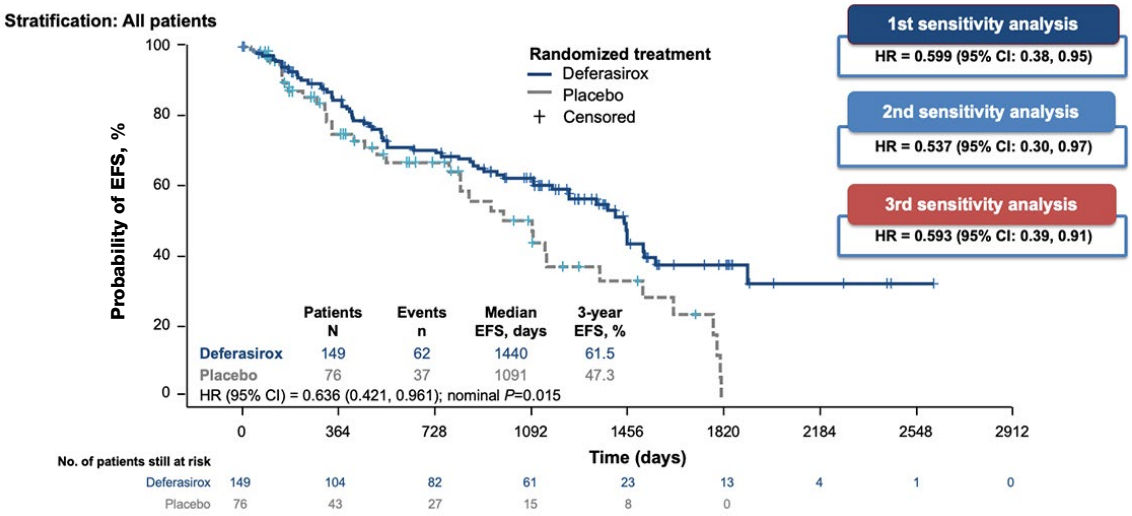
TELESTO study demonstrated the impact of JADENU® (deferasirox) on event-free survival in patients with low- and intermediate- (int-1) risk myelodysplastic syndromes who are experiencing iron overload

Although iron chelation therapy (ICT) has been shown to improve outcomes in lower-risk myelodysplastic syndromes (MDS) patients, the studies were mainly retrospective analyses and registry studies.[1-6] However, considerable debate remained on the clinical utility of ICT in this patient population, and the need for a randomized trial has long been recognized.[7]

The TELESTO study prospectively evaluated event-free survival (EFS) and the safety of ICT with JADENU vs placebo in patients with low/int-1-risk MDS.[8]

The impact of JADENU on Event-Free Survival

Kaplin-Meier plot EFS



TELESTO was a randomized, double-blind, placebo-controlled trial performed in 225 patients with MDS (low/int-1 risk) and transfusional iron overload of which 149 were treated with JADENU and 76 received placebo. The observed hazard ratio of 0.64 (95% CI: 0.42, 0.96) suggests a positive impact of JADENU on EFS (a composite end point defined as death, worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, or progression to acute myeloid leukemia (AML); whichever occurred first).[8]

The primary end point of the TELESTO study was to evaluate EFS (composite end point), defined as the time from randomization to first documented nonfatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML), based on review and confirmation by an independent adjudication committee, or death, whichever occurred first.

Key secondary end points were to assess overall survival, change in serum ferritin level, hematologic improvement in terms of erythroid response (based on International MDS Working Group criteria[9]), change in endocrine function (thyroid and glycemic control), and safety.

Indications

JADENU® (deferasirox) tablets for oral use and JADENU® Sprinkle (deferasirox) granules are indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.

JADENU and JADENU Sprinkle are indicated for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes, and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw), and a serum ferritin >300 mcg/L.

Limitation of Use

The safety and efficacy of JADENU, when administered with other iron chelation therapy, have not been established.

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TELESTO study (continued)

Nonfatal components of the composite primary end point adjudicated by the Endpoint Adjudication Committee

Echocardiographic evidence of worsening cardiac function

- At least 15% absolute decrease in left ventricular ejection fraction (LVEF) from screening value at two consecutive assessments at least 2 weeks apart OR
- LVEF below institutional limits of normal and at least 10% absolute decrease from LVEF screening value at two consecutive assessments at least 2 weeks apart

IMPORTANT SAFETY INFORMATION for JADENU® (deferasirox) tablets and JADENU® Sprinkle (deferasirox) granules

WARNING: RENAL FAILURE, HEPATIC FAILURE, and GASTROINTESTINAL HEMORRHAGE

Renal Failure

- **JADENU can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders**
- **Evaluate baseline renal functions prior to starting or increasing JADENU dosing in all patients. JADENU is contraindicated in adult and pediatric patients with estimated glomerular filtration rate (eGFR) <40 mL/min/1.73 m^2. Measure serum creatinine in duplicate prior to initiation of therapy. Monitor renal function at least monthly. For patients with baseline renal impairment or increased risk of acute renal failure, monitor renal function weekly for the first month, then at least monthly. Reduce the starting dose in patients with preexisting renal disease. During therapy, increase the frequency of monitoring and modify the dose for patients with an increased risk of renal impairment, including use of concomitant nephrotoxic drugs, and pediatric patients with volume depletion or overchelation**

Hepatic Failure

- **JADENU can cause hepatic injury, including hepatic failure and death**
- **Measure serum transaminases and bilirubin in all patients prior to initiating treatment, every 2 weeks during the first month, and at least monthly thereafter**
- **Avoid use of JADENU in patients with severe (Child-Pugh C) hepatic impairment, and reduce the dose in patients with moderate (Child-Pugh B) hepatic impairment**

Gastrointestinal Hemorrhage

- **JADENU can cause gastrointestinal (GI) hemorrhages, which may be fatal, especially in elderly patients who have advanced hematologic malignancies and/or low platelet counts**
- **Monitor patients, and discontinue JADENU for suspected GI ulceration or hemorrhage**

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TELESTO study (continued)

Hospitalization for congestive heart failure

- Overnight stay (ie, change in calendar day) due to congestive heart failure (CHF) confirmed by the presence of the following:
  - At least one of the following symptoms: paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion AND
  - Two or more of the following signs consistent with heart failure: pulmonary edema by radiography, rales, enlarged heart by radiography, peripheral edema, S3 gallop, hepatojugular reflux, neck vein distention, rapid weight gain, elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP AND
  - Treatment with intravenous diuretics, intravenous vasodilators, or intravenous inotropes, mechanical fluid removal (eg, ultrafiltration or dialysis), or insertion of an intra-aortic balloon pump for hemodynamic compromise. Initiation of oral diuretics or intensification (doubling) of the maintenance diuretic dose will also qualify

Liver function impairment

- ALT or AST >2 times the baseline value and >3 times the upper limit of normal (ULN) at two consecutive visits AND
- Total bilirubin >2 mg/dL at two consecutive visits

Liver cirrhosis

- Presence of at least one of the following symptoms/signs: cirrhosis-related ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding due to portal hypertension OR
- Abdominal ultrasonography OR
- Liver biopsy (if clinically indicated)

Acute myloid leukemia (AML) transformation

- Confirmed by bone marrow biopsy

Click here to learn more about the dosing and administration of JADENU

IMPORTANT SAFETY INFORMATION for JADENU® (deferasirox) tablets and JADENU® Sprinkle (deferasirox) granules (continued)

CONTRAINDICATIONS

JADENU is contraindicated in patients with:

- eGFR <40 mL/min/1.73 m^2
- Poor performance status
- Advanced malignancies
- High-risk myelodysplastic syndrome (MDS)
- Platelet counts <50 x 10^9/L
- Known hypersensitivity to deferasirox or any component of JADENU

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WARNINGS AND PRECAUTIONS

Acute Kidney Injury, Including Acute Renal Failure Requiring Dialysis and Renal Tubular Toxicity Including Fanconi Syndrome

JADENU is contraindicated in patients with eGFR <40 mL/min/1.73 m^2. Exercise caution in pediatric patients with eGFR between 40 and 60 mL/min/1.73 m^2. If treatment is needed, use the minimum effective dose and monitor renal function frequently. Individualize dose titration based on improvement in renal injury. For patients with renal impairment (eGFR 40 to 60 mL/min/1.73 m^2), reduce the starting dose by 50%.

JADENU can cause acute kidney injury including renal failure requiring dialysis that has resulted in fatal outcomes. Based on postmarketing experience, most fatalities have occurred in patients with multiple comorbidities and who were in advanced stages of their hematologic disorders. In the clinical trials, adults and pediatric patients treated with deferasirox with no preexisting renal disease experienced dose-dependent mild, nonprogressive increases in serum creatinine and proteinuria. Preexisting renal disease and concomitant use of other nephrotoxic drugs may increase the risk of acute kidney injury in adult and pediatric patients. Acute illnesses associated with volume depletion and overchelation may increase the risk of acute kidney injury in pediatric patients. In pediatric patients, small decreases in eGFR can result in increases in deferasirox exposure, particularly in younger patients with body surface area typical of patients <7 years of age. This can lead to a cycle of worsening renal function and further increases in deferasirox exposure, unless the dose is reduced or interrupted. Renal tubular toxicity, including acquired Fanconi Syndrome, has been reported in patients treated with deferasirox, most commonly in pediatric patients with β-thalassemia and serum ferritin levels <1500 mcg/L.

Evaluate renal glomerular and tubular function before initiating therapy or increasing the dose. Use prediction equations validated for use in adult and pediatric patients to estimate GFR. Obtain serum electrolytes and urinalysis in all patients to evaluate renal tubular function.

Monitor all patients for changes in eGFR and for renal tubular toxicity weekly during the first month after initiation or modification of therapy, and at least monthly thereafter. Dose reduction or interruption may be considered if abnormalities occur in levels of markers of renal tubular function and/or as clinically indicated. Monitor serum ferritin monthly to evaluate for overchelation. Use the minimum dose to establish and maintain a low iron burden. Monitor renal function more frequently in patients with preexisting renal disease or decreased renal function. In pediatric patients, interrupt JADENU during acute illnesses that can cause volume depletion such as vomiting, diarrhea, or prolonged decreased oral intake, and monitor renal function more frequently. Promptly correct fluid deficits to prevent renal injury. Resume therapy as appropriate, based on assessments of renal function, when oral intake and volume status are normal.

Hepatic Toxicity and Failure

JADENU can cause hepatic injury, fatal in some patients. In Study 1, 4 (1.3%) patients discontinued deferasirox because of hepatic toxicity (drug-induced hepatitis in 2 patients and increased serum transaminases in 2 additional patients). Hepatic toxicity appears to be more common in patients >55 years of age. Hepatic failure was more common in patients with significant comorbidities, including liver cirrhosis and multiorgan failure.

Acute liver injury and failure, including fatal outcomes, have occurred in pediatric patients treated with deferasirox. Liver failure occurred in association with acute kidney injury in pediatric patients at risk for overchelation during a volume-depleting event. Interrupt JADENU therapy when acute liver injury, or acute kidney injury, is suspected and during volume depletion. Monitor liver and renal function more frequently in pediatric patients who are receiving JADENU in the 14 to 28 mg/kg/day range, and when iron burden is approaching normal. Use the minimum effective dose to achieve and maintain a low iron burden.

Measure aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and bilirubin in all patients before the initiation of treatment and every 2 weeks during the first month, and at least monthly thereafter. Consider dose modifications or interruption of treatment for severe or persistent elevations.

Avoid the use of JADENU in patients with severe (Child-Pugh C) hepatic impairment. Reduce the starting dose in patients with moderate (Child-Pugh B) hepatic impairment. Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, may be at higher risk for hepatic toxicity.

Gastrointestinal Ulceration, Hemorrhage, and Perforation

Gastrointestinal (GI) hemorrhage, including deaths, has been reported, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Nonfatal upper GI irritation, ulceration, and hemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. Monitor for signs and symptoms of GI ulceration and hemorrhage during JADENU therapy, and promptly initiate additional evaluation and treatment if a serious GI adverse reaction is suspected. The risk of GI hemorrhage may be increased when administering JADENU in combination with drugs that have ulcerogenic or hemorrhagic potential such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants. There have been reports of ulcers complicated with GI perforation (including fatal outcome).

Bone Marrow Suppression

Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events, have been reported in patients treated with deferasirox. Preexisting hematologic disorders may increase this risk. Monitor blood counts in all patients. Interrupt treatment with JADENU in patients who develop cytopenias until the cause of the cytopenia has been determined. JADENU is contraindicated in patients with platelet counts <50 x 10^9/L.

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Age-Related Risk of Toxicity

Elderly Patients: JADENU has been associated with serious and fatal adverse reactions in the postmarketing setting among adults, predominantly in elderly patients. Monitor elderly patients treated with JADENU more frequently for toxicity.

Pediatric Patients: JADENU has been associated with serious and fatal adverse reactions in pediatric patients in the postmarketing setting. These events were frequently associated with volume depletion or with continued EXJADE® (deferasirox) tablets for oral suspension doses in the 20 to 40 mg/kg/day range, equivalent to 14-28 mg/kg/day JADENU, when body iron burden was approaching or was in the normal range. Interrupt JADENU in patients with volume depletion, and resume JADENU when renal function and fluid volume have normalized. Monitor liver and renal function more frequently during volume depletion, and in patients receiving JADENU in the 14 to 28 mg/kg/day range, when iron burden is approaching the normal range. Use the minimum effective dose to achieve and maintain a low iron burden.

Overchelation

For patients with transfusional iron overload, measure serum ferritin monthly to assess the patient's response to therapy and minimize the risk of overchelation. An analysis of pediatric patients treated with EXJADE in pooled clinical trials (n=158) found a higher rate of renal adverse reactions among patients receiving doses >25 mg/kg/day, equivalent to 17.5 mg/kg/day JADENU, while their serum ferritin values were <1000 mcg/L. Consider dose reduction or closer monitoring of renal and hepatic function, and serum ferritin levels during these periods. Use the minimum effective dose to maintain a low iron burden.

If the serum ferritin is <1000 mcg/L at 2 consecutive visits, consider dose reduction, especially if the JADENU dose is >17.5 mg/kg/day *[see Adverse Reactions (6.1)]*. If the serum ferritin is <500 mcg/L, interrupt therapy with JADENU and continue monthly monitoring. Evaluate the need for ongoing chelation for patients whose conditions do not require regular blood transfusions. Use the minimum effective dose to maintain iron burden in the target range. Continued administration of JADENU in the 14 to 28 mg/kg/day range, when the body iron burden is approaching or is within the normal range, can result in life-threatening adverse events.

For patients with NTDT, measure LIC by liver biopsy or by using an FDA-cleared or approved method for monitoring patients receiving deferasirox therapy every 6 months on treatment. Interrupt JADENU administration when the LIC is less than 3 mg Fe/g dw. Measure serum ferritin monthly, and if the serum ferritin falls below 300 mcg/L, interrupt JADENU and obtain a confirmatory LIC.

Hypersensitivity

JADENU may cause serious hypersensitivity reactions (such as anaphylaxis and angioedema), with the onset of the reaction usually occurring within the first month of treatment. If reactions are severe, discontinue JADENU and institute appropriate medical intervention. JADENU is contraindicated in patients with known hypersensitivity to deferasirox products and should not be reintroduced in patients who have experienced previous hypersensitivity reactions on deferasirox products due to the risk of anaphylactic shock.

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Severe Skin Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) which could be life-threatening or fatal, have been reported during deferasirox therapy. Cases of erythema multiforme have been observed. Advise patients of the signs and symptoms of severe skin reactions, and closely monitor. If any severe skin reactions are suspected, discontinue JADENU immediately and do not reintroduce JADENU therapy.

Skin Rash

Rashes may occur during JADENU treatment. For rashes of mild to moderate severity, JADENU may be continued without dose adjustment since the rash often resolves spontaneously. In severe cases, interrupt treatment with JADENU. Reintroduction at a lower dose, with escalation, may be considered after resolution of the rash.

Auditory and Ocular Abnormalities

Auditory disturbances (high-frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) were reported at a frequency of <1% with deferasirox therapy in the clinical studies. The frequency of auditory adverse reactions, irrespective of causality, was increased among pediatric patients who received EXJADE doses >25 mg/kg/day, equivalent to 17.5 mg/kg/day JADENU, when serum ferritin was <1000 mcg/L.

Perform auditory and ophthalmic testing (including slit-lamp examinations and dilated fundoscopy) before starting JADENU treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, monitor more frequently. Consider dose reduction or interruption.

ADVERSE REACTIONS

JADENU was evaluated in healthy subjects, and no clinical data exist for patients treated with JADENU tablets or JADENU Sprinkle granules. JADENU contains the same active ingredient, deferasirox, as EXJADE. For patients with transfusional iron overload, the most common adverse reactions occurring in >5% of patients treated with deferasirox who have β-thalassemia, sickle cell disease, and MDS were abdominal pain, nausea, vomiting, diarrhea, skin rashes, and increases in serum creatinine. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related. In patients with NTDT syndromes, the most frequently occurring (>5%) adverse reactions were diarrhea, rash, and nausea.

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References: 1. Delforge M, Selleslag D, Beguin Y, Triffet A, et al. Adequate iron chelation therapy for at least six months improves survival in transfusion-dependent patients with lower risk myelodysplastic syndromes. *Leuk Res*. 2014;38:557–563. **2.** Leitch HA, Leger CS, Goodman TA, et al. Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. *Clin Leuk*. 2008;2:205–211. **3.** Lyons RM, Marek BJ, Paley C, Esposito J, et al. Relation between chelation and clinical outcomes in lower-risk patients with myelodysplastic syndromes: Registry analysis at 5 years. *Leuk Res*. 2017;56: 88–95. **4.** Neukirchen J, Fox F, Kündgen A, et al. Improved survival in MDS patients receiving iron chelation therapy – a matched pair analysis of 188 patients from the Düsseldorf MDS registry. *Leuk Res*. 2012;36:1067–1070. **5**. Remacha AF, Arrizabalaga B, Villegas A, et al. Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications. *Ann Hematol*. 2015;94(5):779–787. **6.** Rose C, Brechignac S, Vassilief D, et al. Does iron chelation therapy improve survival in regularly transfused lower risk MDS patients? A multicenter study by GFM (Groupe Francophone des Myélodysplasies). *Leuk Res*. 2010;34(7):864–870. **7**. Meerpohl JJ, Schell LK, Rücker G, et al. Deferasirox for managing transfusional iron overload in people with sickle cell disease. *Cochrane Database Syst Rev*. 2014.doi:10.1002/14651858.CD007477.pub3. **8**. Jadenu [prescribing information]. Novartis Pharmaceuticals Corp, East Hanover, NJ. 2020. **9.** Cheson BD, Greenberg PL, Bennett JM, Lowenberg, et al. Clincial application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108:419–425.

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