var drug_url = "daclatasvir";

Daclatasvir *(Daklinza)*

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Drug Summary

Daclatasvir plus sofosbuvir, with or without ribavirin, is an all-oral option for the treatment of genotype 1 or 3 chronic HCV across a variety of patient populations. Based on the results of the phase 3 ALLY trials, daclatasvir and sofosbuvir is an effective, albeit very expensive option for patients with genotype 1 or 3 HCV, including those with cirrhosis, HIV coinfection, or post-liver transplantation. The use of daclatasvir with sofosbuvir has provided an important ribavirin-free oral option for genotype 3 patients, but the 12 week dual therapy has limited efficacy in cirrhotic genotype 3 patients. Cost, lack of coformulation, and the recommendation of baseline NS5A testing in genotype 1a cirrhotic patients make daclatasvir plus sofosbuvir a less compelling option in this subset of patients.

Class and Mechanism

Daclatasvir was discovered as a first-in-class inhibitor of the non-structural viral protein 5A (NS5A), a phosphoprotein that plays an important role in hepatitis C replication. The exact mechanism by which daclatasvir inhibits the NS5A replication complex is unclear, but it is believed that daclatasvir inhibits viral RNA replication and virion assembly. It may also inhibit phosphorylation of the NS4A, and therefore the formation and activation of the HCV replication complex. Based on *in vitro* data,

daclatasvir has shown activity against HCV genotypes 1 through 6, with EC50 values ranging from picomolar to low nanomolar against wild type HCV.

Manufacturer for United States

Bristol-Myers Squibb

Cost and Medication Access

The wholesale acquisition cost (WAC) cost for a 12-week course of daclatasvir is $63,000. Bristol-Myers Squibb has a program for support and financial help related to medication access; see the web site Patient Support Connect, which has information for both patients and professionals. In addition, patients and physicians may call 844-442-6663 for assistance with access to a range of support services for patients and healthcare professionals.

Adverse Effects

Daclatasvir has been well tolerated in clinical studies to date. When taken in combination with sofosbuvir, the most common adverse events observed in clinical studies were fatigue (14%), headache (14%), nausea (8%), and diarrhea (5%). Daclatasvir can potentially cause serious bradycardia when coadministered with sofosbuvir and amiodarone, particularly if the patient is also taking a beta-blocker. Coadministration of daclatasvir, sofosbuvir and amiodarone is therefore not advised.

Key Drug Interactions

For complete information on daclatasvir-related drug interactions, see the Drug Interactions section in the Daclatasvir (*Daklinza*) Prescribing Information.

Clinical Trials

Filter by Category

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A1444040

This open-label phase 2a trial enrolled 211 subjects from 18 centers in the United States. In part 1 of the trial, investigators initially enrolled 88 treatment-naive patients (44 with genotype 1 and 44 with genotype 2 or 3) to receive the interferon-free regimen of daclatasvir 60 mg once daily with sofosbuvir 400 mg once daily, with or without weight-based ribavirin for 24 weeks; one of the study arms that did not include ribavirin had a 7-day lead-in with sofosbuvir alone. The study later expanded (part 2) to include an additional 123 patients with genotype (GT) 1 randomly assigned to a course of daclatasvir plus sofosbuvir, with or without ribavirin for 12 weeks (for 82 treatment naive patients) or 24 weeks (for 41 who had prior treatment failure with telaprevir or boceprevir-based regimens). The SVR12 was 98% for the 126 treatment-naive GT1 patients and 98% for the 41 prior non-responders; 92% of the 26 GT2 patients and 89% of the 18 GT3 patients achieved an SVR12. Response rates did not vary by genotype 1 subtype, treatment duration, presence of ribavirin, or IL28B status. Both medications were generally well-tolerated; the most common adverse effects were fatigue (37%), headache (29%) and nausea (19%) with similar frequency between the treatment groups with or without ribavirin.

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ALLY-1

This open-label study enrolled 60 patients with advanced cirrhosis (Child-Pugh class distribution 20% A, 53% B and 27% C) and 53 patients with post-liver transplant HCV recurrence; both groups received a 12-week course of daclatasvir plus sofosbuvir plus ribavirin (initial dose 600 mg daily and then adjusted up to 1000 mg/day as tolerated based on hemoglobin levels and renal function). Genotypes 1, 2, 3, 4 and 6 were represented; the majority (76%) were genotype 1 and 15% had genotype 3. The overall SVR12 rates were 83% among advanced cirrhotics, with subanalysis by Child Pugh class showing SVR12 rates of 92% with class A, 94% with class B, and 56% with class C. The SVR12 rate was 94% among post-transplant patients. Among genotype 3 patients, 88% (15 of 17) achieved SVR12. The combination was well tolerated with no serious treatment-related adverse events.

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ALLY-2

In this phase 3, open-label trial, patients with HCV genotype 1 through 4 and HIV confection were treated with daclatasvir and sofosbuvir. Previously untreated patients received either an 8-week or 12-week course, whereas treatment-experienced patients were treated with a 12-week course. Patients with cirrhosis were allowed in the enrollment and comprised 10% and 29% of treatment-naive and experienced groups respectively. Overall, 168 (83%) of 203 patients had genotype 1 infection. Among treatment-naive patients, the SVR12 rates were 97% in the 12-week group and 76% in the 8-week group. For the treatment-experienced patients, all of whom received therapy for 12 weeks, the SVR12 rate was 98%.

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ALLY-3

In this parallel-arm phase 3 trial, investigators assigned 101 treatment-naive genotype 3 patients and 51 treatment-experienced genotype 3 patients to a 12-week all-oral regimen of daclatasvir 60 mg once daily and sofosbuvir 400 mg once daily. Cirrhotic patients comprised 19% and 25% of these groups respectively. An SVR12 was achieved in 90% of treatment-naive and 86% of treatment-experienced GT 3 patients, with viral relapse responsible for nearly all the treatment failures. The presence of cirrhosis was associated with a lower SVR12 rate at 63% overall, regardless of treatment experience. This combination was generally safe and well tolerated with the most frequent adverse events being headache, fatigue and nausea.

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ALLY-3+

In this phase 3, open-label, randomized controlled trial, 50 patients (13 treatment-naive and 37 treatment-experienced) with genotype 3 HCV infection and either stage 3 or 4 fibrosis were randomized 1:1 to sofosbuvir plus daclatasvir plus ribavirin (weight-based dosing) for either 12 or 16 weeks. The overall SVR12 rates were 90% for all patients, and 88% and 92% for patients in the 12-week and 16-week arms respectively. All patients with stage 3 fibrosis achieved SVR, compared with 86% (31 of 36) cirrhotic patients. Treatment experience did not appear to influence SVR12 rates.

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COMMAND-1

In this phase 2b randomized, double-blinded, placebo-controlled trial, investigators enrolled treatment-naive patients with HCV genotype 1 or 4 to receive daclatasvir (or placebo) plus peginterferon and ribavirin. The study design consisted of three main arms: peginterferon and ribavirin plus (a) daclatasvir 20 mg, (b) daclatasvir 60 mg, or (c) placebo. In addition, patients in the daclatasvir groups were stratified at week 12 based on HCV RNA levels at weeks 4 and 10; those patients with a a protocal-defined response (HCV RNA less than lower limit of quantitation at week 4 and undetectable at week 1) then were re-randomized to receive an additional 12 weeks of either daclatasvir or placebo, in combination with peginterferon and ribavirin; patients who did not have a protocol-defined response all received placebo with peginterferon for 12 weeks, followed by an additional 24 weeks of peginterferon and ribavirin. Those enrolled in the original placebo group received peginterferon and ribavirin for 48 weeks, with receipt of placebo during the first 24 weeks. Overall, for genotype 1, the SVR12 rates were 65% in the daclatasvir 20 mg arm (95/147), 90% in the 60 mg arm (88/146), and 36% (26/72) in the placebo arm. Among the patients with genotype 4, the SVR12 rates were were 75% (9/12) in the daclatasvir 20 mg arm, 100% (12/12) in the 60 mg arm, and 50% (3/6) in the placebo arm. For patients with genotype 1 HCV, the regimen of daclatasvir with peginterferon and ribavirin was only moderately effective. For patients with genotype 4 HCV, the findings from the relatively small numbers of patients in this study suggest daclatasvir with peginterferon and ribavirin is effective, particularly with the 60 mg dose of daclatasvir.

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COMMAND-4

This phase 3 trial randomized 124 treatment-naive patients with genotype 4 HCV infection, in a 2:1 ratio, to daclatasvir versus placebo combined with peginterferon and ribavirin. The treatment arm had a response-guided strategy that permitted the cessation of therapy at 24 weeks if patients achieved an undetectable HCV RNA at week 4 and 12; the remainder and the placebo arm received a total of 48 weeks of peginterferon plus ribavirin. Most (79%) of the daclatasvir plus peginterferon plus ribavirin group had extended rapid virologic responses allowing 24-week duration. The SVR12 rates were 82% for the daclatasvir arm versus 43% for the placebo arm. There was no significant differences in the safety profile between the daclatasvir plus peginterferon plus ribavirin arm versus the control arm (peginterferon plus ribavirin).

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HALLMARK-DUAL

This was a phase 3 multi-cohort study that enrolled patients from 18 countries, all with genotype 1b HCV infection. The first cohort included 307 treatment-naive patients who were randomized in a 2:1 ratio to receive either daclatasvir 60 mg once daily plus asunaprevir 100 mg twice daily for 24 weeks versus placebo—a comparison designed to evaluate safety and tolerability. The second and third cohorts of the study assigned 205 treatment-experienced patients with GT1b infection with prior non-response to peginterferon plus ribavirin (partial or null responders) and 235 patients ineligible and/or intolerant to peginterferon to 24 weeks of daclatasvir 60 mg once daily plus asunaprevir 100 mg twice daily. The SVR12 rates were 91% for the treatment-naive cohort, 82% for the non-responder

cohort, and 83% for the ineligible/intolerant cohort. The most common adverse events (occurring in 10% or more in any cohort) were headache, fatigue, nausea and asthenia. There were few discontinuations due to adverse events.

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HALLMARK-QUAD

This open-label phase 3 study that enrolled treatment-experienced patients with genotype 1 or 4 infection who were prior null or partial responders to peginterferon and ribavirin to receive a 24-week course of daclatasvir, asunaprevir, peginterferon, and ribavirin. With this treatment regimen, SVR12 was achieved in 329 (93%) of 354 patients with HCV genotype 1 infection, including SVR12 rates of 153 (87%) of 176 patients with GT 1a and 176 (99%) of 178 with genotype 1b. In addition, SVR12 was achieved in 43 (98%) of 44 patients with HCV genotype 4. Prior response to treatment with peginterferon and ribavirin, cirrhosis, or IL28B status did not significantly influence SVR12 response rates. The most commonly reported adverse events were fatigue, headache, pruritus, asthenia, and influenza-like syndrome without safety or tolerability concerns independent of those historically observed with peginterferon plus ribavirin.

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UNITY-1

In this open-label, randomized, phase3, multi-center, international trial, investigators examined the safety and efficacy of the fixed dose combination of daclatasvir-asunaprevir-beclabuvir for 12 weeks in 415 patients with genotype 1 HCV infection without cirrhosis. The trial included treatment-naïve and treatment-experienced patients; all subjects received 12 weeks of therapy. Overall, 379 (91%) of 415 patients achieved an SVR12, including and SVR 12 in 92% in treatment naïve patients and 89% in treatment-experienced patients. This regimen appeared to be safe and well tolerated in this group of cirrhotic patients. The most common adverse events were headache, fatigue, diarrhea, and nausea.

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UNITY-2

This multi-center, randomized, double-blind, phase 3 study examined the safety and efficacy of the fixed dose combination of daclatasvir-asunaprevir-beclabuvir, with or without ribavirin, in 202 patients with genotype 1 HCV infection and compensated (Child-Pugh class A) cirrhosis. The trial included treatment-naïve and treatment-experienced patients; all subjects received 12 weeks of therapy. A high SVR12 rate was observed in all treatment groups, with a trend toward slightly higher rates in treatment-naive (93 to 98%) compared with treatment-experienced (87 to 93%) patients. Viral relapse was the most common cause of treatment failure and occurred more frequently in the ribavirin-free arms. This FDC appeared to be safe and well tolerated in this group of cirrhotic patients. Adverse events including fatigue, headache and anemia, were more common in the ribavirin-containing arms.

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Figures

Figure 1 Daclatasvir Pills

Daclatasvir is available as a 60 mg tablet (light green in color) and 30 mg tablet (darker green in color).

Photographs courtesy of Bristol-Myers Squibb