

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207999Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: April 12, 2016

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Subject: Review evaluates if a REMS is needed for obeticholic acid

Drug: Obeticholic acid

Therapeutic Class: Farnesoid X receptor (FXR) agonist

Dosage and route: 5 mg to 10 mg by mouth once daily

Application Type/Number: NDA 207999

Sponsor: Intercept Pharmaceuticals, Inc.

OSE RCM #: 2015-1479

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to the public. ***

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ocaliva (obeticholic acid) oral tablets is necessary to ensure the benefits of this product outweigh its risks. A new drug application (NDA 207999) for obeticholic acid was received on June 29, 2015, from Intercept Pharmaceuticals, Inc. (Intercept). The Sponsor's proposed indication for obeticholic acid is for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. The Sponsor did not submit a proposed REMS or risk management plan.

1.1 BACKGROUND

1.1.1 Disease Background

Primary biliary cirrhosis (PBC) is a chronic, progressive autoimmune disease of the liver that primarily affects women. Its incidence peaks in the fifth decade of life, and it is uncommon in persons under 25 years of age. PBC is characterized by portal inflammation and immune-mediated destruction of the intrahepatic bile ducts. These changes occur at different rates and with varying degrees of severity in different patients. The loss of bile ducts leads to decreased bile secretion and the retention of toxic substances within the liver, resulting in further hepatic damage, fibrosis, cirrhosis, and eventually, liver failure.¹ When clinical symptoms are present, they most commonly include fatigue (in up to 70% of PBC patients) and pruritis, but may also include osteoporosis, portal hypertension, hyperlipidemia, hepatocellular carcinoma, and autoimmune disease.

PBC is a rare disease with prevalence of less than 1/2000.² It is thought to result from a combination of multiple genetic factors and superimposed environmental triggers, though its exact pathogenesis remains unknown. Several risk factors have been suggested, including exposure to infectious agents and chemicals. Anti-mitochondrial antibodies (AMA) are present in at least 95% of patients with PBC, and are recognized as the disease-specific hallmark.^{3,4,5}

As a result of the widespread use of biochemical liver function tests as part of routine screening, more patients are now diagnosed with asymptomatic PBC, have early histological stages at the time of diagnosis, and receive treatment at earlier stages. However, the lack of symptoms and a slow natural history of disease present challenges for patients to understand the importance of early treatment and compliance. Because no cure exists for primary biliary cirrhosis, treatment

¹ Kaplan, M. M., & Gershwin, M. E. (2005). Primary biliary cirrhosis. *New England Journal of Medicine*, 353(12), 1261-1273.

² Poupon, R. (2010). Primary biliary cirrhosis: a 2010 update. *Journal of hepatology*, 52(5), 745-758.

³ Ibid.

⁴ Kaplan, M. M., & Gershwin, M. E. (2005). Primary biliary cirrhosis. *New England Journal of Medicine*, 353(12), 1261-1273.

⁵ Silveira, M. G., & Lindor, K. D. (2014). Obeticholic acid and budesonide for the treatment of primary biliary cirrhosis. *Expert opinion on pharmacotherapy*, 15(3), 365-372.

focuses on slowing the progress of the disease, relieving symptoms, and preventing complications. Ursodeoxycholic acid (UDCA), a (b) (4), is the only pharmacologic treatment option currently approved in the United States. UDCA has shown to improve parameters of liver biochemistry, including serum bilirubin, the major prognostic marker in PBC. However, in a published study, approximately 40% of PBC patients receiving standard doses of UDCA (13-15 mg/kg/day, as recommended in the labeling) had a suboptimal response.⁶ Typically, one out of three patients does not adequately respond to UDCA therapy and may need additional medical therapy and/or liver transplantation.⁷

1.1.2 Product Background

Obeticholic acid is a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. One of the primary functions of FXR activation is the suppression of cholesterol 7- α -hydroxylase (CYP 7A1), the rate-limiting enzyme in bile acid synthesis.⁸ Obeticholic acid is an analog of the endogenous FXR agonist, the bile acid chenodeoxycholic acid (CDCA). The utility of CDCA has been limited primarily by its low potency at FXR. UDCA is an epimer of CDCA, but also lacks meaningful FXR activity. UDCA was approved for use in PBC in 1997, and is currently the only FDA-approved treatment for PBC. Long-term follow-up of patients treated with UDCA shows a clear survival benefit. However, up to 40% of UDCA-treated patients have a suboptimal or absent response, and are, therefore, at significantly increased risk for progressive hepatic injury and associated outcomes, including the need for liver transplantation. Thus, there is a continued need for new therapeutic options in primary biliary cirrhosis.

Obeticholic acid is derived from CDCA, but is approximately 100-fold more potent at the FXR due to the 6- α ethyl substitution.⁹ The proposed indication of obeticholic acid is the treatment of primary biliary cirrhosis in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Published studies suggest that obeticholic acid may also be useful in the treatment of non-alcoholic steatohepatitis (NASH), portal hypertension, and bile acid diarrhea.

Obeticholic acid will be available in 5 mg and 10 mg oral tablets. The proposed starting dosage in adult patients without moderate or severe hepatic impairment (Child-Pugh Class B or C) who have (b) (4) dosage of UDCA for at least 1 year, or who are intolerant to UDCA, is 5 mg orally once daily. If an adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of obeticholic acid 5 mg once daily and the patient is tolerating the drug, the proposed dosing

⁶ Parés, A. (2014). Treatment of primary biliary cirrhosis: Is there more to offer than ursodeoxycholic acid?. *Clinical Liver Disease*, 3(2), 29-33.

⁷ Poupon, R. (2010). Primary biliary cirrhosis: a 2010 update. *Journal of hepatology*, 52(5), 745-758.

⁸ Forman, B. M., Goode, E., Chen, J., Oro, A. E., Bradley, D. J., Perlmann, T., ... & Evans, R. M. (1995). Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell*, 81(5), 687-693.

⁹ Hirschfield, G. M., Mason, A., Luketic, V., Lindor, K., Gordon, S. C., Mayo, M., ... & Trauner, M. (2015). Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology*, 148(4), 751-761.

recommendation is to increase to 10 mg once daily. A determination on the management of intolerance due to pruritis has not been made at the time this review was finalized. In patients with moderate or severe hepatic impairment (Child-Pugh Class B or C), the proposed recommended starting dosage is 5 mg orally once weekly. This dosage should be increased, if the patient has not achieved an adequate reduction in ALP after 3 months and the patient is tolerating the drug, to 5 mg twice weekly, and then to 5 mg every other day, depending on response and tolerability. At this time, dosing recommendations are still under review. Obeticholic acid is contraindicated in patients with complete biliary obstruction.

Obeticholic acid is currently not marketed outside of the United States; however, in March 2015, a pre-Marketing Authorization Application (MAA) submission meeting was held between the European Medicines Agency Committee for Medicinal Products for Human Use and Intercept, where the overall development plan and filing strategy were discussed.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 207999 relevant to this review:

April 9, 2008: The Sponsor was granted Orphan Drug designation for obeticholic acid.

May 27, 2014: The Sponsor was granted Fast Track designation for obeticholic acid.

June, 29 2015: Intercept completed the rolling submission of NDA 207999 for obeticholic acid for the proposed treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. The submission did not include a proposed REMS.

October 27, 2015: The Mid-cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that there were safety concerns with more fractures and lower HDL-c in patients treated with obeticholic acid than in placebo patients. A REMS was not discussed with the Sponsor.

October 27, 2015: The Sponsor submitted a major amendment to the application, which included datasets to support the use of surrogate efficacy endpoints that were not included with the original submission.

December 17, 2015: The Agency issued a major amendment acknowledgement letter to the Sponsor in response to the October 27, 2015 submission which extended the goal date by three months to allow adequate time for a full review of the application.

March 22, 2016: The Late-cycle communication meeting was held between the Agency and the Sponsor. A REMS was not discussed with the Sponsor.

April 7, 2016: A Gastrointestinal Drugs Advisory Committee meeting was held to discuss NDA 207999. There was a general consensus that the committee agreed:

- Alkaline phosphatase (ALP) supports the application as a surrogate endpoint reasonably likely to predict clinical benefit.
- The Sponsor's proposed dosing schema, starting with a 5 mg dose of obeticholic acid with up-titration to 10 mg, appears reasonable.
- There is adequate data to support the use of obeticholic acid as monotherapy for patients intolerant to UDCA.

- There is insufficient evidence to support the Agency’s proposed dosing of obeticholic acid in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis.
- There is substantial evidence to support accelerated approval of obeticholic acid for the proposed indication, based on its effect on ALP.
- In patients who do not demonstrate reduction in ALP after 6 months of treatment on a maximally tolerated dose, it is reasonable to continue treatment for an additional 6 months.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Intercept Pharmaceuticals, Inc. Original submission NDA 207999, received June 29, 2015.
 - Section 2.5, Clinical Overview
 - Section 2.7.3, Summary of Clinical Efficacy
 - Section 2.7.4, Summary of Clinical Safety
- October 13, 2015, Mid-cycle meeting, Clinical Reviewer Slides.
- Mehta R. Division of Gastrointestinal and Inborn Errors Products, Backgrounder for Advisory Committee meeting, viewed March 4, 2016.
- Stinson J. Division of Bone, Reproductive and Urologic Products, Memorandum of Consultation for Obeticholic Acid, NDA 207999, dated February 1, 2016.
- Intercept Pharmaceuticals, Inc. 120-Day Safety Update Report for Ocaliva (obeticholic acid), received October 30, 2015.
- Intercept Pharmaceuticals, Inc. Proposed prescribing information for obeticholic acid, received June 29, 2015.
 - Updated on September 18, 2015.
 - Updated on March 10, 2016.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The efficacy and safety of obeticholic acid for the treatment of primary biliary cirrhosis were evaluated in two Phase 2 studies (747-201 and 747-202) and one Phase 3 study (747-301) in subjects with primary biliary cirrhosis (PBC). All three studies were randomized, double-blind, and placebo-controlled. Additional data was obtained from the primary treatment phase (PTP) of Study 747-205, an 8-week, open-label, uncontrolled, lipoprotein metabolism study in patients with PBC, to help characterize the mechanism of action of obeticholic acid. According to the Sponsor, the rarity of PBC and the chronic nature of the disease precluded the evaluation of classical clinical outcomes, such as transplant-free survival, and required consideration of potential surrogate endpoints reasonably likely to predict clinical benefit.¹⁰ Therefore, the Agency agreed with this rationale and allowed the Sponsor to use surrogate endpoints, or validated substitutes for the true endpoints (liver transplantation or death), in the clinical

¹⁰ Intercept. Clinical Overview for Obeticholic acid, received June 29, 2015.

program for obeticholic acid. The Sponsor's primary composite endpoint was the percentage of subjects with alkaline phosphatase (ALP) $<1.67 \times \text{ULN}$, total bilirubin $\leq \text{ULN}$, and a $\geq 15\%$ reduction in ALP. As there are no currently marketed products in the pharmacologic class for FXR activation, there is no directly relevant point-of-comparison for what might be a characteristic safety profile for obeticholic acid.

Study 747-201 (Obeticholic acid monotherapy)

Study 747-201 was an international, double-blind, placebo-controlled, parallel group, dose-finding Phase 2 study in subjects with a proven or likely diagnosis of PBC with disease that was sub-optimally controlled by UDCA. In this study, a total of 59 subjects were randomized to once daily doses of obeticholic acid 10 mg (n =20), 50 mg (n =16), or placebo (n =23), which were evaluated as monotherapy. The primary efficacy endpoint of the double-blind phase was the percent change from baseline in ALP at Week 12.

Following 12 weeks of treatment, the mean percent change from baseline in ALP was -44.5% and -37.6% for the 10 mg and 50 mg treatment groups, respectively, in comparison to a 0.4% increase observed in the placebo group. The mean absolute change in ALP from baseline to Week 12 was -233.5 U/L and -161.3 U/L for the 10 mg and 50 mg obeticholic acid groups, respectively, in comparison to an increase of 11.7 U/L in the placebo group. The difference in the change from baseline at Week 12 between each obeticholic acid group and placebo was statistically significant for both the percent and absolute change in ALP (p <0.0001).

Study 747-202 (Obeticholic acid + UDCA)

Study 747-202 was a Phase 2 study similar in design to Study 747-201, evaluating obeticholic acid as add-on therapy to UDCA. A total of 165 subjects were randomized to obeticholic acid add-on doses of 10 mg (n =38), 25 mg (n =48), 50 mg (n =41), or placebo (n =38). All patients remained on their stable dose of UDCA throughout the study. As in Study 747-201, the primary efficacy endpoint was the percent change in serum ALP level from baseline to Week 12.

Following 12 weeks of treatment, the mean percent changes from baseline in ALP were -23.7%, -24.7%, and -21.0% for the 10 mg, 25 mg, and 50 mg obeticholic acid + UDCA groups, respectively, in comparison to -2.7% in the placebo + UDCA group. The mean absolute change in ALP from baseline to Week 12 was -76.9 U/L, -67.4 U/L, and -64.4 U/L for the 10 mg, 25 mg, and 50 mg obeticholic acid groups, respectively, in comparison to -4.9 U/L in the placebo group. The difference in the change from baseline at Week 12 between each obeticholic acid group and placebo was statistically significant for both the percent and absolute change in ALP (p <0.0001).

Study 747-301 (To support second-line indication)

Study 747-301 was a 12-month, international, double-blind, placebo-controlled pivotal Phase 3 study in subjects with a proven or likely diagnosis of PBC with disease that was sub-optimally controlled. This study evaluated obeticholic acid doses of either 10 mg or a titration approach, starting with 5 mg and either titrating up to 10 mg or remaining on 5 mg. Subjects received obeticholic acid either as monotherapy or in combination with UDCA. Subjects in the UDCA arm had to be taking UDCA for at least 12 months (on a stable dose for 3 months) prior to Day 0. In the obeticholic acid monotherapy arm, subjects were eligible for inclusion if they had been unable to tolerate UDCA therapy, and had discontinued UDCA at least 3 months prior to Day 0.

The composite primary endpoints were ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease of ≥15% from baseline. Following completion of the 12-month double-blind period, subjects were eligible to enroll into the long-term safety extension (LTSE) to assess long-term durability for up to 5 years.

Given the limited sample size, data from Studies 747-201 and 747-202 were pooled with Study 747-301 at Month 3 and summarized by monotherapy or in combination with UDCA. According to the Clinical reviewer, data from Studies 747-201 and 747-202 demonstrated that obeticholic acid produced statistically significant and clinically meaningful reductions in ALP and other biochemical analytes, compared with placebo, as a monotherapy or in combination with UDCA. The majority of the reductions in ALP (as well as other liver enzymes) were seen after one month of treatment.

The clinical reviewer also found that the results of Study 747-301 showed both obeticholic acid treatment groups achieved clinically meaningful improvements and statistically significant differences from placebo in achieving the primary composite endpoint ($p < 0.0001$ vs placebo) at all times across the 12-month treatment period. The majority of subjects who responded achieved the endpoint by 3 months and maintained it over the 12-month study duration. A significant difference ($p = 0.0358$) in the percentage of subjects achieving the primary composite endpoint was observed at 6 months between obeticholic acid 5 mg (34%) compared to obeticholic acid 10 mg (51%). At Month 12, comparable efficacy was observed between the obeticholic acid titration arm and the 10 mg fixed dose. Of the 36 subjects in the obeticholic acid titration group who remained on 5 mg, 21 (58%) had achieved the composite endpoint at Month 6. For the group who titrated up to 10 mg at Month 6, mean ALP was 348.1 U/L, 255.9 U/L, and 222.4 U/L at Baseline, Month 6, and Month 12, respectively.

3.2 SAFETY CONCERNS

The overall safety population included a total of 1254 subjects who have been exposed to obeticholic acid in Studies 747-301 LTSE, 747-201 LTSE, and 747-202 LTSE, as well as data from the open-label, uncontrolled primary treatment phase (PTP) of 747-205 (also in subjects with PBC), and data from 16 clinical studies in healthy subjects. Serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation from 6 studies conducted in diseases other than PBC were included in the safety pool. Additionally, a QTc evaluation was performed and concluded that no significant or clinically relevant QTc prolongation effect of obeticholic acid 100 mg was observed.

3.2.1 Deaths

There were 2 deaths reported in the obeticholic acid clinical development program for PBC. The first subject was an 82 y.o. with a history of chronic kidney disease, PBC, ischemic cardiovascular disease, and congestive heart failure (CHF), whose death was attributed to an exacerbation of CHF. The second death was in a 69 y.o. subject with a prosthetic aortic valve whose death was deemed due to sepsis secondary to endocarditis.

3.2.2 Serious Adverse Events (SAEs)

In the LTSE, SAEs were reported in 14 subjects (7%) and 10 subjects (4%) for the obeticholic acid 5 mg and 10 mg treatment groups, respectively. SAEs that were considered related (or

possibly related) to obeticholic acid occurred at doses ranging from 3.3 mg to 25 mg. Slightly more subjects treated with obeticholic acid compared with placebo had SAEs in the system organ classes (SOC) of “Gastrointestinal Disorders,” “Injury, Poisoning, and Procedural Complications,” “Musculoskeletal and Connective Tissue Disorders,” and “Infections and Infestations.”

Within the SOC of Injury, Poisoning, and Procedural Complications, fracture-related SAEs were reported in 3 subjects (4%) of the obeticholic acid 10 mg group, compared with 1 subject (1%) in the placebo group. Therefore, the DGIEP consulted the Division of Bone, Reproductive and Urologic Products (DBRUP), requesting that DBRUP determine if bone fracture is a potential safety signal associated with obeticholic acid. Following his analysis, the DBRUP reviewer concluded that the data do not indicate a bone safety issue with obeticholic acid. Further, the Sponsor notes that these events were not unexpected in a PBC patient population of mostly women, many with relevant medical histories.

With the exception of varicose vein and osteoarthritis, which were each experienced by 2 obeticholic acid-treated subjects (<1%), and dyspnea, which was experienced by 2 placebo-treated subjects (<1%), each SAE was experienced by only 1 subject, indicating no particular pattern or trend for SAEs. The most common reason for treatment discontinuation was due to pruritis (n =13).

3.2.3 Adverse Events of Special Interest (AESIs)

3.2.3.1 Liver Adverse Events and Elevations in Liver Biochemical Tests

A total of 14 subjects (5%) in the obeticholic acid groups reported 25 treatment emergent adverse events (TEAEs) classified as Hepatic Disorders, compared to 1% in the placebo group. Exposure-adjusted incidence rates of hepatic events were 2.4%, 4.5%, 5.2%, 19.8%, and 54.5% for the placebo, titration, 10 mg, 25 mg, and 50 mg obeticholic acid dosing groups, respectively. Event time-to-onset ranged from 15 days to 317 days, with events occurring earlier and more frequently in the higher doses. According to the Clinical reviewer, one subject experienced a treatment-related SAE of jaundice that required hospitalization. This subject’s condition continued to deteriorate, leading to ascites requiring re-hospitalization. Hy’s Law was reported in one placebo subject, one subject in the titration group, and one subject in the 10 mg group.

Elevations of at least 3 times baseline and greater than the upper limit of normal in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been observed (< 1% in obeticholic acid, 2% in placebo). However, such elevations were not associated with hepatic decompensation and were reversible upon discontinuation of obeticholic acid. There are no Boxed Warnings under consideration for the main safety concern of liver adverse events and elevations in liver biochemical tests, which will be included under the Warnings and Precautions section (5.1) of the Prescribing Information.

4 DISCUSSION

Based on the responder analysis developed by DGIEP and evidence from the literature, the clinical reviewer determined that obeticholic acid demonstrated efficacy in the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. The Gastrointestinal Drugs Advisory

Committee concurred that there was sufficient evidence to support the use of surrogate efficacy endpoints and sufficient evidence to support approval of the monotherapy indication. The committee also agreed that there is substantial evidence to support accelerated approval of obeticholic acid for the proposed indication, based on its effect on ALP.

The main safety concern associated with obeticholic acid appears to be the potential for liver adverse events and elevations in liver biochemical tests. However, such elevations were not associated with hepatic decompensation and were reversible upon discontinuation of obeticholic acid. The most likely prescribers of obeticholic acid are hepatologists or gastroenterologists, who should be familiar with the monitoring and clinical management of patients with liver disease, and who inherently understand the risk of hepatic worsening in these conditions, regardless of its association with the disease or treatment.

Many of the AEs seen with obeticholic acid are also associated with the disease state itself. Primary biliary cirrhosis (PBC) is a rare, chronic, progressive autoimmune disease of the liver. It commonly causes debilitating fatigue and pruritis, and may also include osteoporosis, portal hypertension, hyperlipidemia, hepatocellular carcinoma, and autoimmune disease. (b) (4)

Importantly, no cure exists for PBC, so treatment focuses on slowing the progress of the disease and preventing complications. UDCA is the only treatment option currently approved for PBC. However, clinical studies suggest that up to 40% of PBC patients had a suboptimal response to standard doses of UDCA. Without therapeutic intervention, the combined effects of chronic cholestasis and bile duct destruction ultimately lead to liver failure, resulting in liver transplant or death. There is a clear, unmet clinical need for treatment options for patients with PBC with an inadequate response to, or inability to tolerate, UDCA. Lastly, these patients are managed by specialists who would be monitoring for disease progression and other signs of liver injury as part of routine care.

Additionally, as obeticholic acid received orphan product designation and is receiving an accelerated review, (b) (4) is being discussed in order to gain a better understanding of the risks associated with treatment. We will work with DGEIP in the future, as appropriate, should new safety information emerge that might cause us to reconsider the risk-benefit profile of this NME. However, based on the currently available data, DRISK is not recommending a REMS to ensure the benefits of obeticholic acid outweigh the risks. The DGEIP concurs with this recommendation.

5 CONCLUSION AND RECOMMENDATIONS

At this time, risk mitigation measures beyond labeling are not warranted for obeticholic acid for the treatment of PBC. The efficacy of obeticholic acid for the treatment of primary biliary cirrhosis in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA has been demonstrated at a level acceptable to DGEIP, given the rarity of this disorder. The main safety concern associated with the drug appears to be hepatic events and liver function test changes, detected through the routine management of PBC. Based on currently available data, the clinical reviewer concluded that the benefit-risk profile for obeticholic acid is acceptable, and the risks will be communicated to the prescribing community through the labeling.

Should DGIEP have any concerns or questions, or if new safety information becomes available, please contact DRISK.

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/s/

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