calculated slope and 90 % confidence interval of slope (see table below), dose proportionality was demonstrated for both Cmax and AUC across the clinical dose range of 100 mg to 400 mg.

PK Parameters (Unit)	Slope Acceptance Range	Calculated Slope	90% Confidence Interval of Slope
C_{max} /D (ng/mL/mg)	0.8390-1.1610	0.9958	0.9737-1.0180
AUC_{0-t}/D (hr*ng/mL/mg)	0.8390-1.1610	1.0033	0.9796-1.0270
$AUC_{0-\infty}$/D (hr*ng/mL/mg)	0.8390-1.1610	1.0017	0.9783-1.0251

Source: Table on Page 66, Clinical Study Report 22-VIN-0340

(b) (4)

(b) (4) Therefore, the review team recommends deleting the proposed (b) (4)

Appendices

Summary of Bioanalytical Method Validation and Performance

A validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method was used for determining the lacosamide concentrations in human plasma. The method met the acceptance criteria for bioanalytical methods according to the Bioanalytical Method Validation Guidance for Industry the FDA Guidance for the Industry. Description of method validation parameters for Midazolam (validation report VIN-BRD-MV-1185) are summarized in Table 5.

Table 5 Summary of Bioanalytical Method and Validation Characteristics

Analyte	Lacosamide
Internal Standard (IS)	Lacosamide D6
Lower Limit of Quantitation (LLOQ)	50 ng/mL
Standard curve concentrations (ng/mL)	9 concentrations in the range of 50.000ng/mL (LLOQ) to 20000.000ng/mL (ULOQ).
QC Concentrations (ng/mL)	5 concentrations in the range of 50.000ng/mL (LLOQ QC) to 15000.000ng/mL (HQC).
Intraday accuracy and precision	Biases: -12.30% to 11.79%; CV: 1.07% to 15.32%
Inter day accuracy and precision	Biases: -4.85% to 6.30%; CV: 2.52% to 13.00%
Bench-top stability (hrs)	7 hours at ambient temperature
Long-term storage stability (days)	141 Days at -20±5°C and -78±8°C
Processed Sample (hrs)	03 hours at ambient temperature and 92 hours at 5±3°C
Freeze-thaw stability (cycles)	5 Cycles at freezing temperature of -20±5°C and - 78±8°C (thawing done at room temperature in water bath).
Stock stability	07 days at 5±3°C

Source: Method validation report VIN-BRD-MV-1185

Reviewer's Comments: Method validation and sample analysis are acceptable.

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/s/

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