**CLINICAL STUDY PROTOCOL**

# A Multi-Center, Open-Label, Two-Period Cross-Over, Patient-Pilot Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Iron Chelating Activity of DST-0509 (Deferasirox) Tablets in Thalassemia Patients with Inadequate Response to Standard Chelation Therapy

**Investigational Product:** DST-0509 (Deferasirox) Tablets

**IND No.:** 132841

**Phase:** Phase 2

**Protocol Number:** DST-0509-201

**Document Dates**

**Original Protocol:** 01 June 2018

**Sponsor:**
DisperSol Technologies, LLC
111 W. Cooperative Way
Building 3, Suite 300
Georgetown, TX 78626, USA

**Telephone:** 512.696.4740
**Fax:** 512.696.4651
**Email:** justin.keen@dispersoltech.com

## Confidentiality Statement

**PRINCIPAL INVESTIGATOR SIGNATURE SHEET**

**A Multi-Center, Open-Label, Two-Period Cross-Over, Patient-Pilot Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Iron Chelating Activity of DST-0509 (Deferasirox) Tablets in Thalassemia Patients with Inadequate Response to Standard Chelation Therapy**

**Protocol Number:** DST-0509-201

By my signature below, I attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). I will not initiate this study without approval from the appropriate Institutional Review Board (IRB) and I understand that any changes in the protocol must be approved in writing by the DisperSol Technologies, LLC and the IRB before they can be implemented, except where necessary to eliminate immediate hazards to the patient.

**Approval Signature**

Principal Investigator: _____ Date _____
Signature

Printed Name:

Name of Facility:

Address:

City, State, Zip Code:

Phone Number:

Fax Number:

Email Address:

## SPONSOR SIGNATURE SHEET

**A Multi-Center, Open-Label, Two-Period Cross-Over, Patient-Pilot Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Iron Chelating Activity of DST-0509 (Deferasirox) Tablets in Thalassemia Patients with Inadequate Response to Standard Chelation Therapy**

**Protocol Number:** DST-0509-201

By my signature below, I approve this protocol (including appendices).

**Approval Signatures**

DisperSol Technologies, LLC: _____ Date 4 Jun 18

Signature
Justin M. Keen, PhD
Vice President, Operations
DisperSol Technologies, LLC
111 W. Cooperative Way
Building 3, Suite 300
Georgetown, TX 78626
Telephone: 512.686.4740
Fax: 512.686.4651
Email: justin.keen@dispersoltech.com

Medical Affairs: _____ Date 04 Jun 2018

Signature
Harish P. Dave, MD, MBA
Chief Medical Officer
Accelovance, Inc.
2275 Research Blvd., #700
Rockville, MD 20850
Telephone: 240.238.4919
Cell: 301.275.4356
Fax: 240.238.4901
hdave@accelovance.com

**Approval Signatures**

Biostatistician: Mark J. Jaros Date 01 JUN 2018

Signature

Mark J. Jaros, PhD
Consultant, Biostatistics and Programming
Summit Analytical, LLC
8354 Northfield Blvd
Bldg. G, Suite 3700
Denver, CO 80238
Office: (303) 993-6994
Cell: (970) 215-2741
Email: mjaros@summitanalytical.com

## PROTOCOL SYNOPSIS

**TITLE:**
A Multi-Center, Open-Label, Two-Period Cross-Over, Patient-Pilot Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Iron Chelating Activity of DST-0509 (Deferasirox) Tablets in Thalassemia Patients with Inadequate Response to Standard Chelation Therapy

**PROTOCOL NUMBER:**
DST-0509-201

| **INVESTIGATIONAL PRODUCT:** | **US IND No.** |
|---|---|
| DST-0509 (Deferasirox) Tablets | 132841 |

**PHASE:**
2

**PROPOSED INDICATIONS:**

- Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older when current chronic oral chelation therapy with other deferasirox products is inadequate.
- Treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes when current chronic oral chelation therapy with other deferasirox products is inadequate.

**PROPOSED RATIONALE:**

The efficacy of DST-0509 (deferasirox) tablets will be demonstrated in patients who were inadequately controlled on high doses of Jadenu® ("Jadenu") or Exjade® ("Exjade"). Patients are defined as inadequate responders if their liver iron (Fe) concentration (LIC) is at least 5 mg Fe per gram of dry weight (Fe/g dw) and serum ferritin is >800 mcg/L, despite compliance with chronic chelation treatment.

**OBJECTIVES:**

**Primary objectives:**

- This patient-pilot study will assess the safety, overall tolerability, and preliminary evidence DST-0509 tablets iron chelating activity compared to Jadenu or Exjade in patients with transfusion-dependent beta thalassemia (TDT), major or intermedia, or non-TDT (NTDT) patients with inadequate response to available deferasirox chelation therapy, defined as an LIC of at least 5 mg Fe/g dw and a serum ferritin >800 mcg/L.

**Secondary objectives:**

- To determine the single and multiple dose pharmacokinetic (PK) profile of total deferasirox (iron-bound and unbound) plasma concentrations during DST-0509 and Jadenu or Exjade treatments in fed TDT and NTDT patients.

**POPULATION:**

Adult patients (≥18 years) with TDT or NTDT and iron overload currently receiving iron chelation therapy (ICT) with Jadenu or Exjade and demonstrating inadequate response. Inadequate response is defined as serum ferritin levels that are persistently >800 mcg/L, determined by 2 separate assessments over the previous 2-4 weeks and not showing a decreasing trend over these weeks.

Patients should also have an LIC of >5 mg Fe/g dw measured by magnetic resonance imaging (MRI) in the 52 weeks prior to study entry and are receiving the maximal dose of oral commercial deferasirox (DFX), Jadenu: 28 mg/kg or Exjade: 40 mg/kg. Patients should be medication compliant in the opinion of the Investigator and willing to comply with treatment in the study.

**STUDY DESIGN AND DURATION:**

This is a multi-center, open-label, two-period cross-over, patient-pilot study comparing DST-0509 to patient's prior ICT (Exjade or Jadenu) administered orally once daily (QD) for 28-days in each period, with a 7-day washout before the first treatment period, between treatment periods, and at the end of the study before patients recommence their prescription regimens (see Table 6-1). Patients will be randomized to one of two treatment sequences: DST-0509→Exjade/Jadenu or Exjade/Jadenu→DST-0509 (with subjects who were taking Exjade prior to study start receiving Exjade and those taking Jadenu at study start receiving Jadenu). This study is designed to assess the safety, tolerability, evidence of iron chelating activity, and PK profile of DST-0509 compared to Jadenu or Exjade in inadequately responding patients. Inadequate response to standard chelation therapy is defined based on the medical literature [6,7].

Up to 36 patients will be randomized 1:1 into one of two treatment sequences (study arms), of which up to 100% may be on Jadenu or Exjade at study entry, or a mix of the two. The planned randomization will assign up to 18 patients in each of two sequences: Sequence A: DST-0509 crossed to Exjade or Jadenu; Sequence B: Jadenu or Exjade crossed to DST-0509. The comparator treatment will be the patient's current chelation treatment. At the end of the study, patients previously on Jadenu or Exjade will revert to receiving their pre-study medication and dose following a 7-day washout period. A sufficient number of patients will be enrolled so there will be no need to replace study drop-outs. Study duration is approximately 14 weeks for each patient. A Study Flow Diagram is presented after this Synopsis (see Figure 3-1).

**INCLUSION CRITERIA:**

The following are the main inclusion criteria:

1. Written informed consent obtained prior to any study-related procedure being performed;
2. Patients at least 18 years of age or older at the time of consent;
3. Patient with TDT or NTDT syndromes and iron overload currently receiving iron chelation therapy with Jadenu or Exjade and demonstrating inadequate response assessed with serum ferritin and LIC;
4. Stable dosing with Jadenu or Exjade for >3 months prior to screening and receiving the maximal dose (Jadenu: 28 mg/kg or Exjade: 40 mg/kg);
5. Serum ferritin levels that are persistently >800 mcg/L determined by 2 separate assessments during screening over the previous 2-4 weeks prior to study treatment and not showing a decreasing trend over these weeks;
6. An LIC of >5 mg Fe/g dw measured by MRI in the 52 weeks prior to study entry;
7. Compliant with chelation therapy in the 3 months prior to enrollment as assessed by the Investigator:
   - Satisfaction with Iron Chelation Therapy (SICT) Quality of Life (QoL) composite score $\geq$60%, or determined by investigator that at least 75% of medication prescribed on a regular basis was taken (Investigator enquiry into patient prescription refill records, preferably 3 months if available); and
   - Willing to comply with chelation therapy for the duration of the study;
8. Agree not to use other anti-chelating agents concurrently;
9. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1;
10. Women of childbearing potential (WOCBP) must use an adequate method of birth control (double barrier, e.g. hormonal control and barrier contraception) at least 28 days prior to the first administration of the study drug, during the study and for at least 30 days after the last dose of the study drug. (Section 7.5 for details);
11. Male patients whose partners are WOCBP must use an adequate method of birth control (double barrier control) at least 28 days prior to the first administration of the study drug, during the study and for at least 30 days after the last dose of the study drug; and
12. Patient is willing and able to comply with all protocol required visits and assessments.

**EXCLUSION CRITERIA:**

The following are the main exclusion criteria:

1. Patients with life expectancy less than 6 months;

2. Females of childbearing potential not on an adequate method of birth control, or who are pregnant or lactating;
3. History of non-compliance with chelation therapy (determined by the investigator, persistently taking less than 75% of prescribed dose in the 3 months prior to enrollment, or as determined by the Investigator based on medical history, SICT QoL overall score <60% or score in any SICT domain <50%).
4. Screening blood counts of the following:
    a. Absolute neutrophil count < 1500/µL
    b. Platelets < 100,000/µL
    c. Hemoglobin < 8 g/dL; transfusion support is permitted;
5. Screening chemistry values of the following:
    a. Alanine aminotransferase (ALT) and aspartate transaminase (AST) > 2.5 × upper limit of the normal reference range (ULN)
    b. Total bilirubin > 2 × ULN
    c. Creatinine > 1.5 × ULN
    d. Urine protein/creatinine ratio (UPCR) >0.5 mg/mg
    e. Albumin < 2.8 g/dL;
6. History of congestive heart failure New York Heart Association (NYHA) class III or IV or uncontrolled hypertension at screening;
7. History of other malignancy within the previous 3 years, except basal cell or squamous cell carcinoma, or non-muscle invasive bladder cancer;
8. In the opinion of the Investigator, evidence of major inflammatory disease that would affect ferritin levels within 14 days prior to the start of study medication;
9. Major surgery within 30 days prior to the start of study medication;
10. Serious persistent infection within 14 days prior to the start of study medication;
11. Serious concurrent medical condition including central nervous system (CNS) disorders;
12. Requires concomitant treatment with systemic corticosteroids, or any other immunosuppressive agents, or has used such treatment in the past 10 days before study entry (use of prednisone or equivalent <10 mg/day orally or use of inhaled corticosteroids or topical steroids is permitted).
13. Previous history of difficulty swallowing oral medications;
14. Any condition that, in the opinion of the Investigator, would impair the patient's ability to comply with study procedures or study medication; or
15. Concomitant treatment with medications described in 7.4 "Prohibited Medications".

**PATIENT WITHDRAWAL FROM STUDY:**

Patients may be removed from the study for reasons including the following:

1. Significant protocol violation on the part of the Investigator or patient;
2. Significant noncompliance on the part of the patient as determined by the Investigator in consultation with the Medical Monitor;
3. Patient withdraws consent;
4. During the study, patient has the need for medications, supplements, ingredients and herbal therapies that are excluded (see Section 7.4, "Prohibited Medications" for examples in each category; this list is not all inclusive);
5. Unacceptable toxicity based on laboratory or other clinical findings, based on Principal Investigator (PI) opinion;
6. Occurrence of any adverse event (AE) or condition that could, in the Investigator's opinion, interfere with the evaluation of the treatment effect or put the patient at undue risk;
7. Pregnancy; or

8. Other criteria, at the Investigator's discretion in consultation with the Medical Monitor.

**DOSAGE FORMS AND ROUTE OF ADMINISTRATION:**

DST-0509 will be supplied in 360 mg, 180 mg and 90 mg tablets. Jadenu is commercially available as tablets and Exjade as tablets for oral suspension and will be provided by the patient with their ongoing prescription. Dosing will be at equivalent (mg for mg) doses of DST-0509 or Jadenu. If converting from Exjade, the dose will be scaled for each treatment by 28 mg/40 mg (treatment/Exjade).

This is an open-label crossover study. Patients will receive Exjade or Jadenu at their previous stable dose. DST-0509 is taken with food, Jadenu is taken with or without a light meal, and Exjade is recommended to be taken without food. However, either Jadenu or Exjade can be administered according to the patient's previous regimen.

**OUTCOME VARIABLES:**

The primary outcome of the study will be the safety, overall tolerability, and preliminary evidence of DST-0509 iron chelating activity compared to Jadenu or Exjade.

**Iron chelation**

Serum ferritin will be assessed at screening (Visits 1 and 2) and on Days 1, 28, 36 and 63. Change from baseline in each treatment period will be assessed as the main efficacy variable for serum ferritin.

Efficacy responders, i.e., the proportion of patients who achieve serum ferritin <800 mcg/L, will be evaluated.

**Pharmacokinetics**

Trough deferasirox levels will be collected in the Screening period at approximately -4 and -2 weeks. Blood samples for PK analysis will be collected predose (-0.5 hour for trough level) and at 1, 2, 4, and 8 hours post dose on Days 1, 7, 28, 36, 42 and 63. The PK parameters of DST-0509 and Jadenu or Exjade will be derived from the concentration time data. The allowed sampling "window" is ±15 min for the 1 and 2 hour time points, and ±30 min for the 4 hour time point. For the 8 hour time point, the allowable window is ± 1 hour.

The goal of the PK analyses will be to characterize the PK of the inadequate responder population on their current DFX therapy at the end of 4 weeks compared to 4 weeks of therapy with DST-0509. The hypothesis is that a significant proportion of inadequate responders will have low exposures on current therapy compared to exposure with DST-0509.

**Exploratory Pharmacogenomics**

A blood sample will be taken at Visit 2 to collect germline DNA to allow for later exploratory sub-analyses of genotype vs exposures.

**SAFETY AND TOLERABILITY ASSESSMENTS:**

*Exposure and safety parameters*

At each clinic visit, treatment exposure will be estimated with compliance rates based on patient diary cards and pill counts, and tolerability will be assessed by general enquiry and specific iron chelation tolerability questions as well as by patient diaries concerning tolerability. Study patients will receive a diary to record gastrointestinal (GI) adverse events (AEs) of special interest (AESI) during the course of the study. Patients will be given the Bristol Stool Chart with diary and instructed on its use. All AE's will be monitored throughout the trial after the first dose.

Patient safety will be monitored per clinical standard of care including routine laboratory monitoring. This will include monthly CBC, chemistry panel, and urinalysis assessments. Urine will be collected to measure protein: creatinine ratio and serum CRP will be assessed.

*Compliance*

Patients will be responsible for supplying their own Jadenu or Exjade during the study. Pill counts will be performed at each visit in order to characterize patient compliance (calculated as % doses taken per protocol).

Additional measures of compliance will include Investigator enquiry into patient prescription refill records if available, satisfaction with iron chelation therapy (SICT) questionnaire [ref 8; Appendix D] and use of patient diaries.

*Dose reductions*

Dose reductions/interruptions of DST-0509 and Jadenu/Exjade are discouraged. However, in the event of a severe or higher AE lasting for 7 or more days, the PI, at their discretion, may reduce the dose by 25-33% or interrupt dosing. The maximum interruption allowable is seven days. Dose re-escalation is not permitted. When AE resolves or is mild, the patient may restart study from last dose visit per PI or Medical Monitor (MM) discretion.

*Dose suspension*

Dosing with either treatment should be suspended in event of significant cytopenia (platelet count <50,000/ml or ANC <1,500/ml). If cytopenia has not recovered to Grade 1 or less after suspension of treatment for 7 days, the patient will be withdrawn from the study.

**STATISTICAL ANALYSES:**

A comprehensive statistical analysis plan (SAP) will be written and approved prior to database lock for this study that describes the final analyses to be completed for safety, efficacy, and pharmacokinetic endpoints.

Data collected in this study will be presented using summary tables, figures, and patient data listings. Summary tables will present data by treatment group and by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the number of patients (n), the mean, median, standard deviation, minimum and maximum, and coefficient of variations (%CV). Categorical variables will be summarized by frequencies and percentages. Confidence intervals will be provided where appropriate for derived endpoints. Figures will be used to support the presentation of certain data. Sensitivity analyses may be performed to examine the effect of missing data.

All confidence intervals (CIs), statistical tests, and resulting p values will be reported as 2-sided. Significance will be assessed at $\alpha = 0.05$ level and the significance level will not be adjusted for multiple comparisons in the exploratory efficacy endpoint analyses.

Four analysis populations are defined for this study as follows:

- Safety Population: All patients who received the planned study medication. The Safety Population will be used to assess safety and tolerability. Patients in the Safety Population will be analyzed with actual treatment.
- Intent-to-Treat (ITT) Population: The ITT population comprises all patients who received at least 1 dose of study medication and had at least 1 evaluable efficacy measurement after the first dose of DST-0509. Patients in the ITT population will be analyzed as randomized to treatment sequence.
- Per Protocol (PP) Population: The PP population comprises all randomized patients who completed the study according to all protocol requirements.
- PK Population: All patients who receive planned study medication and have sufficient post Baseline plasma samples obtained and assayed for drug concentration levels to allow for computation of PK parameters will be included in the PK Population. Patients will be included in the PK Population after review of the plasma concentration data. The rationale for inclusion or exclusion in the PK Population will be documented and listed.

Planned efficacy analyses will include examination of changes in iron chelation. Analysis by TDT and NTDT stratification will depend on recruitment status. Descriptive summaries of serum ferritin at each time point in each study period will be completed. Change from baseline in serum ferritin will be assessed with a mixed model for repeated measures (MMRM) to assess changes within each treatment period and time. Categorical summaries will be presented for efficacy responders, i.e., the proportion of patients who achieve serum ferritin <800 mcg/L.

Pharmacokinetic parameters will be derived using model-independent methods (non-compartmental analysis: NCA) as implemented in Phoenix 7, WinNonlin (version 7.1) and will be based on DST-0509 and Jadenu plasma concentrations from patients in the PK Population.

Pharmacokinetic parameter estimates will be estimated for each treatment. Both single dose PK parameter estimates (following the first dose in a treatment sequence) and multiple dose pharmacokinetic parameter estimates will be completed to characterize DST-0509 and Jadenu. Other pharmacokinetic parameters may be defined as data are explored in the Phase 2 study.

Safety analyses will be performed on the Safety Population. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 20.1). Incidences (number and percent) of Treatment Emergent AEs (TEAEs), those events that started after dosing or worsened in severity after dosing, will be presented by treatment group. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication. Laboratory data and vital sign information will be summarized by treatment group as summary statistics for value and change from Baseline at each individual time point. Summary statistics will include n, mean, median, standard deviation (SD), minimum, and maximum. Details for the additional safety endpoints will be provided in the SAP.

**SAMPLE SIZE DETERMINATION:**

The primary endpoints in this patient-pilot study are safety and tolerability with special interest in gastrointestinal AEs such as diarrhea. Evidence of DST-0509 iron chelating activity is also of special interest but is considered preliminary for this study and will not be considered in sample size estimations. If the underlying true probability of a diarrhea AE is 12% (Jadenu label 2015[2]), then there will be a 98% probability of observing at least one event in this study with a total sample size of 30 subjects. The table below presents a range of diarrhea AE rates provided from Jadenu clinical trials and the probability of observing at least 1 or 2 for our planned sample size. Given the same adverse event rate for diarrhea, there will be an 89% probability of observing at least two events in this study.

| Underlying | Probability of Observing at Least 1 Diarrhea AE | | |
|---|---|---|---|
| Event Rate | N=24 | N=30 | N=36 |
| 9% | 0.90 | 0.94 | 0.97 |
| 12% | 0.95 | 0.98 | 0.99 |
| 21% | >0.99 | >0.99 | >0.99 |
| Underlying | Probability of Observing at Least 2 Diarrhea Events | | |
| Event Rate | N=24 | N=30 | N=36 |
| 9% | 0.65 | 0.77 | 0.85 |
| 12% | 0.80 | 0.89 | 0.94 |
| 21% | 0.97 | 0.99 | >0.99 |

It is expected that most reasonably common AEs will be observed in this small study and will provide information for future studies.

**SITES:**

To be determined

**SPONSOR:**

DisperSol Technologies, LLC

## STUDY FLOW DIAGRAM

**Treatment A (28 days) = DST-0509**
**Treatment B (28 days) = Jadenu/Exjade[1]**


| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | | 3 | 4 | 5 | 6 | | 7 | 8 | 9 | 10 | 11 |
| Day | -28 to -15 | -14 to -8 | -7 to -1 | 1 | 7 | 14 | 28 | 29-35 | 36 | 42 | 49 | 63 | 70 |
| **Period** | **Screening** | **Eligibility** | **Washout[2] (7-day)** | **Period 1** | | | | **Washout (7-day)** | **Period 2** | | | | **Washout (7-day)[3]** |

*Up to 36 patients are planned.

1. Subjects taking Exjade prior to study start will receive Exjade (treatment B) in the assigned Period 1 or cross-over Period 2. Those patients taking Jadenu prior to study start will receive Jadenu (treatment B) in the assigned Period 1 or cross-over Period 2. Dosing will be at equivalent (mg for mg) doses of DST-0509 for Jadenu. If crossing over from Exjade to DST-0509, or vice versa, the dose will be scaled to 28 mg/40 mg (DST-0509/Exjade).
2. For all patients entering the trial, a 7-day washout is required.
3. Visit 11 will be a phone call from study staff to the patient. The phone call will confirm that the patient has conducted the 7-day washout period before recommencing prior iron chelation therapy. AEs and concomitant medications will also be collected by phone on Visit 11.

## SCHEDULE OF PROCEDURES

| Period | Screening | Eligibility | 7-day Washout[1] | Period 1 Treatment (DST-0509 or Jadenu/Exjade) | | | | 7-day Washout | Period 2 Treatment (Jadenu/Exjade or DST-0509) | | | | 7-day Washout[11] and Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | | **3** | **4** | **5** | **6** | | **7** | **8** | **9** | **10/ET** | **11** |
| **Day** | -28 to -15 | -14 to -8 | -7 to -1 | 1 | 7 | 14 | 28 | 29-35 | 36 | 42 | 49 | 63 | 70 |
| **Window (days)** | | | | | ±1 | ±1 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±1 |
| Informed Consent | X | | | | | | | | | | | | |
| Medical and Surgical History | X | | | | | | | | | | | | |
| Prior Medications | X | | | | | | | | | | | | |
| Body weight and Height | X | | | | | | | | | | | | |
| Washout Instructions[2] | | X | | | | | X | | | | | X | |
| Eligibility Review | X | X | | X | | | | | | | | | |
| Randomization | | | | X | | | | | | | | | |
| Dispense Investigational Product[3] | | | | X | | | | | X | | | | |
| Safety | | | | | | | | | | | | | |
| Vital signs[4] | X | | | X | | X | X | | X | | X | X | |
| Physical Examination[5] | X | | | X | | X | X | | X | | X | X | |
| Electrocardiogram (ECG) | | | | X | | | | | X | | | | |
| Chemistry, Hematology (CBC) and Urinalysis[6] | X | | | X | | X | X | | X | | X | X | |
| Serum CRP | X | X | | X | | | X | | X | | | X | |
| Urine Pregnancy Test[7] | X | | | | | | | | | | | | |
| Urine for Protein:Creatinine | X | | | X | | X | X | | X | | X | X | |
| ECOG PS (Appendix C) | X | | | X | | | X | | X | | | X | |
| Adverse Events | | | | X | X | X | X | | X | X | X | X | X |
| Concomitant Medications | X | | | X | X | X | X | | X | X | X | X | X |
| Dispense gastrointestinal AESI diary and Bristol Stool Chart | X | | | X | | | | | X | | | | |

| Period | Screening | Eligibility | 7-day Washout[1] | Period 1 Treatment (DST-0509 or Jadenu/Exjade) | | | | 7-day Washout | Period 2 Treatment (Jadenu/Exjade or DST-0509) | | | | 7-day Washout[11] and Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | | **3** | **4** | **5** | **6** | | **7** | **8** | **9** | **10/ET** | **11** |
| **Day** | -28 to -15 | -14 to -8 | -7 to -1 | 1 | 7 | 14 | 28 | 29-35 | 36 | 42 | 49 | 63 | 70 |
| **Window (days)** | | | | | ±1 | ±1 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±1 |
| and diary | | | | | | | | | | | | | |
| Review gastrointestinal AESI diary | | X | | X | X | X | X | | X | X | X | X | |
| Review Bristol Stool Chart diary | | X | | X | X | X | X | | X | X | X | X | |
| Collect gastrointestinal AESI diary | | | | X | | | X | | | | | X | |
| Collect Bristol Stool Chart diary | | | | X | | | X | | | | | X | |
| Treatment Compliance[8] | | | | X | X | X | X | | X | X | X | X | |
| Administer SICT questionnaire[8] | | X | | | | | | | | | | | |
| Efficacy Assessments | | | | | | | | | | | | | |
| Ferritin monitoring | X | X | | X | | | X | | X | | | X | |
| Pharmacogenetic monitoring | | X | | | | | | | | | | | |
| Pharmacokinetics | | | | | | | | | | | | | |
| Trough sampling[9] | X | X | | | | | | | | | | | |
| Pharmacokinetic sampling[9] | | | | X | X | | X | | X | X | | X | |
| Next Visit Instructions[10] | | | | X | X | X | X | | X | X | X | | |

Abbreviations AESI = adverse events of special interest; CBC = complete blood count; CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group Performance Status; SICT = satisfaction with iron chelating therapy; ET = Early Termination.

1. Instructions for washout provided at Eligibility visit (Visit 2).
2. For patients on iron chelation therapy prior to randomization, and for washout for all patients between periods and after last treatment.
3. DST-0509 will be supplied in 360 mg, 180 mg and 90 mg tablets. Patients will receive Jadenu or Exjade at their previous stable dose. All treatments will be administered daily orally with food in the morning. Dosing will be at equivalent (mg for mg) doses of DST-0509 for Jadenu. If crossing over from Exjade to DST-0509, or vice versa, the dose will be scaled to 28 mg/40 mg (DST-0509/Exjade).
4. Vital signs will include the measurement of blood pressure, heart rate, respiratory rate and body temperature.
5. A full physical examination will be performed at Screening, Day 28 and Day 63. A brief physical examination will be performed on Day 1, 14, 36, and 49.

6. Chemistry, Hematology (CBC) and Urinalysis measurements are described in Section 7.11.1.
7. Urine Pregnancy Test will be performed for women of childbearing potential.
8. At clinic visits, dosing will be observed by site staff. Initial and returned pill counts will be used to calculate compliance (% doses taken per protocol). Additional measures of compliance will include Investigator enquiry into patient prescription refill records if available, satisfaction with iron chelation therapy (SICT) questionnaire [ref 8; Appendix D] and use of patient diaries.
9. A trough sample will be collected at Visit 1 and Visit 2. Blood samples for pharmacokinetic sampling will be drawn predose (-0.5 hour for trough levels) and at 1, 2, 4, and 8 hours post dose on Days 1, 7, 28, 36, 42 and 63. The allowed sampling "window" is ±15 min before 4 hours and ±30 min at 4 hours respectively. For the 8-hour time point the allowable sampling window is ± 1 hour. A 7-day washout period will occur at the end of study on Day 63; completion confirmed by a follow-up phone call on Day 71 to inquire on adverse events and concomitant medications.
10. Patients are instructed not take their medication before they arrive for their next visit.
11. A 7-day washout period will occur at the end of study on Day 63; completion confirmed by a follow-up phone call on Day 70 to inquire on adverse events and concomitant medications.

**TABLE OF CONTENTS**

**LIST OF TABLES**



**LIST OF FIGURES**

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation/Term | Definition |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine aminotransferase |
| ANOVA | Analysis of Variance |
| AST | Aspartate aminotransferase |
| BLQ | Below the Limit of Quantification |
| BMI | Body Mass Index |
| CBC | Complete Blood Count |
| CBER | Center for Biologics Evaluation and Research |
| cGMP | Current Good Manufacturing Practices |
| CRA | Clinical Research Associate |
| CRF (eCRF) | Case Report Form (electronic CRF) |
| CRP | C-reactive protein |
| CFR | Code of Federal Regulations |
| CNS | Central nervous system |
| DFX | Deferasirox |
| dw | Dry weight |
| ECG | Electrocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's Brochure |

| Abbreviation/Term | Definition |
|---|---|
| IC | Informed Consent |
| ICH | International Conference on Harmonisation |
| ICT | Iron chelation therapy |
| IND | Investigational New Drug Application |
| ITT | Intent-to-Treat |
| IRB | Institutional Review Board or Independent Review Board |
| IUD | Intrauterine Device |
| IVRS | Interactive Voice Response System |
| LIC | Liver iron concentration |
| LLN | Lower Limit of Normal |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MMRM | Mixed model for repeated measures |
| NCA | Non-compartmental analysis |
| NTDT | Non-transfusion-dependent thalassemia |
| NYHA | New York Heart Association |
| QoL | Quality of Life |
| PI | Principal Investigator |
| PT | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SICT | Satisfaction with Iron Chelation Therapy |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SUSAR | Serious unexpected suspected adverse reactions |
| TDT | Transfusion-dependent thalassemia |

| Abbreviation/Term | Definition |
|---|---|
| UGT | Uridine diphosphate glucuronosyltransferase |
| ULN | Upper Limit of Normal |
| WOCBP | Woman of childbearing potential |

# 1. INTRODUCTION

## *1.1* Background

Commercial deferasirox (DFX) is an orally active chelator that is selective for iron (as $Fe^{3+}$). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although DFX has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of DFX. The clinical significance of these decreases is uncertain [1].

DFX is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older; and for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia syndromes and with a liver iron concentration of at least 5 mg of iron per gram of dry weight (Fe/g dw) and a serum ferritin greater than 300 mcg/L [1].

DFX is formulated as a tablet for suspension as Exjade®. The package insert (Appendix A; Novartis, Exjade) recommends that Exjade be dispersed in water or fruit juice [1]. Additionally, DFX is also available as an oral film coated tablet or granules (Appendix B; Novartis, Jadenu®) [2] that presents improved bioavailability versus Exjade without the need to disperse prior to administration.

The goal of DisperSol Technologies, LLC ("DisperSol") is to develop a patient friendly formulation of deferasirox, DST-0509 (Deferasirox) Tablets, which will be more consistently bioavailable than existing marketed products, and more bioavailable in situations where poor bioavailability has compromised the iron binding capability of the drug. It therefore offers the potential to be a therapeutic option in the difficult to treat arena of iron overload and may help treat refractory iron overloaded patients who are not responding to current therapies.

DST-0509 is manufactured using a thermokinetic mixing process, or fusion process to produce drug-polymer composites, and specifically an amorphous drug-polymer intermediate. The process has been repeatedly demonstrated in the pharmaceutical literature to produce amorphous drug-polymer intermediates with compounds that could not be successfully melt-extruded owing to their high melting points. The composition provides improved DFX solubility and dissolution properties that may result in enhanced bioavailability and reduced pharmacokinetic variability in patients. These attributes are expected to translate into less variability in response, and improved efficacy in non-responders as compared to existing marketed DFX products.

The FDA approved initial dose of Exjade is 20 mg/kg and may be titrated up to 40 mg/kg [1]. The dosing of Jadenu is initially 7 or 14 mg per kg body weight (depending on the indication) orally, once daily [2]. The maximum recommended dosage of Jadenu is 28 mg per kg body weight orally, once daily [2]. Galanello, et al reported that ICL670 (Exjade) was well tolerated, and no safety problems occurred up to 80 mg/kg following administration of a single dose [4].

DFX is absorbed following oral administration with median times to maximum plasma concentration ($T_{max}$) of about 1.5 to 4 hours. The $C_{max}$ and AUC of DFX increase approximately linearly after both single administration and under steady-state conditions. Exposure to DFX increased by an accumulation factor of 1.3-2.3 after multiple doses. The absolute bioavailability (AUC) of DFX tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (AUC) of DFX was variably increased when taken with a meal [1,2].

DFX is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of DFX confined to the blood cells was 5% in humans. The volume of distribution at steady-state of DFX is 14.37 ± 2.69 L in adults. Glucuronidation is the main metabolic pathway for DFX, with subsequent biliary excretion.

DFX and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of DFX and metabolites is minimal (8% of the administered dose). The mean elimination half-life ($t_{1/2}$) ranged from 8-16 hours following oral administration [1,2]

### *1.2* Clinical Studies

In patients with transfusional iron overload, the most frequently occurring (>5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In DFX-treated patients with non-transfusion-dependent thalassemia syndromes, the most frequently occurring (>5%) adverse reactions are diarrhea, rash and nausea [1,2].

Overall, in patients treated with Exjade and Jadenu, gallstones and related biliary disorders were reported in about 2% of patients. Elevations of liver transaminases were reported as an adverse reaction in 2% of patients. Elevations of transaminases greater than 10 times the upper limit of the normal range, suggestive of hepatitis, were uncommon (0.3%). During post-marketing experience, hepatic failure, sometimes fatal, has been reported with the DFX dispersible tablet formulation, especially in patients with pre-existing liver cirrhosis. There have been post-marketing reports of metabolic acidosis [3]. The majority of these patients had renal impairment, renal tubulopathy (Fanconi syndrome) or diarrhea, or conditions where acid-base imbalance is a known complication. Cases of serious acute pancreatitis were observed without

documented underlying biliary conditions. As with other iron chelator treatment, high-frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with DFX. In a retrospective meta-analysis of 2,102 adult and pediatric beta-thalassemia patients with transfusional iron overload treated with DFX dispersible tablets (two randomized and four open-label studies of up to five years' duration), a mean creatinine clearance decrease of 13.2% in adult patients (95% CI: -14.4% to -12.1%; n=935), and 9.9% (95% CI: -11.1% to -8.6%; n=1,142) in pediatric patients, was observed during the first year of treatment. In 250 patients who were followed for up to five years, no further decrease in mean creatinine clearance levels was observed [1,2,5].

A food effect study involving administration of DFX as Jadenu to healthy subjects under fasting conditions and with a low-fat (fat content <7% of total calories) or high-fat (fat content >50% of total calories) meal indicated that the AUC and $C_{max}$ were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and $C_{max}$ were increased by 18% and 29%, respectively. The increases in $C_{max}$ due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that DFX as Jadenu should be taken on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories) [5].

To date, two Phase 1 studies with DST-0509 have been performed. A non-US Phase 1 pilot PK study (OPA-P8-807; Study 101) has been completed in Canada. The study was titled, "Single Dose Crossover Comparative Oral Bioavailability Under Fasting Conditions and Food Effect Pilot Study of Two Deferasirox Formulations and Jadenu 360 mg Tablets in Healthy Male and Female Volunteers". This Phase 1 study was a first-in-human, single center, single dose, crossover oral bioavailability pilot study. The purpose of the Phase 1 study was to provide PK data for two oral dose formulations of DST-0509 following oral administration to healthy subjects in fed and fasted states, compared with Jadenu. The results showed that as hypothesized, the Test (DST-0509) and Reference (Jadenu) formulations were not bioequivalent, with higher bioavailability on a molar basis for the DST-0509 test formulations.

The second Phase 1 study (DIS-P4-592; Study 102) has been completed in Canada. The study was titled "Single Dose Crossover Oral Bioavailability Study of a New Deferasirox Formulation Compared to Exjade Dispersible Tablets and Jadenu Tablets in Healthy Male and Female Volunteers.," This was a single center, single dose, randomized, 3-period, 3-sequence crossover, oral bioavailability study of DST-0509 compared with Exjade and Jadenu in fasted healthy volunteers. The results showed less variability in $C_{max}$ and AUC with DST-0509 versus Exjade,

and meaningfully enhanced absorption of DST-0509 versus Exjade and Jadenu. The enhanced bioavailability and reduced PK variability observed in Study 102 on an equivalent molar basis are expected to translate into less variability in response and improved efficacy in patients who do not respond well to currently available DFX products.

This current pilot study is a multicenter, open-label, two-period crossover design that evaluates the safety, tolerability, pharmacokinetics and preliminary evidence of iron chelating activity of DST-0509 as compared to Jadenu and Exjade in transfusion-dependent thalassemia patients with transfusional iron overload, requiring iron chelation therapy and demonstrating an inadequate response to Jadenu or Exjade for greater than 3 months duration. Up to 36 patients will be evaluated (18 in each treatment arm), however, the balanced randomization may enroll fewer patients based on recruitment status.

Rationale for the study design is detailed in Section 3.2.

# 2 OBJECTIVES

## *2.1* Primary

This patient-pilot study will assess the safety, overall tolerability, and preliminary evidence of DST-0509 iron chelating activity compared to Jadenu or Exjade in patients with transfusion-dependent beta thalassemia (TDT), major or intermedia, or non-TDT patients with inadequate response to available deferasirox chelation therapy, defined as a liver iron (Fe) concentration (LIC) of at least 5 mg Fe/g dw and a serum ferritin greater than 800 mcg/L.

## *2.2* Secondary

To determine the single and multiple dose pharmacokinetic (PK) profile of total deferasirox (iron-bound and unbound) plasma concentrations during DST-0509 and Jadenu or Exjade treatments in fed TDT and NTDT patients.

# 3 INVESTIGATIONAL PLAN

## *3.1* Overall Study Design

This is a multi-center, open-label, two-period cross-over, patient-pilot study comparing DST-0509 to Exjade or Jadenu administered orally once daily (QD) for 28-days in each period, with a 7-day washout before study entry and between treatment periods (see Table 6-1). Patients will be randomized to one of two treatment sequences: DST-0509→Exjade/Jadenu or Exjade/Jadenu→DST-0509 (with subjects who were taking Exjade prior to study start receiving Exjade and those taking Jadenu at study start receiving Jadenu). This study is designed to assess the safety, tolerability, evidence of iron chelating activity, and PK profile of DST-0509 compared to Jadenu or Exjade in inadequately responding patients. Inadequate response to standard chelation therapy is defined from the medical literature [6,7].

Up to 36 patients will be randomized 1:1 into one of two treatment sequences (study arms), of which up to 100% may be on Jadenu or Exjade at study entry, or a mix of the two. The planned randomization will assign up to 18 patients in each of two sequences: Sequence A: DST-0509 crossed to Exjade or Jadenu; Sequence B: Jadenu or Exjade crossed to DST-0509. The comparator treatment will be the patient's current chelation treatment. At the end of the study, patients previously on Jadenu or Exjade will revert to receiving their pre-study medication and dose following a 7-day washout period. A sufficient number of patients will be enrolled so there will be no need to replace study drop-outs. Study duration is approximately 14 weeks for each patient. A Study Flow Diagram is presented after this Synopsis (see Figure 3-1).

## Figure 3-1: Study Flow Diagram

**Treatment A (28 days) = DST-0509**
**Treatment B (28 days) = Jadenu/Exjade[1]**


| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | | 3 | 4 | 5 | 6 | | 7 | 8 | 9 | 10 | 11 |
| Day | -28 to -15 | -14 to -8 | -7 to -1 | 1 | 7 | 14 | 28 | 29-35 | 36 | 42 | 49 | 63 | 70 |
| **Period** | **Screening** | **Eligibility** | **Washout[2] (7-day)** | **Period 1** | | | | **Washout (7-day)** | **Period 2** | | | | **Washout (7-day)[3]** |

*Up to 36 patients are planned.

1. Subjects taking Exjade prior to study start will receive Exjade (treatment B) in the assigned Period 1 or cross-over Period 2. Those patients taking Jadenu prior to study start will receive Jadenu (treatment B) in the assigned Period 1 or cross-over Period 2. Dosing will be at equivalent (mg for mg) doses of DST-0509 for Jadenu. If crossing over from Exjade to DST-0509, or vice versa, the dose will be scaled to 28 mg/40 mg (DST-0509/Exjade).
2. For all patients entering the trial, a 7-day washout is required.
3. Visit 11 will be a phone call from study staff to the patient. The phone call will confirm that the patient has conducted the 7-day washout period before recommencing prior iron chelation therapy. AEs and concomitant medications will also be collected by phone on Visit 11.

### *3.2* Discussion of Study Design

This multi-dose 2-period, 2-arm crossover design was selected to adequately evaluate and compare the safety, tolerability and efficacy of DST-0509 compared to Jadenu and Exjade.

A 7-day washout period will be employed before the first treatment period, in between study treatments and at the end of the study, in order to clear the patient's system of any previous iron chelation treatment.

The choice of the drug strength used was justified based on analytical, pharmacokinetic and safety grounds. Furthermore, this strength was the Reference Listed Drug recommended by the FDA as follows. The FDA approved initial dose of DFX is 20 mg/kg and may be titrated up to 40 mg/kg with the Exjade formulation [1]. The dosing of Jadenu is initially 7 or 14 mg per kg body weight (depending on the indication) orally, once daily [2]. The maximum recommended dosage of DFX as Jadenu is 28 mg per kg body weight orally, once daily [2].

A food effect study involving administration of DFX as Jadenu to healthy subjects under fasting conditions and with a low-fat (fat content <7% of total calories) or high-fat (fat content >50% of total calories) meal indicated that the AUC and $C_{max}$ were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and $C_{max}$ were increased by 18% and 29%, respectively. The increases in $C_{max}$ due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that DFX as Jadenu should be taken on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories) [2].

Because DFX is rated in the pregnancy category C1, women will be included in the present study, provided they consent to take appropriate measures to prevent pregnancy for at least 28 days prior to the first administration of the study drug, during the study and for at least 30 days after the last dose of the study drug. Additionally, if the participant is using systemic contraceptives, she must use an additional non-hormonal form of acceptable method of contraception during the study and for at least 30 days after the last dose of the study drug.

# 4 SELECTION AND WITHDRAWAL OF PATIENTS

The study will enroll up to 36 patients and no study drop-outs will be replaced. Patients who have provided written informed consent and an authorization for disclosure of protected health information must meet all of the following criteria to qualify for entry into the study.

## *4.1* Inclusion Criteria

1. Written informed consent obtained prior to any study-related procedure being performed;
2. Patients at least 18 years of age or older at the time of consent;
3. Patient with TDT or NTDT syndromes and iron overload currently receiving iron chelation therapy with Jadenu or Exjade and demonstrating inadequate response assessed with serum ferritin and LIC;
4. Stable dosing with Jadenu or Exjade for >3 months prior to screening and receiving the maximal dose (Jadenu: 28 mg/kg or Exjade: 40 mg/kg);
5. Serum ferritin levels that are persistently >800 mcg/L determined by 2 separate assessments during screening over the previous 2-4 weeks prior to study treatment and not showing a decreasing trend over these weeks;
6. An LIC of >5 mg Fe/g dw measured by MRI in the 52 weeks prior to study entry;
7. Compliant with chelation therapy in the 3 months prior to enrollment as assessed by the Investigator:
    a. Satisfaction with Iron Chelation Therapy (SICT) Quality of Life (QoL) composite score $\geq$60%, or determined by investigator that at least 75% of medication prescribed on a regular basis was taken (Investigator enquiry into patient prescription refill records, preferably 3 months if available); and
    b. Willing to comply with chelation therapy for the duration of the study;
8. Agree not to use other anti-chelating agents concurrently;
9. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1;
10. Women of childbearing potential (WOCBP) must use an adequate method of birth control (double barrier, e.g. hormonal control and barrier contraception) at least 28

days prior to the first administration of the study drug, during the study and for at least 30 days after the last dose of the study drug. (Section 7.5 for details);

11. Male patients whose partners are WOCBP must use an adequate method of birth control (double barrier control) at least 28 days prior to the first administration of the study drug, during the study and for at least 30 days after the last dose of the study drug; and
12. Patient is willing and able to comply with all protocol required visits and assessments.

### *4.2* Exclusion Criteria

1. Patients with life expectancy less than 6 months;
2. Females of childbearing potential not on an adequate method of birth control, or who are pregnant or lactating;
3. History of non-compliance with chelation therapy (determined by the investigator, persistently taking less than 75% of prescribed dose in the 3 months prior to enrollment, or as determined by the Investigator based on medical history, SICT QoL overall score <60% or score in any SICT domain <50%);
4. Screening blood counts of the following:
    a. Absolute neutrophil count < 1500/µL
    b. Platelets < 100,000/µL
    c. Hemoglobin < 8 g/dL; transfusion support is permitted;
5. Screening chemistry values of the following:
    a. Alanine aminotransferase (ALT) and aspartate transaminase (AST) > 2.5 × upper limit of the normal reference range (ULN)
    b. Total bilirubin > 2 × ULN
    c. Creatinine > 1.5 × ULN
    d. Urine protein/creatinine ratio (UPCR) >0.5 mg/mg
    e. Albumin < 2.8 g/dL;
6. History of congestive heart failure New York Heart Association (NYHA) class III or IV or uncontrolled hypertension at screening;

7. History of other malignancy within the previous 3 years, except basal cell or squamous cell carcinoma, or non-muscle invasive bladder cancer;
8. In the opinion of the Investigator, evidence of major inflammatory disease that would affect ferritin levels within 14 days prior to the start of study medication;
9. Major surgery within 30 days prior to the start of study medication;
10. Serious persistent infection within 14 days prior to the start of study medication;
11. Serious concurrent medical condition including central nervous system (CNS) disorders;
12. Requires concomitant treatment with systemic corticosteroids, or any other immunosuppressive agents, or has used such treatment in the past 10 days before study entry (use of prednisone or equivalent <10 mg/day orally or use of inhaled corticosteroids or topical steroids is permitted).
13. Previous history of difficulty swallowing oral medications;
14. Any condition that, in the opinion of the Investigator, would impair the patient's ability to comply with study procedures or study medication; or
15. Concomitant treatment with medications described in Section 7.4 "Prohibited Medications".

### *4.3* Patient Withdrawal Criteria

Patients may be removed from the study for reasons including the following:

1. Significant protocol violation on the part of the Investigator or patient;
2. Significant noncompliance on the part of the patient as determined by the Investigator in consultation with the Medical Monitor;
3. Patient withdraws consent;
4. During the study, patient has the need for medications, supplements, ingredients and herbal therapies that are excluded (see Section 7.4, "Prohibited Medications" for examples in each category; this list is not all inclusive);
5. Unacceptable toxicity based on laboratory or other clinical findings, based on PI opinion;

6. Occurrence of any adverse event (AE) or condition that could, in the Investigator's opinion, interfere with the evaluation of the treatment effect or put the patient at undue risk;
7. Pregnancy; or
8. Other criteria, at the Investigator's discretion in consultation with the Medical Monitor.

# 5 STUDY TREATMENTS

## *5.1* Identity of Investigational Product

The investigational product for the open-label crossover study treatment will be DST-0509 supplied in 360 mg, 180 mg and 90 mg film coated tablets supplied by DisperSol Technologies, LLC (Georgetown, TX 78626, USA; see Investigator's Brochure [9]).

The methods used in, and the facilities and controls used for the manufacturing, processing, packaging, and holding of this drug substance conform with Current Good Manufacturing Practices (cGMP) in accordance with 21 CFR Parts 210 and 211. DisperSol will maintain certificates of analysis for each ingredient, documenting its purity and potency.

The following will be printed on the bottle label: Study ID, Lot/Batch No., placeholders for Site No., Screen No., Patient Initials and Date Dispensed.

Jadenu is commercially available as tablets, and Exjade as tablets for suspension, and both will be ordered by prescription and provided by the patient. Dosing will be at equivalent (mg for mg) doses of DST-0509 or Jadenu. If converting from Exjade to DST-0509, the dose will be scaled for each treatment by 28 mg/40 mg (DST-0509/Exjade).

## *5.2* Investigational Product Storage and Accountability

Investigational product will be stored at room temperature in a locked area with limited access.

Investigational product will be shipped to the study site. The Principal Investigator or designee will inventory and acknowledge receipt of all shipments of investigational product. The Principal Investigator or designee must keep accurate records of investigational product via the master investigational product accountability logs and the patient investigational product accountability logs. Supplies of investigational product will be checked and accountability records will be reviewed by the Clinical Research Associate (CRA) at monitoring visits. The completed accountability logs will be collected by the CRA at the close of the study. At the end of the study, all unused, partially used, empty or unopened kits or bottles will be returned to DisperSol or its designee for destruction. A written explanation will be required for any missing product.

Investigational supplies are to be used only in accordance with this protocol and under supervision of the Principal Investigator. All records must be available for inspection by Accelovance, Inc. and DisperSol personnel or their designees, and are subject to inspections by the regulatory authorities at any time.

### *5.3* Methods of Assigning Patients to Treatment Groups

Each clinical site will be assigned a unique 2-digit number. At each clinical site, a unique 3-digit screening number will be assigned to each patient after written IC is obtained. Patient screening numbers will be assigned sequentially at the site. Each patient will have a unique identifier that combines both the site and screening number. At Visit 3 (Day 1), a randomization number will be assigned centrally (by Accelovance, Inc. or by Interactive Voice Response System [IVRS], in accordance with the investigational product manufacturer) to each patient in a sequential manner as they become eligible for randomization. The randomization number will correspond to a predetermined treatment. Screening and randomization numbers must not be re-used once assigned, even if the patient does not take the investigational product.

Subjects who were taking Exjade prior to study start will receive Exjade at their prescribed dose during the study and those taking Jadenu at study start will receive Jadenu at their prescribed dose.

### *5.4* Administration of Investigational Product

DST-0509 will be supplied in 360 mg, 180 mg and 90 mg tablets. Jadenu is commercially available as tablets and Exjade as tablets for oral suspension and will be provided by the patient with their ongoing prescription. Dosing will be at equivalent (mg for mg) doses of DST-0509 or Jadenu. If converting from Exjade, the dose will be scaled for each treatment by 28 mg/40 mg (treatment/Exjade).

This is an open-label crossover study. Patients will receive Exjade or Jadenu at their previous stable dose. DST-0509 is taken with food, Jadenu is taken with or without a light meal, and Exjade is recommended to be taken without food. However, either Jadenu or Exjade can be administered according to the patient's previous regimen.

Each subject will be provided with sufficient DST-0509 for the respective treatment period and site staff will ensure prescription for Jaden and Exjade are sufficient for the respective treatment periods. The first dose will be taken at Visit 3 (Day 1) and the final dose will be taken at Visit 10 (Day 63).

### *5.5* Treatment Accountability and Compliance

At clinic visits, dosing will be observed by site staff. Accountability of investigational product consumption between visits will be evaluated by site staff through patient interview and the

counting of investigational product at Visits 3 through 10 (Days 1 through 63). The patient will be asked to bring the used and unused containers to each visit.

Lost or discarded investigational product should not be included in the calculation. Compliance will be determined at the Investigator's discretion but is recommended to be defined as 100% consumption of the scheduled intakes of investigational products. Dosing instructions are provided at Visit 3 (Day 1) and Visit 7 (Day 36); however, further counseling will be provided when compliance is unacceptable.

### *5.6* Blinding and Unblinding Method

Not applicable: this is an open-label study.

## 6 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Table 6-1 represents the procedures and assessments at each of the scheduled visits. Details of each visit are provided in Section 6.1 through Section 6.5.

## Table 6-1. SCHEDULE OF PROCEDURES

| Period | Screening | Eligibility | 7-day Washout[1] | Period 1 Treatment (DST-0509 or Jadenu/Exjade) | | | | 7-day Washout | Period 2 Treatment (Jadenu/Exjade or DST-0509) | | | | 7-day Washout[11] and Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | | **3** | **4** | **5** | **6** | | **7** | **8** | **9** | **10/ET** | **11** |
| **Day** | -28 to -15 | -14 to -8 | -7 to -1 | 1 | 7 | 14 | 28 | 29-35 | 36 | 42 | 49 | 63 | 70 |
| **Window (days)** | | | | | ±1 | ±1 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±1 |
| Informed Consent | X | | | | | | | | | | | | |
| Medical and Surgical History | X | | | | | | | | | | | | |
| Prior Medications | X | | | | | | | | | | | | |
| Body weight and Height | X | | | | | | | | | | | | |
| Washout Instructions[2] | | X | | | | | X | | | | | X | |
| Eligibility Review | X | X | | X | | | | | | | | | |
| Randomization | | | | X | | | | | | | | | |
| Dispense Investigational Product[3] | | | | X | | | | | X | | | | |
| Safety | | | | | | | | | | | | | |
| Vital signs[4] | X | | | X | | X | X | | X | | X | X | |
| Physical Examination[5] | X | | | X | | X | X | | X | | X | X | |
| Electrocardiogram (ECG) | | | | X | | | | | X | | | | |
| Chemistry, Hematology (CBC) and Urinalysis[6] | X | | | X | | X | X | | X | | X | X | |
| Serum CRP | X | X | | X | | | X | | X | | | X | |
| Urine Pregnancy Test[7] | X | | | | | | | | | | | | |
| Urine for Protein:Creatinine | X | | | X | | X | X | | X | | X | X | |
| ECOG PS (Appendix C) | X | | | X | | | X | | X | | | X | |
| Adverse Events | | | | X | X | X | X | | X | X | X | X | X |
| Concomitant Medications | X | | | X | X | X | X | | X | X | X | X | X |
| Dispense gastrointestinal AESI diary and Bristol Stool Chart | X | | | X | | | | | X | | | | |

| Period | Screening | Eligibility | 7-day Washout[1] | Period 1 Treatment (DST-0509 or Jadenu/Exjade) | | | | 7-day Washout | Period 2 Treatment (Jadenu/Exjade or DST-0509) | | | | 7-day Washout[11] and Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | | **3** | **4** | **5** | **6** | | **7** | **8** | **9** | **10/ET** | **11** |
| **Day** | -28 to -15 | -14 to -8 | -7 to -1 | 1 | 7 | 14 | 28 | 29-35 | 36 | 42 | 49 | 63 | 70 |
| **Window (days)** | | | | | ±1 | ±1 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±1 |
| and diary | | | | | | | | | | | | | |
| Review gastrointestinal AESI diary | | X | | X | X | X | X | | X | X | X | X | |
| Review Bristol Stool Chart diary | | X | | X | X | X | X | | X | X | X | X | |
| Collect gastrointestinal AESI diary | | | | X | | | X | | | | | X | |
| Collect Bristol Stool Chart diary | | | | X | | | X | | | | | X | |
| Treatment Compliance[8] | | | | X | X | X | X | | X | X | X | X | |
| Administer SICT questionnaire[8] | | X | | | | | | | | | | | |
| Efficacy Assessments | | | | | | | | | | | | | |
| Ferritin monitoring | X | X | | X | | | X | | X | | | X | |
| Pharmacogenetic monitoring | | X | | | | | | | | | | | |
| Pharmacokinetics | | | | | | | | | | | | | |
| Trough sampling[9] | X | X | | | | | | | | | | | |
| Pharmacokinetic sampling[9] | | | | X | X | | X | | X | X | | X | |
| Next Visit Instructions[10] | | | | X | X | X | X | | X | X | X | | |

Abbreviations AESI = adverse events of special interest; CBC = complete blood count; CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group Performance Status; SICT = satisfaction with iron chelating therapy; ET = Early Termination.

1. Instructions for washout provided at Eligibility visit (Visit 2).
2. For patients on iron chelation therapy prior to randomization, and for washout for all patients between periods and after last treatment.
3. DST-0509 will be supplied in 360 mg, 180 mg and 90 mg tablets. Patients will receive Jadenu or Exjade at their previous stable dose. All treatments will be administered daily orally with food in the morning. Dosing will be at equivalent (mg for mg) doses of DST-0509 for Jadenu. If crossing over from Exjade to DST-0509, or vice versa, the dose will be scaled to 28 mg/40 mg (DST-0509/Exjade).
4. Vital signs will include the measurement of blood pressure, heart rate, respiratory rate and body temperature.
5. A full physical examination will be performed at Screening, Day 28 and Day 63. A brief physical examination will be performed on Day 1, 14, 36, and 49.

6. Chemistry, Hematology (CBC) and Urinalysis measurements are described in Section 7.11.1.
7. Urine Pregnancy Test will be performed for women of childbearing potential.
8. At clinic visits, dosing will be observed by site staff. Initial and returned pill counts will be used to calculate compliance (% doses taken per protocol). Additional measures of compliance will include Investigator enquiry into patient prescription refill records if available, satisfaction with iron chelation therapy (SICT) questionnaire [ref 8; Appendix D] and use of patient diaries.
9. A trough sample will be collected at Visit 1 and Visit 2. Blood samples for pharmacokinetic sampling will be drawn predose (-0.5 hour for trough levels) and at 1, 2, 4, and 8 hours post dose on Days 1, 7, 28, 36, 42 and 63. The allowed sampling "window" is ±15 min before 4 hours and ±30 min at 4 hours respectively. For the 8-hour time point the allowable sampling window is ± 1 hour. A 7-day washout period will occur at the end of study on Day 63; completion confirmed by a follow-up phone call on Day 71 to inquire on adverse events and concomitant medications.
10. Patients are instructed not take their medication on the morning before they arrive for their next visit.
11. A 7-day washout period will occur at the end of study on Day 63; completion confirmed by a follow-up phone call on Day 70 to inquire on adverse events and concomitant medications.

### *6.1* Screening (Visit 1; Days -28 to -15)

Procedures as identified in Table 6-1.

- Written Informed Consent
- Medical and surgical history
- Prior medications
- Body weight and height
- Eligibility review
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature)
- Physical examination (full)
- Chemistry, hematology (CBC) and urinalysis
- Serum C-reactive protein (CRP)
- Urine Pregnancy Test (women of childbearing potential only)
- Urine for protein and creatinine
- ECOG PS (see Appendix C)
- Concomitant medications
- Dispense gastrointestinal AESI diary
- Dispense Bristol Stool Chart and diary
- Ferritin monitoring
- Trough PK sampling

### *6.2* Eligibility (Visit 2; Days -14 to -8)

Procedures as identified in Table 6-1.

- Washout Instructions
- Eligibility Review
- Serum CRP
- Review gastrointestinal AESI diary
- Review Bristol Stool Chart and diary
- Administer SICT questionnaire (see Appendix D)
- Ferritin monitoring
- Pharmacogenetic monitoring

- Trough PK sampling (patients will be instructed not to take study medication before they arrive at the next visit)

Staff will discuss the randomization date for their randomization (Visit 3, Day 1) and ensure that the patient is aware of the 7-day washout period and procedure prior to Day 1.

## *6.3* Randomization and Period Treatment 1

### 6.3.1 Visit 3 (Day 1)

Procedures as identified in Table 6-1.

- Eligibility Review
- Randomization: subjects who were taking Exjade prior to study start will receive Exjade during the study and those taking Jadenu at study start will receive Jadenu.
- Dispense Investigational Product (see instructions in Section 5.4)
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature)
- Physical Examination (brief)
- 12-Lead electrocardiogram (ECG), predose/pre-sampling
- Chemistry, Hematology (CBC) and Urinalysis
- Serum CRP
- Urine for protein and creatinine
- ECOG PS (see Appendix C)
- Adverse Events
- Concomitant Medications
- Collect gastrointestinal AESI diary and Bristol Stool Chart diary
- Review gastrointestinal AESI diary
- Review Bristol Stool Chart diary
- Dispense gastrointestinal AESI diary and Bristol Stool Chart and diary
- Treatment compliance
- Ferritin monitoring
- Pharmacokinetic sampling at predose (-0.5 hour) and 1, 2, 4, and 8 hours postdose
- Patients are instructed not to take study medication on the morning before they arrive for their next visit

### 6.3.2 Visit 4 (Day 7 ±1 day)

Procedures as identified in Table 6-1.

- Adverse Events
- Concomitant Medications
- Review GI AESI diary
- Review Bristol Stool Chart diary
- Treatment Compliance
- Pharmacokinetic sampling at predose (-0.5 hour) and 1, 2, 4, and 8 hours postdose
- Patients are instructed not to take study medication on the morning before they arrive for their next visit

### 6.3.3 Visit 5 (Day 14 ±1 day)

Procedures as identified in Table 6-1.

- Vital Signs (blood pressure, heart rate, respiratory rate and body temperature)
- Physical examination (brief)
- Chemistry, Hematology (CBC) and Urinalysis
- Urine for protein and creatinine
- Adverse Events
- Concomitant Medications
- Review GI AESI diary
- Review Bristol Stool Chart diary
- Treatment Compliance
- Patients are instructed not to take study medication on the morning before they arrive for their next visit

### 6.3.4 Visit 6 (Day 28 ±1 day)

Procedures as identified in Table 6-1.

- Provide washout instructions
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature)
- Physical Examination (full)
- Chemistry, Hematology (CBC) and Urinalysis
- Serum CRP

- Urine for protein and creatinine
- ECOG PS (see Appendix C)
- Adverse Events
- Concomitant Medications
- Collect gastrointestinal AESI diary
- Collect Bristol Stool Chart diary
- Review gastrointestinal AESI diary
- Review Bristol Stool Chart diary
- Treatment Compliance
- Ferritin monitoring
- Pharmacokinetic sampling at predose (-0.5 hour) and 1, 2, 4, and 8 hours postdose
- Patients are instructed not to take study medication on the morning before they arrive for their next visit

## *6.4* Period Treatment 2 (Crossover)

After a 7-day washout period the patients will attend the following visits for assessment of the second treatment.

### 6.4.1 Visit 7 (Day 36 ±1 day)

Procedures as identified in Table 6-1.

- Dispense Investigational Product (see instructions in Section 5.4)
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature)
- Physical Examination (brief)
- 12-Lead ECG (predose/pre-sampling)
- Chemistry, Hematology (CBC) and Urinalysis
- Serum CRP
- Urine for protein and creatinine
- ECOG PS (see Appendix A)
- Adverse Events
- Concomitant Medications
- Dispense gastrointestinal AESI diary
- Dispense Bristol Stool Chart and diary
- Review gastrointestinal AESI diary

- Review Bristol Stool Chart diary
- Treatment Compliance
- Ferritin monitoring
- Pharmacokinetic sampling at predose (-0.5 hour) and 1, 2, 4, and 8 hours postdose
- Patients are instructed not to take study medication on the morning before they arrive for their next visit

### 6.4.2 Visit 8 (Day 42 ±1 day)

Procedures as identified in Table 6-1.

- Adverse Events
- Concomitant Medications
- Review gastrointestinal AESI diary
- Review Bristol Stool Chart dairy
- Treatment Compliance
- Pharmacokinetic sampling at predose (-0.5 hour) and 1, 2, 4, and 8 hours postdose
- Patients are instructed not to take study medication on the morning before they arrive for their next visit

### 6.4.3 Visit 9 (Day 49 ±1 day)

Procedures as identified in Table 6-1.

- Vital Signs (blood pressure, heart rate, respiratory rate and body temperature)
- Physical examination (brief)
- Chemistry, Hematology (CBC) and Urinalysis
- Urine for protein and creatinine
- Adverse Events
- Concomitant Medications
- Review gastrointestinal AESI diary
- Review Bristol Stool Chart diary
- Treatment Compliance
- Patients are instructed not to take study medication on the morning before they arrive for their next visit

### 6.4.4 Visit 10 (Day 63 ±1 day)/Early Termination (ET)

Procedures as identified in Table 6.1.

- Washout Instructions
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature)
- Physical Examination (full)
- Chemistry, Hematology (CBC) and Urinalysis
- Serum CRP
- Urine for protein and creatinine
- ECOG PS (see Appendix C)
- Adverse Events
- Concomitant Medications
- Collect gastrointestinal AESI diary
- Collect Bristol Stool Chart diary
- Review gastrointestinal AESI diary
- Review Bristol Stool Chart diary
- Treatment Compliance
- Ferritin monitoring
- Pharmacokinetic sampling at predose (-0.5 hour) and 1, 2, 4, and 8 hours postdose (not performed for ET)

## *6.5* Follow-up (Phone Call; Day 70 ±1 day)

Patients will be called 7 days after the last dose of investigational product to assess if they have undergone the 7-day washout period, before recommencing iron chelation treatment with their prior therapy, and they will be asked if there were any new or ongoing adverse events or concomitant medication use.

## *6.6* Early Termination Procedures

The term "Early Termination" refers to a patient's non-completion of a study whether by his or her own choice or the Investigator's decision or due to discontinuation of the study by DisperSol.

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Investigator to keep the patient in the study. Should the patient decide to

withdraw, an attempt will be made to conduct an early termination visit, which will include all procedures normally done at Visit 10 (Day 63) and, the patient should be requested to undergo a 7-day washout and have a phone call to confirm as in the Follow-up (Day 70) procedures.

The primary reason for a patient withdrawing prematurely should be selected from the following categories:

***Adverse Event or Serious Adverse Event*** - events that are associated with discontinuation.

***Noncompliance with protocol*** - The patient failed to adhere to the protocol requirements. The deviation necessitated premature termination from the study.

***Pregnancy*** - The patient became pregnant after enrolling the study. Pregnant patients are withdrawn from the study as soon as the Principal Investigator is aware of the condition.

***Laboratory Abnormality*** - Laboratory abnormality that does not meet the definition of an AE.

***Withdrawal of Consent*** - The patient desires to withdraw from further participation in the study in the absence of an adverse event or a medical need to withdraw.

***Lost to Follow-up*** - The patient did not return for follow-up visit(s) following dispensing of test drug.

***Other*** - causes of premature termination from the study other than the above, such as theft or loss of investigational product, termination of study by DisperSol, etc.

The Investigator should notify Accelovance, Inc. promptly when a patient is withdrawn, or if the study is stopped at his/her site by the IRB or if the Investigator elects to stop the study.

### *6.7* Patient Completion Criteria

For purposes of this study, patients who have not discontinued investigational product early will be defined as study completers; interruption/missed dosing will be discussed with the PI. if the subject does not have the Follow-up (Day 70) phone to confirm washout, the subject will still be considered a completer.

### *6.8* Protocol Deviations

This study is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee will document the deviation. The protocol deviations will be reviewed by the Medical Monitor throughout the study.

# 7 DETAILED DESCRIPTION OF ASSESSMENTS

## *7.1* Informed Consent

Written IC will be obtained from each patient before any study procedures are performed. All potentially eligible patients for the study will be given a copy of the Institutional Review Board (IRB)-approved informed consent form to read.

The protocol will be discussed in detail with each potentially eligible patient. The PI or qualified designee will explain all aspects of the study in lay language and answer all the patient's questions regarding the study. The PI will inform the patient as to the nature, aims, duration, potential hazards, and procedures to be performed during the study and that his/her medical records may be reviewed. The PI will also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

The study patient must sign the IC form if he/she decides to participate in the study. No study procedures will be performed, and investigational products will not be released to any patient who has not signed the IC form.

## *7.2* Medical History

A complete medical and surgical history will be obtained at Screening (Visit 1).

## *7.3* Prior Medications and Concomitant Medications

Any therapy taken within 30 days of Visit 3 (Day 1) by the patient will be reported as prior medication. Any therapy started or stopped by the patient during the study after randomization will be regarded as concomitant therapy.

All prior and concomitant medications (prescription and over the counter, vitamins, and mineral supplements, and/or herbs) will be documented and must include the following information:

- Medication name
- Indication
- Dose
- Route of administration
- Start date

- Stop date or "Ongoing"

### *7.4* Prohibited Medications

Glucuronidation is the main metabolic pathway for DFX, with subsequent biliary excretion. Deconjugation of glucuronides in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur [1, 2].

DFX is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. The concomitant use of DFX with potent uridine diphosphate glucuronosyltransferase (UGT) inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) is prohibited, as these compounds may result in a decrease in DFX efficacy due to a possible decrease in DFX concentration. CYP450-catalyzed (oxidative) metabolism of DFX appears to be minor in humans (about 8%). Deconjugation of glucuronide metabolites in the intestine and subsequent reabsorption (enterohepatic recycling) was confirmed in a healthy volunteer study in which the administration of cholestyramine 12 g twice daily (strongly binds to DFX and its conjugates) 4 and 10 hours after a single dose of DFX resulted in a 45% decrease in DFX exposure (AUC) by interfering with the enterohepatic recycling of DFX [1, 2].

The concomitant use of DFX with bile acid sequestrants is prohibited, as these agents may result in a decrease in DFX efficacy. In healthy volunteers, the administration of cholestyramine after a single dose of DFX resulted in a 45% decrease in DFX exposure (AUC). Although DFX has a lower affinity for aluminum than for iron, avoid use of DFX with aluminum-containing antacid preparations due to the mechanism of action of DFX [1, 2].

If a patient begins taking a prohibited medication, the Medical Monitor should be notified of the deviation for approval to continue in the study. Notable prohibited medications include, for example, repaglinide, theophylline and midazolam.

### *7.5* Contraceptive Use

Female patients of childbearing potential, or male patients who have partners with childbearing potential, have to take appropriate measures to prevent pregnancy for at least 28 days prior to the first administration of the study drug, during the study, and for at least 3 weeks after the last dose of the study drug. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Additionally, if the participant is using systemic contraceptives, she must use an additional non-hormonal form of acceptable method of contraception during the study and for at least 30 days after the last dose of the study drug.

### *7.6* Washout

There will be a 7-day washout period before initial treatment with study drug, a second 7-day washout after the crossover and before treatment with the second study drug, and a third 7-day washout period at the end of the study on Day 63.

### *7.7* Eligibility Review

Eligibility criteria are reviewed at the visits prior to randomization. If laboratory values are abnormal, the test may be repeated within an interval (to be determined) that allows results to be reviewed prior to randomization.

Screen Failure: A screen failure is defined as a patient who consented but who has not been randomized.

### *7.8* Clinical Assessments

Vital signs will be assessed as described in Table 6-1.

Resting blood pressure, heart rate, respiratory rate, and body temperature will be measured at Screening, and Days 1, 14, 28, 36, 49, and 63.

### *7.9* Physical Examination

Physical examinations will be performed as described in Table 6-1. The examination will be brief or complete as follows:

- A brief physical examination consisting of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems will be performed on Days 1, 14, 36, and 49.

- A complete physical examination consisting of an evaluation of the general body, skin, head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, extremities, and the neurological and musculoskeletal systems will be performed at Screening, Day 28, and on Day 63.

Any clinically significant finding observed at the baseline visit before dosing on Day 1 will be considered medical history. Any new or worsened clinically significant finding observed at a post-randomization visit will be considered an adverse event.

## *7.10* Ferritin Monitoring

Ferritin (mcg/L) will be assessed in serum or plasma (at Screening, Eligibility and on Days 1, 28, 36 and 63) with enzyme-linked immunosorbent assays (ELISA) by routine laboratory methods.

## *7.11* Laboratory Assessments and Procedures

### 7.11.1 Laboratory Assessments

Laboratory assessments will be performed at scheduled visit as described in Table 6-1.

Safety laboratory tests selected include comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, and total bilirubin); complete blood count (white blood cell count, hemoglobin, hematocrit, platelet count, differential); PT and PTT; standard urinalysis panel (pH, protein, glucose, ketone, color, specific gravity, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen) and serum CRP.

Urine will be collected for the assessment of protein and creatinine on Days 1, 14, 28, 36, 49 and 63 of both treatments.

Urine pregnancy tests will be conducted on all women of childbearing potential at Screening.

### 7.11.2 Pharmacokinetics

Trough samples will be collected at Visit 1 and 2. Blood samples for PK analysis will be collected predose (-0.5 hour) and at 1, 2, 4, and 8 hours postdose on Days 1, 7, 28, 36, 42 and 63. The allowed sampling “window” is ±15 min for the 1 and 2 hour time points, and ±30 min for the 4 hour time point. For the 8 hour time point, the allowable window is ± 1 hour.

### 7.11.3 Collection, Shipment, and Retention of Laboratory Samples

All safety laboratory analyses will be performed by either a central or local laboratory. If a central laboratory is utilized, central laboratory will provide all collection materials and instructions for sample collection, packaging, and shipment. Samples for chemistry, hematology (CBC) and urinalysis will be collected at Screening and on Days 1, 14, 28, 36, 49 and 63. Samples for serum CRP will be collected at Screening and on Days 1, 28, 36, and 63.

## *7.12* Randomization and/or Treatment Assignment

At Visit 3 patients will be randomized and study treatment assigned.

## *7.13* Bristol Stool Chart

Patient's will be instructed to rate their stool using the Bristol Stool Chart in Figure 7-1.

**Figure 7-1: Bristol Stool Chart**


## *7.14* Gastrointestinal AESI Diary

In addition, safety will also assess adverse events of special interest (AESI) including selected gastrointestinal AEs of diarrhea, constipation, nausea, vomiting, and abdominal pain.

# 8 STATISTICAL METHODS

Complete details of the statistical and PK analyses will be specified in the statistical analysis plan (SAP). The SAP will be written and finalized prior to database lock. The key aspects of those analyses are summarized below.

## *8.1* Sample Size Determination

The primary endpoints in this patient-pilot study are safety and tolerability with special interest in gastrointestinal AEs such as diarrhea. Evidence of DST-0509 iron chelating activity is also of special interest but is considered preliminary for this study and will not be considered in sample size estimations. If the underlying true probability of a diarrhea AE is 12% (Jadenu label 2015[2]), then there will be a 98% probability of observing at least one event in this study with a total sample size of 30 subjects. The table below presents a range of diarrhea AE rates provided from Jadenu clinical trials and the probability of observing at least 1 or 2 for our planned sample size. Given the same adverse event rate for diarrhea, there will be an 89% probability of observing at least two events in this study.

| Underlying | Probability of Observing at Least 1 Diarrhea AE | | |
|---|---|---|---|
| Event Rate | N=24 | N=30 | N=36 |
| 9% | 0.90 | 0.94 | 0.97 |
| 12% | 0.95 | 0.98 | 0.99 |
| 21% | >0.99 | >0.99 | >0.99 |
| Underlying | Probability of Observing at Least 2 Diarrhea Events | | |
| Event Rate | N=24 | N=30 | N=36 |
| 9% | 0.65 | 0.77 | 0.85 |
| 12% | 0.80 | 0.89 | 0.94 |
| 21% | 0.97 | 0.99 | >0.99 |

It is expected that most reasonably common AEs will be observed in this small study and will provide information for future studies.

## *8.2* Analysis Populations

Four analysis populations are defined for this study as follows:

- Safety Population: All patients who received the planned study medication. The Safety Population will be used to assess safety and tolerability. Patients in the Safety Population will be analyzed with actual treatment.

- Intent-to-Treat (ITT) Population: The ITT population comprises all patients who received at least 1 dose of study medication and had at least 1 evaluable efficacy measurement after the first dose of DST-0509. Patients in the ITT population will be analyzed as randomized to treatment sequence.
- Per Protocol (PP) Population: The PP population comprises all randomized patients who completed the study according to all protocol requirements.
- PK Population: All patients who receive planned study medication and have sufficient post Baseline plasma samples obtained and assayed for drug concentration levels to allow for computation of PK parameters will be included in the PK Population. Patients will be included in the PK Population after review of the plasma concentration data. The rationale for inclusion or exclusion in the PK Population will be documented and listed.

### *8.3* Data Handling

In this study, no imputations for missing data will be completed. All analyses will be completed using observed data.

For pharmacokinetic analysis, the handling of concentration Data Below the Limit of Quantification (BLQ) will be completed as follows. For calculation of mean concentrations and generation of mean concentration-time profiles, all below the limit of quantification (BLQ) values will be set to zero except when an individual BLQ falls between two quantifiable values, in which case it will be treated as missing data.

For the pharmacokinetic analysis and individual concentration vs time plots, a concentration that is BLQ is assigned a value of zero if it occurs in a profile before the first measurable concentration. If a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLQ is treated as missing data. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration) it is treated as missing data. In the case where less than 3 consecutive measurable concentrations of DFX is observed, the AUC parameters will not be estimated for that specific study period. If a predose concentration of DFX is detected, the patient's data can be included in the pharmacokinetic and statistical analysis without adjustment, if the predose concentration is equal to or less than 5% of the $C_{max}$ value of the corresponding period. If the predose concentration is greater than 5% of the $C_{max}$ value, the patient will be dropped from all pharmacokinetic and statistical evaluations.

## *8.4* Randomization

This study will investigate 2 treatment groups:

| Group (Treatment) | Treatment Assignment |
|---|---|
| 1 (A/B) | DST-0509 / Jadenu (Exjade) |
| 2 (B/A) | Jadenu (Exjade) / DST-0509 |

A computer-generated randomization scheme will be used to obtain a balanced allocation to each treatment group.

## *8.5* Statistical Analyses

A comprehensive statistical analysis plan (SAP) will be written and approved prior to database lock for this study that describes the final analyses to be completed for safety, efficacy, and pharmacokinetic endpoints.

Data collected in this study will be presented using summary tables, figures, and patient data listings. Summary tables will present data by treatment group and by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the number of patients (n), the mean, median, standard deviation, minimum and maximum, and coefficient of variations (%CV). Categorical variables will be summarized by frequencies and percentages. Confidence intervals will be provided where appropriate for derived endpoints. Figures will be used to support the presentation of certain data. Sensitivity analyses may be performed to examine the effect of missing data.

All confidence intervals (CIs), statistical tests, and resulting p values will be reported as 2-sided. Significance will be assessed at $\alpha = 0.05$ level and the significance level will not be adjusted for multiple comparisons in the exploratory efficacy endpoint analyses.

### 8.5.1 Demographics and Baseline Characteristics

Demographic data (age, gender, race, body weight, height, and BMI) will be recorded.

### 8.5.2 Efficacy Analyses

Planned efficacy analyses will include examination of changes in iron chelation. Analysis by TDT and NTDT stratification will depend on recruitment status. Descriptive summaries of serum ferritin at each time point in each study period will be completed. Change from baseline in

serum ferritin will be assessed with a mixed model for repeated measures (MMRM) to assess changes within each treatment period and time. Categorical summaries will be presented for efficacy responders, i.e., the proportion of patients who achieve serum ferritin <800 mcg/L.

### 8.5.3 Safety Analyses

**Adverse Events**

Adverse experiences will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 20.0 or higher) and summarized by System Organ Class (SOC) and Preferred Term for each treatment group. All AEs will be captured after the first dose through the final visit (Visit 11) or the ET visit.

Adverse events will be summarized by presenting:

- the number and percentage of patients experiencing any AE
- the number and percentage of patients experiencing any AE grouped by SOC
- the number and percentage of patients experiencing any SAE
- the number and percentage of patients experiencing any AE associated with study discontinuation.

Gastrointestinal Adverse Events of Special Interest (GI AESI)

In addition, safety will also include assessing adverse events of special interest (AESI) including selected gastrointestinal AEs of diarrhea, constipation, nausea, vomiting, and abdominal pain.

**Other Safety and Tolerability Parameters**

At each clinic visit, treatment exposure will be estimated with compliance rates based on patient diary cards and pill counts, and tolerability will be assessed by general enquiry and specific iron chelation tolerability questions as well as by patient diaries concerning tolerability. Study patients will receive a diary to record gastrointestinal (GI) adverse events (AEs) of special interest (AESI) during the course of the study. Patients will be given the Bristol Stool Chart with diary and instructed on its use to help them characterize the nature of the bowel movements. All AE's will be monitored throughout the trial.

Patient safety will be monitored per clinical standard of care including routine laboratory monitoring. This will include monthly CBC, chemistry panel, and urinalysis assessments. Urine will be collected to measure protein: creatinine ratio and serum CRP will be assessed.

*Compliance*

Patients will be responsible for supplying their own Jadenu or Exjade during the study. Pill counts will be performed at each visit in order to characterize patient compliance (calculated as % doses taken per protocol). Additional measures of compliance will include Investigator enquiry into patient prescription refill records if available, satisfaction with iron chelation therapy (SICT) questionnaire [ref 8; Appendix D] and use of patient diaries.

*Dose reductions*

Dose reductions/interruptions of DST-0509 and Jadenu/Exjade are discouraged. However, in the event of a severe or higher AE lasting for >7 days, the PI, at their discretion, may reduce the dose by 25-33% or interrupt dosing. Max interruption is seven days. Dose re-escalation is not permitted. When AE resolves or is mild, the patient may restart study from last dose visit per PI or Medical Monitor (MM) discretion.

*Dose suspension*

Dosing with either treatment should be suspended in event of significant cytopenia – platelet count <50,000/ml or ANC <1,500/ml. If cytopenia has not recovered to Grade 1 or less after suspension of treatment for 7 days, the patient will be withdrawn from the study. The rationale for inclusion or exclusion of these subjects in the PK Population will be documented and listed.

**Clinical Laboratory Parameters**

Clinical laboratory measurements (serum chemistry, hematology and urinalysis) and changes from baseline will be summarized descriptively for each visit with the mean, median, standard deviation (SD), minimum and maximum, by treatment group.

Additionally, shifts from low, normal or high at baseline to low, normal or high at the end-of-treatment will be tabulated and presented by treatment group.

**Vital Signs**

Vital signs will be summarized descriptively for the mean, median, SD, minimum, and maximum by treatment group.

**ECOG Performance Status**

The ECOG performance status will be assessed at Screening Visit 1, and on Days 1, 28, 36 and 63. (see Appendix C). Changes from baseline will be presented with categorical descriptive statistics.

**ECG Evaluation**

ECG will be evaluated on Day 1 (Visit 3) and must be acquired predose and before blood samples are collected, and after a 5 min rest in supine position to avoid artifacts. Results will be provided in a patient listing.

**Bristol Stool Chart Assessment**

The Bristol Stool Chart (Section 7.13) will be used to evaluate average stool consistency: "What was the average stool consistency for the last 24 hours?" Stool Consistency will be presented with categorical description (N, % of patients) by visit for each consistency parameter: hard, lumpy, sausage, snake, soft, mushy or liquid. No formal inferential analysis will be conducted.

### 8.5.4 Pharmacokinetic Analyses

#### 8.5.4.1 Pharmacokinetic Parameters

Blood samples for PK analysis will be collected predose (-0.5 hour) and at 1, 2, 4, and 8 hours postdose on Days 1, 7, 28, 36, 42 and 63. The PK parameters of DST-0509 and Jadenu and Exjade will be derived from the concentration-time data. The allowed sampling "window" is ±15 min for the 1 and 2 hour time points, and ±30 min for the 4 hour time point. For the 8 hour time point, the allowable window is ± 1 hour.

Total (iron-bound and unbound) DFX plasma concentrations produced by the administration of the studied formulations (DST-0509 and Jadenu/Exjade) will be determined in order to establish the pharmacokinetic profile of each treatment.

Pharmacokinetic parameter estimates will be estimated for each treatment. Both single dose PK parameter estimates (following the first dose in a treatment sequence) and multiple dose PK parameter estimates will be completed to characterize DST-0509 and Jadenu/Exjade. The following parameters will be estimated for this study for each treatment:

## Table 8-1. PHARMACOKINETIC PARAMETERS

| Pharmacokinetic Parameter | Description (Computation Method) |
|---|---|
| **Following first dose in each treatment sequence:** | |
| $C_{max}$ | Peak exposure, Maximum plasma concentration. |
| $t_{max}$ | Time to maximum plasma concentration. |
| $C_{last}$ | Last quantifiable plasma concentration (last value observed above assay BLQ). |
| $t_{last}$ | Time of last quantifiable plasma concentration. |
| $\lambda_z$ | Terminal rate constant (lambda_z). |
| $t_{1/2}$ | Terminal half-life: Computed as $t_{1/2} = \frac{ln(2)}{\lambda_z}$ |
| AUC $_{(0\text{-}t)}$ | Exposure: Area Under the Plasma Curve from time 0 to the last quantifiable concentration (t). Calculated using the linear trapezoidal rule. |
| $AUC_{(0\text{-}24)}$ | Exposure: Area Under the Plasma Curve from time 0 to 24 hours post dosing. Calculated using the linear trapezoidal rule. |
| $AUC_{(0\text{-}\infty)}$ | Exposure: Area Under the Plasma Curve from time 0 extrapolated to infinity. Calculated as follows: $AUC_{inf} = AUC_{0\text{-}t} + \left(\frac{C_{last}}{\lambda_z}\right)$ where $C_{last}$ is the last quantifiable concentration. |
| CL/F | Apparent oral clearance, computed as Dose / $AUC_{(0\text{-}\infty)}$ |
| $AUMC_{(0\text{-}\infty)}$ | Area under the first moment curve extrapolated to infinity, computed as: $\text{AUMClast} + \frac{\text{Tlast} \cdot Clast_{obs}}{\lambda_z} + \frac{Clast_{obs}}{\lambda_z^2}$ |
| MRT | Mean residence time based on concentration-time data extrapolated to infinity, computed as $AUMC_{(0\text{-}\infty)}$ / $AUC_{(0\text{-}\infty)}$ |
| **Multiple dose pharmacokinetic parameters within each sequence:** | |
| Tau | The (assumed equal) dosing interval for steady-state data. |
| $T_{max}$ | Time of maximum concentration sampled during a dosing interval. |
| $T_{min}$ | Time of minimum concentration sampled during a dosing interval. |
| $C_{min}$ | Minimum concentration between dose time and dose time + Tau (at $T_{min}$). |
| $C_{avg}$ | Average concentration over the dosing interval, computed as $AUC_{0\text{-}tau}$/tau. |
| %_Fluctuation | $100*(C_{max}\text{-}C_{min})/C_{avg}$, for $C_{min}$ and $C_{max}$ between dose time and Tau. |
| $Cl_{ss}/F$ | An estimate of apparent oral clearance after multiple dosing, computed as $Dose/AUC_{0\text{-}tau}$. |
| $C_{max}$ | Maximum concentration between dose time and dose time + Tau (at $T_{max}$). |
| $AUC_{0\text{-}tau}$ | Area Under the Plasma Concentration curve from the time of the dose to the end of the dosing interval. |

Additional PK parameters may be derived as need to characterize both single dose and multiple dose PK profiles.

All reported sampling time deviations will be taken into consideration for evaluation of PK parameters. In the case where concentrations of study medications cannot be determined due to bioanalytical or clinical reasons; these values will be set to missing for the statistical and pharmacokinetic analysis.

The main absorption and disposition parameters will be estimated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule will be used to estimate the area under the curve (linear trapezoidal linear interpolation) and the terminal phase will be estimated by maximizing the coefficient of determination estimated from the log-linear regression model. However, disposition parameters may be estimated for individual concentration-time profiles on Day 1 where the terminal log-linear phase cannot be reliably characterized. Descriptive statistics will be calculated for plasma concentrations at each individual time point and for all pharmacokinetic parameters. The individual plasma concentration/time profiles will be presented using the actual sampling times whereas the mean plasma concentration/time profiles will be presented using the theoretical sampling times.

Pharmacokinetic parameters will be derived using model-independent methods (non-compartmental analysis: NCA) as implemented in Phoenix 7, WinNonlin (version 7.1) and will be based on DST-0509 and Jadenu plasma concentrations from patients in the PK Population.

#### 8.5.4.2 Statistical Analysis

Statistical analyses will be generated using SAS (version 9.0 or higher) for the Mixed procedure. The natural logarithmic transformation of PK parameters as well as the rank-transformation of $T_{max}$ will be used for all statistical inference. Subjects who do not have parameters for both DST-0509/Jadenu or DST-0509/Exjade treatments will not be included in the respective statistical bioequivalent analyses.

Exposure pharmacokinetic parameters ($C_{max}$, AUC) will be statistically analyzed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model will be the treatment received, the period at which it was given as well as the sequence in which each treatment is received. A random factor will also be added for the patient effect (nested within sequence).

The 90% confidence interval for the exponential of the difference in LS means between Treatments will be computed. If there are sufficient data for both Jadenu and Exjade, both will serve as reference in the respective analysis, no pooling of data between the reference treatments (Jadenu, Exjade) will be performed.

# 9 ADVERSE EVENT MONITORING

## *9.1* Definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation following the patient's first dose of investigational product that does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable or unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition (including the physical examination), or abnormal results of diagnostic procedures (including laboratory test abnormalities).

Events should be considered AEs if they:

- result in discontinuation from the study,
- require treatment or any other therapeutic intervention,
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality),
- are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

**Clinically Significant Laboratory Changes:** It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each abnormal result, the Investigator needs to ascertain whether the abnormality presents a clinically significant change from baseline. If the change is due to the expected course of the patient's underlying disease (e.g., elevated cholesterol in a study of dyslipidemia), it is not considered an adverse event unless the abnormality is more severe than expected. A laboratory test may be confirmed by repeat testing or other diagnostic tests before being considered an adverse event. If the laboratory abnormality is a significant change from baseline for the patient, then it should be considered an adverse event.

An Adverse Event is not:

- A surgical procedure
- A situation where an untoward event did not occur, (e.g. a social hospitalization)
- The disease being studied, unless progression is more severe than anticipated
- Lack of efficacy
- Baseline conditions that have not worsened in severity or frequency
- Clinically significant abnormal laboratory findings or test results related to the disease being studied (unless more severe than expected)

### *9.2* Procedures

An untoward event that occurs after screening and before the first dose of investigational product will be recorded as an update to the medical history.

Some events may make the patient ineligible for randomization. Unanticipated events should be reported to the IRB, according to its requirements.

Patients will be questioned at every visit after the first dose until Visit 11 or ET regarding the occurrence and nature of any AEs. All AEs will be reported, whether or not they are deemed to be related to investigational product.

A description of the event or diagnosis including dates, severity, relationship to the investigational product, action taken with the study drug and outcome, and whether or not the event was also serious, must be reported on the AE CRF for each adverse event recorded in the patient's chart.

### *9.3* Severity

Adverse events are first graded according to seriousness and then severity. The seriousness of an event is determined by the regulatory criteria in Section 9.6.

The Investigator will evaluate the severity of each AE. Adverse events will be graded as

Mild: Awareness of symptoms but easily tolerated

Moderate: Discomfort enough to interfere with but not prevent daily activity

Severe: Unable to perform usual activity

### *9.4* Relationship

The Investigator will judge the likelihood that the AE was related to the investigational product according to the following criteria

Not related: There is no temporal or causal relationship to the investigational product.

Related: There is a possible temporal or causal relationship to the investigational product.

### *9.5* Action Taken and Outcome

The Action Taken with investigational product for every AE will be reported as either: Dose Not Changed, Dose Reduced, Dose Interrupted, Dose Withdrawn or Not Applicable if patient is not taking the study drug at the time of the adverse event. The outcome of each AE will be entered as either: Recovered/Resolved, Recovered/Resolved with Sequelae, Not Recovered/Not Resolved, Fatal, or Unknown.

### *9.6* Adverse Event Follow-up

Investigators should follow AEs until the event has resolved, the condition has stabilized, is well characterized, or referred for appropriate medical management, whichever comes first. Events and follow-up information occurring after the last visit should be recorded in the source documentation. Investigators are not obliged to solicit adverse events after a patient's final visit; however, if an Investigator learns of an Serious AE (SAE) that is believed to be possibly related to the investigational product, an SAE Report Form should be submitted.

### *9.7* Unexpected Adverse Event

As defined by 21 CFR 312.32 (a), an unexpected adverse drug experience is:

"An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's

Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation."

The study Sponsor will expedite reporting to Center for Biologics Evaluation and Research (CBER) all serious unexpected suspected adverse reactions (SUSARs) as defined in the Investigator's Brochure (IB) [9]: initial reporting by the Sponsor for nonfatal or non-life-threatening SUSARs must be submitted to CBER as soon as possible but no later than within 15 calendar days following the Sponsor's initial receipt of the information, and for fatal or life-threatening SUSARs, initial reports must be submitted no later than 7 calendar days following the Sponsor's initial receipt of the information. Any relevant additional information obtained by the Sponsor that pertains to a previously submitted IND Safety Report must be submitted as a Follow-up IND Safety Report without delay as soon as the information is available but no later than 15 calendar days after the Sponsor receives the information.

Such expedited reports will comply with the applicable regulatory requirements and with the FDA's Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies (21 CFR 312.32).

### *9.8* Serious Adverse Events

An AE that results in any of the following outcomes is serious:

- Death (note that death is the outcome of an SAE and the cause of death should be listed as the AE)
- Life-threatening event
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Any other important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalization for elective surgery for a prior condition that did not worsen or for social reasons will not be treated as serious.

### 9.8.1 Serious Adverse Event Reporting

Any SAE which occurs after the first dose is administered until Visit 11 (Day 70) must be reported to Accelovance, Inc. whether or not it is judged related to the investigational product. Accelovance, Inc. must be notified within 24 hours after the site becomes aware of the SAE. Accelovance, Inc. has the responsibility to notify DisperSol of the event.

If the Principal Investigator determines that the event is serious, the following procedures will be followed:

- The Investigator will report the SAE directly to Accelovance, Inc. Accelovance Inc.'s contacts are:

  Medical Monitor:

  Nadia Tullio, MD
  Medical Monitor
  Accelovance, Inc.
  2275 Research Blvd., #700
  Rockville, MD 20850
  Telephone: 240.238.4961
  **SAE FAX number:** 866.857.8839
  atullio@accelovance.com

  Project Manager:

  Piyush Sheladia, M.S.
  Project Manager II
  Accelovance, Inc.
  2275 Research Blvd, Suite 700
  Rockville, MD 20850
  Office: 240.238.4958
  Cell: 240.515.1762
  Fax: 240.238.4901
  psheladia@accelovance.com

- The Investigator will provide, at a minimum, the protocol number, patient's initials, patient number, date of the SAE, SAE term and relationship to investigational product. The SAE Report Form should be faxed to 866-857-8839 within 24 hours of awareness of the SAE with any supporting data or copies of CRF pages.

- The Investigator will notify the Institutional Review Board (IRB) of the SAE within the timeframe specified by the IRB. An initial report followed promptly by a complete report will be forwarded to the IRB, or in accordance with the IRB policy.

### 9.8.2 Serious Adverse Event Follow-Up

The patient will be observed and monitored carefully until

- the event resolves, or
- the event/condition has stabilized (e.g., in the case of persistent impairment), or
- the event returns to baseline, if a baseline value is available.

The Investigator and Medical Monitor will determine if additional follow-up is required. Follow-up information relating to an SAE must be submitted to Accelovance, Inc. as soon as additional data related to the event are available. All efforts must be taken to obtain follow-up information promptly.

Follow-up information may consist of:

- A hospital discharge summary for patients who are hospitalized or hospitalized over a prolonged period due to the SAE. If possible, the discharge summary should be obtained when it becomes available.
- A copy of the autopsy report, if a death occurs and an autopsy is performed, should be obtained if possible when it becomes available.

Any SAEs that are ongoing at Day 63 or ET should be followed as described above until Day 70. For ongoing SAEs, the Principal Investigator must submit follow-up reports to Accelovance, Inc. regarding the patient's subsequent course until the case is closed.

Post-study SAEs: SAEs with onset after Day 63/ET may be reported up to and including Day 70, and should be recorded in the source documents and an SAE Report Form should be submitted as in Section 9.8.1.

## *9.9* Pregnancy

Any pregnancy occurring during this study will be reported within 24 hours of notification of the Investigator. The Investigator will promptly notify the Medical Monitor about the pregnancy and complete a Pregnancy Report Form. The Pregnancy Report Form will be faxed to the Medical Monitor via the SAE Fax number.

# 10 INVESTIGATOR OBLIGATIONS

## *10.1* Ethical and Regulatory Considerations

This study will be conducted in accordance with 21 CFR Parts 11, 50 Subparts A and B, 54, 56, 312 and the ICH GCP E6.

## *10.2* Institutional Review Board

The Principal Investigator will ensure that an appropriately constituted Institutional Review Board (IRB), in compliance with the requirements of 21 CFR 56, reviews and approves the clinical study before the study is initiated. IRB approval must refer to the study by exact protocol title, number, and amendment number (if applicable), identify the documents reviewed, and state the date of review.

The Principal Investigator will ensure that DisperSol approves any changes to the IC template prior to submission to the IRB.

Should changes to the IC form become necessary during the study, the Principal Investigator will ensure that the changes are approved by DisperSol prior to submission to the IRB. Should changes to the study protocol become necessary, the Principal Investigator will ensure that the protocol amendment is approved by the IRB prior to implementation. The Principal Investigator will ensure that protocol administrative changes have been reviewed by the IRB.

The Principal Investigator will ensure that Accelovance is provided with a copy of the IRB approval documents and a copy of the IRB-approved IC form before the study is initiated (Accelovance will provide copies to DisperSol).

## *10.3* Informed Consent

A properly executed, written IC, in compliance with 21 CFR Part 56 and a HIPAA authorization, will be obtained from each patient prior to enrollment and the initiation of screening evaluations required by this protocol. A copy of the IC form planned for use will be reviewed by DisperSol for acceptability and submitted by or on behalf of the Investigator, together with the protocol, to the IRB for review and approval prior to the start of the study. Consent forms will be written in the language fully comprehensible to the prospective patient.

All revisions of the protocol must be reflected in the IC form, if applicable, and reviewed and approved by the IRB. Patients must be made aware of those applicable changes in the protocol and must consent to participate in the revised protocol.

### *10.4* Patient Confidentiality

All communications, reports, and patient samples will be identified only by a coded number and/or initials to maintain patient confidentiality. All records will be kept confidential to the extent permitted by law. If a waiver or authorization separate from the statement in the IC is required for permitting access to a patient's medical records (e.g., HIPAA), the Investigator will obtain such authorization prior to enrolling a patient in the study. The Principal Investigator should keep a separate log of patients, codes, names, and addresses. Documents which identify the patient by name (for example, the IC form) should be kept in strict confidence.

DisperSol and its business associates agree to keep all patient information confidential. Only coded, blinded data will be released. Data resulting from analyses will be entered into a database that is not accessible to the public. Patient data will be identified only by the patient screen number, randomization number and initials, and not by any other annotation or identifying information.

DisperSol and its business associates will take every possible step to reduce the risk of releasing information to the public that would enable patients to be personally identified.

### *10.5* Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local indemnification requirements. The civil liability of the Investigator, the persons instructed by him, the hospital, practice, or institute in which they are employed, and the liability of the Sponsor in respect of financial loss due to personal injury and other damage, which may arise as a result of the carrying out of this study, are governed by the applicable law. As a precautionary measure, the Investigator, the persons instructed by him and the hospital, practice or institute are included in such cover in regard to work done by them in carrying out this study to the extent that the claims are not covered by their own professional indemnity insurance. The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study. Such insurance is taken out by the Sponsor in

accordance with regulations in the country concerned. To the extent that payments are made under such insurance, the right to claim damages from the Sponsor extinguishes.

# 11 STUDY MONITORING

## *11.1* Clinical Monitoring

An initiation meeting will be conducted by Accelovance, Inc. or an approved representative. At this meeting the protocol, the procedure for completing the CRFs, and pertinent aspects of the CRFs will be reviewed with the Principal Investigator and all study staff.

Monitoring visits will be conducted during the study. The Principal Investigator will make a reasonable amount of time available to the CRA on reasonable notice to assist with monitoring.

At each visit, the CRA will review the CRFs and source documents to ensure that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol.

## *11.2* Auditing Procedures

In addition to the monitoring visits outlined above, an investigational site may undergo a quality assurance audit. Accelovance, Inc. or DisperSol representatives or a regulatory agency such as the FDA may conduct the audit. If a regulatory agency requests an audit of the study site, the Investigator is required to inform Accelovance, Inc. (and DisperSol Technologies, LLC) immediately.

# 12 CHANGES TO THE PROTOCOL AND STUDY TERMINATION

## *12.1* Protocol Amendment and Administrative Change

All changes to the protocol must be documented by amendments, or administrative changes where applicable, and the amended protocol must be signed by DisperSol and the Investigators. The amended protocol and a revised IC form, if necessary, will be submitted to the IRB for approval. If the protocol modifications affect the CRFs, they will also be revised and provided to the site.

## *12.2* Termination of the Study

DisperSol and the Principal Investigator reserve the right to terminate the study at any time. In terminating the study, DisperSol and the Principal Investigator will ensure that adequate consideration is given to the protection of each patient's interest.

# 13 SOURCE DOCUMENTS, CASE REPORT FORMS AND RECORD RETENTION

## *13.1* Source Documents

The Investigator will complete and maintain source documents for each patient participating in the study. The source documents should contain all demographic and medical information, including laboratory data. The patient's source documents file should also indicate that he/she is participating in the clinical study, referencing the study number and the investigational product.

All information required by the protocol should be documented in the source records. An explanation must be given for any omissions. Each evaluation recorded will be performed at the time specified in the protocol.

## *13.2* Case Report Forms

Case Report Forms (CRFs) will be provided by Accelovance, Inc. All information on the CRFs must be traceable back to the source documents. All information must be entered on the CRF and made available as soon as possible after the patient's visit, in order that the CRA may verify the validity and completeness of the data and permit prompt transmission of the data. The Principal Investigator should review all CRFs for completeness, accuracy, and legibility before the CRA reviews and collects the data.

## *13.3* Record Retention

The Principal Investigator will maintain adequate records so that the conduct of the study can be fully documented and monitored. Copies of protocols, CRFs, test result originals, all investigational product accountability records, correspondence, patient IC forms, and any other documents relevant to the conduct of the study will be kept on file by the Principal Investigator. Study documents will not be destroyed. For regulatory inspections, it will be necessary to have access to complete study patient records, provided that patient confidentiality is maintained.

Per the Clinical Development Agreement between DisperSol and Accelovance, Inc., Investigators must retain patients' records for a period of 2 years after FDA approval or until written approval to destroy the documentation is provided by DisperSol. The documentation must be retained longer if so required by local law. Investigators must notify Accelovance, Inc. and DisperSol, in writing, of changes in address, sales of practices or site closures in order to make arrangements for the maintenance of study files.

## 14 FINAL REPORT/PUBLICATION STATEMENT

Any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the Investigator(s) and DisperSol. In the case of multicenter studies, it is mandatory that the first publication be made based on the totality of data obtained from all centers, analyzed as stipulated in the protocol, and presented and interpreted as documented in the final Clinical Study Report. The resulting publication will name Principal Investigators according to the policy of the chosen journal. Where it is not permitted for all Principal Investigators to be included as authors, the publication will name all Principal Investigators within the publication.

Individual Investigators may publish data arising from their own patients. The Principal Investigator will provide DisperSol with copies of written publications (including abstracts and posters) at least 60 days in advance of submission. This review is to permit DisperSol to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged (including patent protection), to allow adequate input or supplementary information that may not have been available to the Principal Investigator, and to allow establishment of co-authorship.

Investigators participating in multicenter studies must agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication, unless this has been agreed to otherwise by all other Investigators and DisperSol. However, in the event that no publication of the overall results has been submitted after approval of the Clinical Study Report, Investigators may publish results of one or more center's patients to the same review as outlined above. DisperSol will circulate proposed multicenter publications to all Principal Investigators for review.

Data will be reviewed by all participating Investigators prior to publication. DisperSol will have 60 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

## 15 REFERENCES

1. EXJADE [Label] (08/2016). Drugs@FDA, FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed September 9, 2016.
2. Jadenu [Label] (10/22/2015). NDA 206910, Drugs@FDA, FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed December 7, 2015.
3. EXJADE_Summary of Product Characteristics_2016.
4. Galanello et al. Safety, Tolerability, and Pharmacokinetics of ICL670, a New Orally Active Iron Chelating Agent in Patients with Transfusion-Dependent Iron Overload Due to b-Thalassemia. Journal of Clinical Pharmacology, 2003;43:565-572.
5. FDA Medical/Pharmacology Reviews NDA #21-882.
6. Galanello R, Piga A, Cappellini MD, Forni GL, Zappu A, Origa R, Dutreix C, Belleli R, Ford JM, Rivière GJ, Balez S, Alberti D, Séchaud R. Effect of food, type of food, and time of food intake on deferasirox bioavailability: recommendations for an optimal deferasirox administration regimen. J Clin Pharmacol. 2008 Apr;48(4):428-35.
7. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):265-271.
8. Elalfy MS, Massoud W, Elsherif NH, Labib JH, Elalfy OM, Elaasar S, von Mackensen S. A new tool for the assessment of satisfaction with iron chelation therapy (ICT-Sat) for patients with β-thalassemia major. Pediatr Blood Cancer. 2012 Jun;58(6):910-5.
9. DisperSol Technologies, LLC. (February 3, 2017). Investigator's Brochure – DST-0509 tablets).

## APPENDIX A: EXJADE LABEL

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use EXJADE safely and effectively. See full prescribing information for EXJADE.**

**EXJADE® (deferasirox) tablets, for oral suspension**
**Initial U.S. Approval: 2005**

**WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE**
***See full prescribing information for complete boxed warning***

**Exjade may cause:**
- **renal toxicity, including failure (5.1)**
- **hepatic toxicity, including failure (5.2)**
- **gastrointestinal hemorrhage (5.3)**

**Exjade therapy requires close patient monitoring, including laboratory tests of renal and hepatic function. (5)**

**RECENT MAJOR CHANGES**

| | |
|---|---|
| Indications and Usage (1) | 5/2013 |
| Dosage and Administration (2) | 5/2013 |
| Warnings and Precautions (5) | 10/2013 |

**INDICATIONS AND USAGE**

Exjade is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is based on reduction in serum ferritin and liver iron concentration (LIC). An improvement in survival or disease-related symptoms has not been established. (1.1)

Exjade is 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 (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight and a serum ferritin greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established. (1.2)

Limitation of Use
Controlled clinical trials of Exjade in patients with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusion have not been performed. (1.3)

The safety and efficacy of Exjade when administered with other iron chelation therapy have not been established. (1.3)

**DOSAGE AND ADMINISTRATION**

- In patients with transfusional iron overload, the recommended initial daily dose is 20 mg per kg body weight once daily, as oral suspension. Calculate dose to the nearest whole tablet. (2.1)
- In patients with NTDT syndromes, the recommended initial daily dose is 10 mg per kg body weight once daily, as oral suspension. Calculate dose to the nearest whole tablet. (2.2)
- Monitor serum ferritin monthly and adjust dose accordingly. (2.1, 2.2)
- Monitor LIC every 6 months and adjust dose accordingly. (2.2)
- Do not chew or swallow tablets whole. (2.3)
- Take on an empty stomach at least 30 minutes before food. Disperse tablets by stirring in an appropriate amount of water, orange juice, or apple juice. (2.3)
- Reduce the starting dose in patients with moderate (Child-Pugh B) hepatic impairment by 50%. Avoid the use of Exjade in patients with severe (Child-Pugh C) hepatic impairment. (2.4)
- Reduce the starting dose by 50% in patients with renal impairment (CrCl 40–60 mL/min). (2.4)

**DOSAGE FORMS AND STRENGTHS**

Tablets for oral suspension: 125 mg, 250 mg, 500 mg. (3)

**CONTRAINDICATIONS**

- Serum creatinine greater than 2 times the age-appropriate upper limit of normal or creatinine clearance less than 40 mL/min. (4)
- Patients with poor performance status. (4)
- Patients with high-risk myelodysplastic syndromes (MDS). (4)
- Patients with advanced malignancies. (4)
- Patients with platelet counts <50 x $10^9$/L. (4)
- Known hypersensitivity to deferasirox or any component of Exjade. (4)

**WARNINGS AND PRECAUTIONS**

- Renal toxicity: Measure serum creatinine and creatinine clearance in duplicate before starting therapy. Monitor renal function during Exjade therapy and reduce dose or interrupt therapy for toxicity. (2.4, 5.1)
- Hepatic toxicity: Monitor hepatic function. Reduce dose or interrupt therapy for toxicity. (5.2)
- Fatal and nonfatal gastrointestinal bleeding, ulceration, and irritation: Risk may be greater in patients who are taking Exjade in combination with drugs that have known ulcerogenic or hemorrhagic potential. (5.3)
- Bone marrow suppression: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during Exjade therapy. Interrupt therapy for toxicity. (5.4)
- Elderly: Monitor closely for toxicity due to the greater frequency of decreased hepatic, renal, and/or cardiac function. (5.5)
- Serious and severe hypersensitivity reactions: Discontinue Exjade and institute medical intervention. (5.6)
- Severe skin reactions including Stevens Johnson Syndrome: Discontinue Exjade and evaluate. (5.7)

**ADVERSE REACTIONS**

In patients with transfusional iron overload, the most frequently occurring (>5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In Exjade-treated patients with NTDT syndromes, the most frequently occurring (>5%) adverse reactions are diarrhea, rash and nausea. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**DRUG INTERACTIONS**

- Avoid the use of Exjade with aluminum-containing antacid preparations. (7.1)
- Exjade increases the exposure of the CYP2C8 substrate repaglinide. Consider repaglinide dose reduction and monitor blood glucose levels. (7.3)
- Avoid the use of Exjade with CYP1A2 substrate theophylline. (7.4)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Based on animal studies, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 10/2013**

FULL PRESCRIBING INFORMATION: CONTENTS*



* Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3393658

**FULL PRESCRIBING INFORMATION**

**WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE**

**Renal Failure**

- **Exjade can cause acute renal failure and death, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders.**
- **Measure serum creatinine and determine creatinine clearance in duplicate prior to initiation of therapy and monitor renal function at least monthly thereafter. For patients with baseline renal impairment or increased risk of acute renal failure, monitor creatinine weekly for the first month, then at least monthly. Consider dose reduction, interruption, or discontinuation based on increases in serum creatinine [see *Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)*].**

**Hepatic Failure**

- **Exjade 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 Exjade in patients with severe (Child-Pugh C) hepatic impairment and reduce the dose in patients with moderate (Child Pugh B) hepatic impairment [see *Dosage and Administration (2.4), Warnings and Precautions (5.2)*].**

**Gastrointestinal Hemorrhage**

- **Exjade 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 Exjade for suspected GI ulceration or hemorrhage [see *Warnings and Precautions (5.3)*].**

## 1 INDICATIONS AND USAGE

### 1.1 Treatment of Chronic Iron Overload Due to Blood Transfusions (Transfusional Iron Overload)

Exjade is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. This indication is based on a reduction of liver iron concentrations and serum ferritin levels [see *Clinical Studies (14)*]. An improvement in survival or disease-related symptoms has not been established [see *Indications and Usage (1.3)*].

### 1.2 Treatment of Chronic Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

Exjade is 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 greater than 300 mcg/L. This indication is based on achievement of an LIC less than 5 mg Fe/g dw [see *Clinical Studies (14)*]. An improvement in survival or disease-related symptoms has not been established.

### 1.3 Limitation of Use

Controlled clinical trials of Exjade with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusions have not been performed [see *Clinical Studies (14)*].

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Transfusional Iron Overload

Exjade therapy should only be considered when a patient has evidence of chronic transfusional iron overload. The evidence should include the transfusion of at least 100 mL/kg of packed red blood cells (e.g., at least 20

units of packed red blood cells for a 40 kg person or more in individuals weighing more than 40 kg), and a serum ferritin consistently greater than 1000 mcg/L.

Prior to starting therapy, obtain:

- serum ferritin level
- baseline serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (Cockcroft-Gault method) [see *Dosage and Administration (2.4), Warnings and Precautions (5.1)*]
- serum transaminases and bilirubin [see *Dosage and Administration (2.4), Warnings and Precautions (5.2)*]
- baseline auditory and ophthalmic examinations [see *Warnings and Precautions (5.9)*]

The recommended initial dose of Exjade for patients 2 years of age and older is 20 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.

After commencing therapy, monitor serum ferritin monthly and adjust the dose of Exjade, if necessary, every 3-6 months based on serum ferritin trends. Make dose adjustments in steps of 5 or 10 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals. In patients not adequately controlled with doses of 30 mg per kg (e.g., serum ferritin levels persistently above 2500 mcg/L and not showing a decreasing trend over time), doses of up to 40 mg per kg may be considered. Doses above 40 mg per kg are not recommended.

If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting therapy with Exjade [see *Warnings and Precautions (5.10)*].

**2.2 Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes**

Exjade therapy should only be considered when a patient with NTDT syndrome has an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L.

Prior to starting therapy, obtain:

- LIC by liver biopsy or by an FDA-cleared or approved method for identifying patients for treatment with deferasirox therapy
- Serum ferritin level on at least 2 measurements 1 month apart [see *Clinical Studies (14)*]
- Baseline serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (Cockcroft-Gault method) [see *Dosage and Administration (2.4), Warnings and Precautions (5.1)*]
- Serum transaminases and bilirubin [see *Dosage and Administration (2.4), Warnings and Precautions (5.2)*]
- Baseline auditory and ophthalmic examinations [see *Warnings and Precautions (5.9)*]

Initiating therapy:

- The recommended initial dose of Exjade is 10 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.
- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 20 mg/kg/day after 4 weeks.

During therapy:

- Monitor serum ferritin monthly. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw.
- Monitor LIC every 6 months.
- After 6 months of therapy, if the LIC remains greater than 7 mg Fe/g dw, increase the dose of deferasirox to a maximum of 20 mg/kg/day. Do not exceed a maximum of 20 mg/kg/day.
- If after 6 months of therapy, the LIC is 3–7 mg Fe/g dw, continue treatment with deferasirox at no more than 10 mg/kg/day.

- When the LIC is less than 3 mg Fe/g dw, interrupt treatment with deferasirox and continue to monitor the LIC.
- Monitor blood counts, hepatic function, and renal function [see *Warnings and Precautions (5.1, 5.2, 5.4)*].

Restart treatment when the LIC rises again to more than 5 mg Fe/g dw.

**2.3 Administration**

Do not chew tablets or swallow them whole.

Take Exjade once daily on an empty stomach at least 30 minutes before food, preferably at the same time each day. Completely disperse tablets by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Disperse doses of less than 1 g in 3.5 ounces of liquid and doses of 1 g or greater in 7 ounces of liquid. After swallowing the suspension, resuspend any residue in a small volume of liquid and swallow. Do not take Exjade with aluminum-containing antacid products [see *Drug Interactions (7.1)*].

**2.4 Use in Patients with Baseline Hepatic or Renal Impairment**

*Patients with Baseline Hepatic Impairment*

Mild (Child-Pugh A) hepatic impairment: No dose adjustment is necessary.

Moderate (Child-Pugh B) hepatic impairment: Reduce the starting dose by 50%.

Severe (Child-Pugh C) hepatic impairment: Avoid Exjade [see *Warnings and Precautions (5.2), Use in Specific Populations (8.7)*].

*Patients with Baseline Renal Impairment*

For patients with renal impairment (ClCr 40–60 mL/min), reduce the starting dose by 50% [see *Use in Specific Populations (8.6)*]. Do not use Exjade in patients with serum creatinine greater than 2 times the upper limit of normal or creatinine clearance less than 40 mL/min [see *Contraindications (4)*].

**2.5 Dose Modifications for Increases in Serum Creatinine on Exjade**

For serum creatinine increases while receiving Exjade [see *Warnings and Precautions (5.1)*] modify the dose as follows:

**Transfusional Iron Overload**

*Adults and Adolescents (ages 16 years and older):*

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, reduce the dose by 10 mg per kg.

*Pediatric Patients (ages 2–15 years):*

- Reduce the dose by 10 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate upper limit of normal.

*All Patients (regardless of age):*

- Discontinue therapy for serum creatinine greater than 2 times the age-appropriate upper limit of normal or for creatinine clearance <40 mL/min. [see *Contraindications (4)*]

**Non-Transfusion-Dependent Thalassemia Syndromes**

*Adults and Adolescents (ages 16 years and older):*

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, interrupt therapy if the dose is 5 mg per kg, or reduce by 50% if the dose is 10 or 20 mg per kg.

*Pediatric Patients (ages 10–15 years):*

- Reduce the dose by 5 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate upper limit of normal.

*All Patients (regardless of age):*

- Discontinue therapy for serum creatinine greater than 2 times the age-appropriate upper limit of normal or for creatinine clearance <40 mL/min [see *Contraindications (4)*].

**2.6 Dose Modifications Based on Concomitant Medications**

*UDP-glucuronosyltransferases (UGT) Inducers*

Concomitant use of UGT inducers decreases Exjade systemic exposure. Avoid the concomitant use of potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) with Exjade. If you must administer Exjade with 1 of these agents, consider increasing the initial dose of Exjade by 50%, and monitor serum ferritin levels and clinical responses for further dose modification [see *Dosage and Administration (2.1, 2.2), Drug Interactions (7.5)*].

*Bile Acid Sequestrants*

Concomitant use of bile acid sequestrants decreases Exjade systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with Exjade. If you must administer Exjade with 1 of these agents, consider increasing the initial dose of Exjade by 50%, and monitor serum ferritin levels and clinical responses for further dose modification [see *Dosage and Administration (2.1, 2.2), Drug Interactions (7.6)*].

**3 DOSAGE FORMS AND STRENGTHS**

- 125 mg tablets
  Off-white, round, flat tablet with beveled edge and imprinted with "J" and "125" on one side and "NVR" on the other.
- 250 mg tablets
  Off-white, round, flat tablet with beveled edge and imprinted with "J" and "250" on one side and "NVR" on the other.
- 500 mg tablets
  Off-white, round, flat tablet with beveled edge and imprinted with "J" and "500" on one side and "NVR" on the other.

**4 CONTRAINDICATIONS**

Exjade is contraindicated in patients with:

- Serum creatinine greater than 2 times the age-appropriate upper limit of normal or creatinine clearance less than 40 mL/min [see *Warning and Precautions (5.1)*];
- Poor performance status;
- High-risk myelodysplastic syndromes;
- Advanced malignancies;
- Platelet counts <50 x $10^9$/L;
- Known hypersensitivity to deferasirox or any component of Exjade [see *Warnings and Precautions (5.6), Adverse Reactions (6.2)*].

**5 WARNINGS AND PRECAUTIONS**

**5.1 Renal Toxicity, Renal Failure, and Proteinuria**

Exjade can cause acute renal failure, fatal in some patients and requiring dialysis in others. Postmarketing experience showed that most fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. In the clinical trials, Exjade-treated patients experienced dose-

dependent increases in serum creatinine. In patients with transfusional iron overload, these increases in creatinine occurred at a greater frequency compared to deferoxamine-treated patients (38% versus 14%, respectively, in Study 1 and 36% versus 22%, respectively, in Study 3) [see *Adverse Reactions (6.1, 6.2)*].

Measure serum creatinine in duplicate (due to variations in measurements) and determine the creatinine clearance (estimated by the Cockcroft-Gault method) before initiating therapy in all patients in order to establish a reliable pretreatment baseline. Monitor serum creatinine weekly during the first month after initiation or modification of therapy and at least monthly thereafter. Monitor serum creatinine and/or creatinine clearance more frequently if creatinine levels are increasing. Dose reduction, interruption, or discontinuation based on increases in serum creatinine may be necessary [see *Dosage and Administration (2.5)*].

Exjade is contraindicated in patients with creatinine clearance less than 40 mL/minute or serum creatinine greater than 2 times the age appropriate upper limit of normal.

Renal tubular damage, including Fanconi's Syndrome, has been reported in patients treated with Exjade, most commonly in children and adolescents with beta-thalassemia and serum ferritin levels <1500 mcg/L.

Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of Exjade-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1. In clinical trials in patients with transfusional iron overload, Exjade was temporarily withheld until the urine protein/creatinine ratio fell below 0.6 mg/mg. Monthly monitoring for proteinuria is recommended. The mechanism and clinical significance of the proteinuria are uncertain [see *Adverse Reactions (6.1)*].

### 5.2 Hepatic Toxicity and Failure

Exjade can cause hepatic injury, fatal in some patients. In Study 1, 4 patients (1.3%) discontinued Exjade 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 greater than 55 years of age. Hepatic failure was more common in patients with significant comorbidities, including liver cirrhosis and multiorgan failure [see *Adverse Reactions (6.1)*].

Measure transaminases (AST and 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 Exjade in patients with severe (Child-Pugh C) hepatic impairment. Reduce the starting dose in patients with moderate (Child-Pugh B) hepatic impairment [see *Dosage and Administration (2.4), Use in Specific Populations (8.7)*]. Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment may be at higher risk for hepatic toxicity.

### 5.3 Gastrointestinal (GI) Hemorrhage

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 Exjade [see *Adverse Reactions (6.1)*]. Monitor for signs and symptoms of GI ulceration and hemorrhage during Exjade therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. The risk of gastrointestinal hemorrhage may be increased when administering Exjade in combination with drugs that have ulcerogenic or hemorrhagic potential, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants.

### 5.4 Bone Marrow Suppression

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

### 5.5 Increased Risk of Toxicity in the Elderly

Exjade has been associated with serious and fatal adverse reactions in the postmarketing setting, predominantly in elderly patients. Monitor elderly patients treated with Exjade more frequently for toxicity [see *Use in Specific Populations (8.5)*].

### 5.6 Hypersensitivity

Exjade may cause serious hypersensitivity reactions (such as anaphylaxis and angioedema), with the onset of the reaction usually occurring within the first month of treatment [*see Adverse Reactions (6.2)*]. If reactions are severe, discontinue Exjade and institute appropriate medical intervention. Exjade is contraindicated in patients with known hypersensitivity to Exjade.

### 5.7 Severe Skin Reactions

Severe skin reactions, including Stevens-Johnson syndrome (SJS) and erythema multiforme, have been reported during Exjade therapy [see *Adverse Reactions (6.2)*]. If SJS or erythema multiforme is suspected, discontinue Exjade and evaluate.

### 5.8 Skin Rash

Rashes may occur during Exjade treatment [see *Adverse Reactions (6.1)*]. For rashes of mild to moderate severity, Exjade may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, interrupt treatment with Exjade. Reintroduction at a lower dose with escalation may be considered in combination with a short period of oral steroid administration.

### 5.9 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 Exjade therapy in the clinical studies. Perform auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) before starting Exjade treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, monitor more frequently. Consider dose reduction or interruption.

### 5.10 Overchelation

For patients with transfusional iron overload, measure serum ferritin monthly to assess for possible overchelation of iron. If the serum ferritin falls below 500 mcg/L, consider interrupting therapy with Exjade, since overchelation may increase Exjade toxicity [see *Dosage and Administration (2.1)*].

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 Exjade 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 Exjade and obtain a confirmatory LIC [see *Clinical Studies (14)*].

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

The following adverse reactions are also discussed in other sections of the labeling:

- Renal Toxicity, Renal Failure, and Proteinuria [see *Warnings and Precautions (5.1)*]
- Hepatic Toxicity and Failure [see *Warnings and Precautions (5.2)*]
- Gastrointestinal (GI) Hemorrhage [see *Warnings and Precautions (5.3)*]
- Bone Marrow Suppression [see *Warnings and Precautions (5.4)*]
- Hypersensitivity [see *Warnings and Precautions (5.6)*]

- Severe Skin Reactions [see *Warnings and Precautions (5.7)*]
- Skin Rash [see *Warnings and Precautions (5.8)*]
- Auditory and Ocular Abnormalities [see *Warnings and Precautions (5.9)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Transfusional Iron Overload**

A total of 700 adult and pediatric patients were treated with Exjade (deferasirox) for 48 weeks in premarketing studies. These included 469 patients with beta-thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 45% were male, 70% were Caucasian and 292 patients were <16 years of age. In the sickle cell disease population, 89% of patients were black. Median treatment duration among the sickle cell patients was 51 weeks. Of the 700 patients treated, 469 (403 beta-thalassemia and 66 rare anemias) were entered into extensions of the original clinical protocols. In ongoing extension studies, median durations of treatment were 88-205 weeks.

Six hundred twenty-seven patients with MDS were enrolled across 5 uncontrolled trials. These studies varied in duration from 1 to 5 years. The discontinuation rate across studies in the first year was 46% (AEs 20%, withdrawal of consent 10%, death 8%, other 4%, lab abnormalities 3%, and lack of efficacy 1%). Among 47 patients enrolled in the study of 5-year duration, 10 remained on Exjade at the completion of the study.

Table 1 displays adverse reactions occurring in >5% of Exjade-treated beta-thalassemia patients (Study 1), sickle cell disease patients (Study 3), and patients with MDS (MDS pool). Abdominal pain, nausea, vomiting, diarrhea, skin rashes, and increases in serum creatinine were the most frequent adverse reactions reported with a suspected relationship to Exjade. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.

**Table 1. Adverse Reactions* Occurring in >5% of Exjade-treated Patients in Study 1, Study 3, and MDS Pool**

| | Study 1 (Beta-thalassemia) | | Study 3 (Sickle Cell Disease) | | MDS Pool |
|---|---|---|---|---|---|
| | EXJADE N=296 | Deferoxamine N=290 | EXJADE N=132 | Deferoxamine N=63 | EXJADE N=627 |
| Preferred Term | n (%) | n (%) | n (%) | n (%) | n (%) |
| Abdominal Pain** | 63 (21) | 41 (14) | 37 (28) | 9 (14) | 145 (23) |
| Diarrhea | 35 (12) | 21 (7) | 26 (20) | 3 (5) | 297 (47) |
| Creatinine Increased*** | 33 (11) | 0 (0) | 9 (7) | 0 | 89 (14) |
| Nausea | 31 (11) | 14 (5) | 30 (23) | 7 (11) | 161 (26) |
| Vomiting | 30 (10) | 28 (10) | 28 (21) | 10 (16) | 83 (13) |
| Rash | 25 (8) | 9 (3) | 14 (11) | 3 (5) | 83 (13) |

*Adverse reaction frequencies are based on adverse events reported regardless of relationship to study drug.
**Includes 'abdominal pain', 'abdominal pain lower', and 'abdominal pain upper' which were reported as adverse events.
***Includes 'blood creatinine increased' and 'blood creatinine abnormal' which were reported as adverse events. Also see Table 2.

In Study 1, a total of 113 (38%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) and 25 (8%) patients required dose reductions. Increases in serum creatinine appeared to be dose related [see *Warnings and Precautions (5.1)*]. In this study, 17 (6%) patients treated with Exjade developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits. Of these, 2 patients had liver biopsy proven drug-induced hepatitis and both discontinued Exjade therapy [see *Warnings and Precautions (5.2)*]. An additional 2 patients, who did not have elevations in SGPT/ALT >5 times the upper limit of normal, discontinued Exjade because of increased SGPT/ALT. Increases in transaminases did not appear to be dose related. Adverse reactions that led to discontinuations included

abnormal liver function tests (2 patients) and drug-induced hepatitis (2 patients), skin rash, glycosuria/proteinuria, Henoch Schönlein purpura, hyperactivity/insomnia, drug fever, and cataract (1 patient each).

In Study 3, a total of 48 (36%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) [see *Warnings and Precautions (5.1)*]. Of the patients who experienced creatinine increases in Study 3, 8 Exjade-treated patients required dose reductions. In this study, 5 patients in the Exjade group developed elevations in SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits and 1 patient subsequently had Exjade permanently discontinued. Four additional patients discontinued Exjade due to adverse reactions with a suspected relationship to study drug, including diarrhea, pancreatitis associated with gallstones, atypical tuberculosis, and skin rash.

In the MDS pool, in the first year, a total of 229 (37%) patients treated with Exjade had increases in serum creatinine >33% above baseline on 2 consecutive occasions (Table 2) and 8 (3.5%) patients permanently discontinued [see *Warnings and Precautions (5.1)*]. A total of 5 (0.8%) patients developed SGPT/ALT levels >5 times the upper limit of normal at 2 consecutive visits. The most frequent adverse reactions that led to discontinuation included increases in serum creatinine, diarrhea, nausea, rash, and vomiting. Death was reported in the first year in 52 (8%) of patients [see *Clinical Studies (14)*].

**Table 2. Number (%) of Patients with Increases in Serum Creatinine or SGPT/ALT in Study 1, Study 3, and MDS Pool**

| | Study 1 (Beta-thalassemia) | | Study 3 (Sickle Cell Disease) | | MDS Pool |
|---|---|---|---|---|---|
| Laboratory Parameter | EXJADE N=296 n (%) | Deferoxamine N=290 n (%) | EXJADE N=132 n (%) | Deferoxamine N=63 n (%) | EXJADE N=627 n (%) |
| **Serum Creatinine** | | | | | |
| Creatinine increase >33% at 2 consecutive postbaseline visits | 113 (38) | 41 (14) | 48 (36) | 14 (22) | 229 (37) |
| Creatinine increase >33% and >ULN at 2 consecutive postbaseline visits | 7 (2) | 1 (0) | 3 (2) | 2 (3) | 126 (20) |
| **SGPT/ALT** | | | | | |
| SGPT/ALT >5 x ULN at 2 postbaseline visits | 25 (8) | 7 (2) | 2 (2) | 0 | 9 (1) |
| SGPT/ALT >5 x ULN at 2 consecutive postbaseline visits | 17 (6) | 5 (2) | 5 (4) | 0 | 5 (1) |

**Non-Transfusion-Dependent Thalassemia Syndromes**

In Study 4, 110 patients with NTDT received 1 year of treatment with Exjade 5 or 10 mg/kg/day and 56 patients received placebo in a double-blind, randomized trial. In Study 5, 130 of the patients who completed Study 4 were treated with open-label Exjade at 5, 10, or 20 mg/kg/day (depending on the baseline LIC) for 1 year [see *Clinical Studies (14)*]. Table 3 displays adverse reactions occurring in >5% in any group. The most frequent adverse reactions with a suspected relationship to study drug were nausea, rash, and diarrhea.

**Table 3. Adverse Reactions Occurring in >5% in NTDT Patients**

| | Study 4 | | Study 5 |
|---|---|---|---|
| | EXJADE N=110 n (%) | Placebo N=56 n (%) | EXJADE N=130 n (%) |
| **Any adverse reaction** | **31 (28)** | **9 (16)** | **27 (21)** |
| Nausea | 7 (6) | 4 (7) | 2 (2) |
| Rash | 7 (6) | 1 (2) | 2 (2) |
| Diarrhea | 5 (5) | 1 (2) | 7 (5) |

In Study 4, 1 patient in the placebo 10 mg/kg/day group experienced an ALT increase to >5 times ULN and >2 times baseline (Table 4). Three Exjade-treated patients (all in the 10 mg/kg/day group) had 2 consecutive serum creatinine level increases >33% from baseline and >ULN. Serum creatinine returned to normal in all 3 patients (in 1 spontaneously and in the other 2 after drug interruption). Two additional cases of ALT increase and 2 additional cases of serum creatinine increase were observed in the 1-year extension of Study 4.

**Table 4. Number (%) of NTDT Patients with Increases in Serum Creatinine or SGPT/ALT**

| | Study 4 | | Study 5 |
|---|---|---|---|
| | EXJADE N=110 | Placebo N=56 | EXJADE N=130 |
| **Laboratory Parameter** | **n (%)** | **n (%)** | **n (%)** |
| Serum creatinine (>33% increase from baseline and >ULN at ≥2 consecutive postbaseline values) | 3 (3%) | 0 | 2 (2%) |
| SGPT/ALT (>5 x ULN and >2 x baseline) | 1 (1%) | 1 (2%) | 2 (2%) |

*Proteinuria*

In clinical studies, urine protein was measured monthly. Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of Exjade-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1 [see *Warnings and Precautions (5.1)*].

*Other Adverse Reactions*

In the population of more than 5,000 patients with transfusional iron overload who have been treated with Exjade during clinical trials, adverse reactions occurring in 0.1% to 1% of patients included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue, pharyngolaryngeal pain, early cataract, hearing loss, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, and renal tubulopathy (Fanconi's Syndrome). Adverse reactions occurring in 0.01% to 0.1% of patients included optic neuritis, esophagitis, and erythema multiforme. Adverse reactions which most frequently led to dose interruption or dose adjustment during clinical trials were rash, gastrointestinal disorders, infections, increased serum creatinine, and increased serum transaminases.

**6.2 Postmarketing Experience**

The following adverse reactions have been spontaneously reported during post-approval use of Exjade in the transfusional iron overload setting. Because these reactions are reported voluntarily from a population of uncertain size, in which patients may have received concomitant medication, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), leukocytoclastic vasculitis, urticaria, alopecia

Immune system disorders: hypersensitivity reactions (including anaphylaxis and angioedema)

Renal and urinary disorders: acute renal failure, tubulointerstitial nephritis

Hepatobiliary disorders: hepatic failure

Gastrointestinal disorders: gastrointestinal hemorrhage

Blood and lymphatic system disorders: worsening anemia

## 7 DRUG INTERACTIONS

### 7.1 Aluminum Containing Antacid Preparations

The concomitant administration of Exjade and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, avoid use of Exjade with aluminum-containing antacid preparations due to the mechanism of action of Exjade.

### 7.2 Agents Metabolized by CYP3A4

Deferasirox may induce CYP3A4 resulting in a decrease in CYP3A4 substrate concentration when these drugs are coadministered. Closely monitor patients for signs of reduced effectiveness when deferasirox is administered with drugs metabolized by CYP3A4 (e.g., alfentanil, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, hormonal contraceptive agents, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, tolvaptan, tipranavir, triazolam, ticagrelor, and vardenafil) [see *Clinical Pharmacology (12.3)*].

### 7.3 Agents Metabolized by CYP2C8

Deferasirox inhibits CYP2C8 resulting in an increase in CYP2C8 substrate (e.g., repaglinide and paclitaxel) concentration when these drugs are coadministered. If Exjade and repaglinide are used concomitantly, consider decreasing the dose of repaglinide and perform careful monitoring of blood glucose levels. Closely monitor patients for signs of exposure related toxicity when Exjade is coadministered with other CYP2C8 substrates [see *Clinical Pharmacology (12.3)*].

### 7.4 Agents Metabolized by CYP1A2

Deferasirox inhibits CYP1A2 resulting in an increase in CYP1A2 substrate (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, theophylline, tizanidine) concentration when these drugs are coadministered. An increase in theophylline plasma concentrations could lead to clinically significant theophylline induced CNS or other adverse reactions. Avoid the concomitant use of theophylline or other CYP1A2 substrates with a narrow therapeutic index (e.g., tizanidine) with Exjade. Monitor theophylline concentrations and consider theophylline dose modification if you must coadminister theophylline with Exjade. Closely monitor patients for signs of exposure related toxicity when Exjade is coadministered with other drugs metabolized by CYP1A2 [see *Clinical Pharmacology (12.3)*].

### 7.5 Agents Inducing UDP-glucuronosyltransferase (UGT) Metabolism

Deferasirox is a substrate of UGT1A1 and to a lesser extent UGT1A3. The concomitant use of Exjade with potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in Exjade efficacy due to a possible decrease in deferasirox concentration. Avoid the concomitant use of potent UGT inducers with Exjade. Consider increasing the initial dose of Exjade if you must coadminister these agents together [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3)*].

### 7.6 Bile Acid Sequestrants

Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with Exjade due to a possible decrease in deferasirox concentration. If you must coadminister these agents together, consider increasing the initial dose of Exjade [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Pregnancy Category C*

There are no adequate and well-controlled studies with Exjade in pregnant women. Administration of deferasirox to animals during pregnancy and lactation resulted in decreased offspring viability and an increase in renal anomalies in male offspring at exposures that were less than the recommended human exposure. Exjade should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryofetal developmental studies, pregnant rats and rabbits received oral deferasirox during the period of organogenesis at doses up to (100 mg per kg/day in rats and 50 mg per kg/day in rabbits) 0.8 times the maximum recommended human dose (MRHD) on a $mg/m^2$ basis. These doses resulted in maternal toxicity but no fetal harm was observed.

In a prenatal and postnatal developmental study, pregnant rats received oral deferasirox daily from organogenesis through lactation day 20 at doses (10, 30, and 90 mg per kg/day) 0.08, 0.2, and 0.7 times the MRHD on a $mg/m^2$ basis. Maternal toxicity, loss of litters, and decreased offspring viability occurred at 0.7 times the MRHD on a $mg/m^2$ basis, and increases in renal anomalies in male offspring occurred at 0.2 times the MRHD on a $mg/m^2$ basis.

### 8.3 Nursing Mothers

It is not known whether Exjade is excreted in human milk. Deferasirox and its metabolites were excreted in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from deferasirox and its metabolites, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Of the 700 patients with transfusional iron overload who received Exjade during clinical studies, 292 were pediatric patients 2-<16 years of age with various congenital and acquired anemias, including 52 patients age 2-<6 years, 121 patients age 6-<12 years and 119 patients age 12-<16 years. Seventy percent of these patients had beta-thalassemia. Children between the ages of 2-<6 years have a systemic exposure to Exjade approximately 50% of that of adults [see *Clinical Pharmacology (12.3)*]. However, the safety and efficacy of Exjade in pediatric patients was similar to that of adult patients, and younger pediatric patients responded similarly to older pediatric patients. The recommended starting dose and dosing modification are the same for children and adults [see *Clinical Studies (14), Indications and Usage (1), Dosage and Administration (2.1)*].

Growth and development in patients with chronic iron overload due to blood transfusions were within normal limits in children followed for up to 5 years in clinical trials.

Sixteen pediatric patients (10 to <16 years of age) with chronic iron overload and NTDT were treated with Exjade in clinical studies. The safety and efficacy of Exjade in these children was similar to that seen in the adults. The recommended starting dose and dosing modification are the same for children and adults with chronic iron overload in NTDT [see *Clinical Studies (14), Indications and Usage (1.2), Dosage and Administration (2.2)*].

Safety and effectiveness have not been established in pediatric patients with chronic iron overload due to blood transfusions who are less than 2 years of age or pediatric patients with chronic iron overload and NTDT who are less than 10 years of age.

### 8.5 Geriatric Use

Four hundred thirty-one (431) patients ≥65 years of age were studied in clinical trials of Exjade in the transfusional iron overload setting. The majority of these patients had myelodysplastic syndrome (MDS) (n=393). In these trials, elderly patients experienced a higher frequency of adverse reactions than younger patients. Monitor elderly patients for early signs or symptoms of adverse reactions that may require a

dose adjustment. Elderly patients are at increased risk for toxicity due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

### 8.6 Renal Impairment

For patients with renal impairment (ClCr 40–60 mL/min), reduce the starting dose by 50% [see *Dosage and Administration (2.4), Clinical Pharmacology (12.3)*]. Exjade is contraindicated in patients with a creatinine clearance <40 mL/min or serum creatinine >2 times the age-appropriate upper limit of normal [see *Contraindications (4)*].

Exjade can cause renal failure. Monitor serum creatinine and calculate creatinine clearance (using Cockcroft-Gault method) during treatment in all patients. Reduce, interrupt or discontinue Exjade dosing based on increases in serum creatinine [see *Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)*].

### 8.7 Hepatic Impairment

In a single dose (20 mg/kg) study in patients with varying degrees of hepatic impairment, deferasirox exposure was increased compared to patients with normal hepatic function. The average total (free and bound) AUC of deferasirox increased 16% in 6 patients with mild (Child-Pugh A) hepatic impairment, and 76% in 6 patients with moderate (Child-Pugh B) hepatic impairment compared to 6 patients with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only 1 patient.

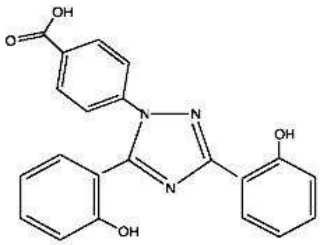
Avoid the use of Exjade in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, the starting dose should be reduced by 50%. Closely monitor patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment for efficacy and adverse reactions that may require dose titration [see *Dosage and Administration (2.4), Warnings and Precautions (5.2)*].

## 10 OVERDOSAGE

Cases of overdose (2-3 times the prescribed dose for several weeks) have been reported. In 1 case, this resulted in hepatitis which resolved without long-term consequences after a dose interruption. Single doses up to 80 mg per kg per day in iron overloaded beta-thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy volunteers, single doses of up to 40 mg per kg per day were tolerated. There is no specific antidote for Exjade. In case of overdose, induce vomiting and employ gastric lavage.

## 11 DESCRIPTION

Exjade (deferasirox) is an iron chelating agent. Exjade tablets for oral suspension contain 125 mg, 250 mg, or 500 mg deferasirox. Deferasirox is designated chemically as 4-[3,5-Bis (2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-benzoic acid and its structural formula is:




Deferasirox is a white to slightly yellow powder. Its molecular formula is $C_{21}H_{15}N_3O_4$ and its molecular weight is 373.4.

*Inactive Ingredients:* Lactose monohydrate (NF), crospovidone (NF), povidone (K30) (NF), sodium lauryl sulphate (NF), microcrystalline cellulose (NF), silicon dioxide (NF), and magnesium stearate (NF).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Exjade (deferasirox) is an orally active chelator that is selective for iron (as $Fe^{3+}$). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

### 12.2 Pharmacodynamics

Pharmacodynamic effects tested in an iron balance metabolic study showed that deferasirox (10, 20, and 40 mg per kg per day) was able to induce a mean net iron excretion (0.119, 0.329, and 0.445 mg Fe/kg body weight per day, respectively) within the clinically relevant range (0.1-0.5 mg per kg per day). Iron excretion was predominantly fecal.

### 12.3 Pharmacokinetics

*Absorption*

Exjade is absorbed following oral administration with median times to maximum plasma concentration ($t_{max}$) of about 1.5-4 hours. The $C_{max}$ and AUC of deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to deferasirox increased by an accumulation factor of 1.3-2.3 after multiple doses. The absolute bioavailability (AUC) of deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (AUC) of deferasirox was variably increased when taken with a meal.

*Distribution*

Deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state ($V_{ss}$) of deferasirox is 14.37 ± 2.69 L in adults.

*Metabolism*

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). Deconjugation of glucuronide metabolites in the intestine and subsequent reabsorption (enterohepatic recycling) was confirmed in a healthy volunteer study in which the administration of cholestyramine 12 g twice daily (strongly binds to deferasirox and its conjugates) 4 and 10 hours after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC) by interfering with the enterohepatic recycling of deferasirox.

*Excretion*

Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox and metabolites is minimal (8% of the administered dose). The mean elimination half-life ($t_{1/2}$) ranged from 8-16 hours following oral administration.

*Drug Interactions*

Midazolam: In healthy volunteers, the concomitant administration of Exjade and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam peak concentration by 23% and exposure by 17%. In the clinical setting, this effect may be more pronounced. The study was not adequately designed to conclusively assess the potential induction of CYP3A4 by deferasirox [see *Drug Interactions (7.2)*].

Repaglinide: In a healthy volunteer study, the concomitant administration of Exjade (30 mg per kg/day for 4 days) and the CYP2C8 probe substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold of control and an increase in $C_{max}$ of 62% [see *Drug Interactions (7.3)*].

Theophylline: In a healthy volunteer study, the concomitant administration of Exjade (repeated dose of 30 mg per kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an approximate doubling of the theophylline AUC and elimination half-life. The single dose $C_{max}$ was not affected, but an increase in theophylline $C_{max}$ is expected to occur with chronic dosing [see *Drug Interactions (7.4)*].

Rifampicin: In a healthy volunteer study, the concomitant administration of Exjade (single dose of 30 mg per kg) and the potent UDP-glucuronosyltransferase (UGT) inducer rifampicin (600 mg/day for 9 days) resulted in a decrease of deferasirox systemic exposure (AUC) by 44% [see *Drug Interactions (7.5)*].

Cholestyramine: The concomitant use of Exjade with bile acid sequestrants may result in a decrease in Exjade efficacy. In healthy volunteers, the administration of cholestyramine after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC) [see *Drug Interactions (7.6)*].

*In vitro* studies:

- Cytochrome P450 Enzymes: Deferasirox inhibits human CYP3A4, CYP2C8, CYP1A2, CYP2A6, CYP2D6, and CYP2C19 *in vitro*.
- Transporter Systems: The addition of cyclosporin A (PgP/MRP1/MRP2 inhibitor) or verapamil (PgP/MRP1 inhibitor) did not influence ICL670 permeability *in vitro*.

*Pharmacokinetics in Specific Populations*

Pediatric: Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox was less than in adult patients. In children <6 years of age, systemic exposure was about 50% lower than in adults.

Geriatric: The pharmacokinetics of deferasirox have not been studied in elderly patients (65 years of age or older).

Gender: Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males.

Renal Impairment: Compared to patients with MDS and ClCr >60 mL/min, patients with MDS and ClCr 40 to 60 mL/min (n=34) had approximately 50% higher mean deferasirox trough plasma concentrations.

### 12.6 QT Prolongation

The effect of 20 and 40 mg per kg per day of deferasirox on the QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg), parallel group study in 182 healthy male and female volunteers age 18-65 years. No evidence of prolongation of the QTc interval was observed in this study.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week oral carcinogenicity study in Wistar rats showed no evidence of carcinogenicity from deferasirox at doses up to 60 mg per kg per day (0.48 times the MRHD on a $mg/m^2$ basis). A 26-week oral carcinogenicity study in p53 (+/-) transgenic mice has shown no evidence of carcinogenicity from deferasirox at doses up to 200 mg per kg per day (0.81 times the MRHD on a $mg/m^2$ basis) in males and 300 mg per kg per day (1.21 times the MRHD on a $mg/m^2$ basis) in females.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was positive in 1 of 3 *in vivo* oral rat micronucleus tests.

Deferasirox at oral doses up to 75 mg per kg per day (0.6 times the MRHD on a $mg/m^2$ basis) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

## 14 CLINICAL STUDIES

**Transfusional Iron Overload**

The primary efficacy study, Study 1, was a multicenter, open-label, randomized, active-comparator control study to compare Exjade (deferasirox) and deferoxamine in patients with beta-thalassemia and transfusional hemosiderosis. Patients ≥2 years of age were randomized in a 1:1 ratio to receive either oral Exjade at starting doses of 5, 10, 20, or 30 mg per kg once daily or subcutaneous Desferal (deferoxamine) at starting doses of 20 to 60 mg per kg for at least 5 days per week based on LIC at baseline (2-3, >3-7, >7-14, and >14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values <7 mg Fe/g dry weight were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

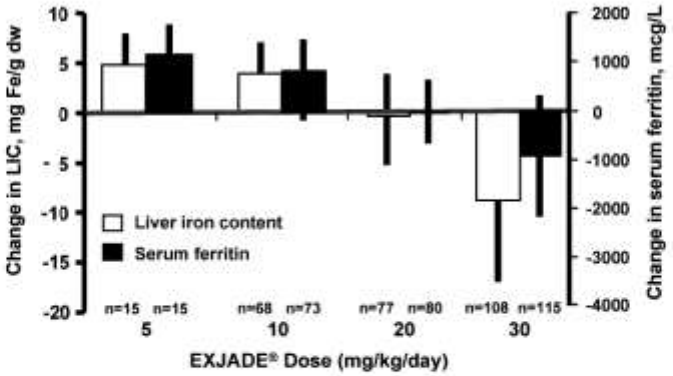
Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of ≥3 mg Fe/g dry weight for baseline values ≥10 mg Fe/g dry weight, reduction of baseline values between 7 and <10 to <7 mg Fe/g dry weight, or maintenance or reduction for baseline values <7 mg Fe/g dry weight.

A total of 586 patients were randomized and treated, 296 with Exjade and 290 with deferoxamine. The mean age was 17.1 years (range, 2-53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (Exjade n=276; deferoxamine n=277) who had LIC evaluated at baseline and 12 months or discontinued due to an adverse event. The percentage of patients achieving the primary endpoint was 52.9% for Exjade and 66.4% for deferoxamine. The relative efficacy of Exjade to deferoxamine cannot be determined from this study.

In patients who had an LIC at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with Exjade and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin was observed with Exjade doses of 20 to 30 mg per kg per day. Exjade doses below 20 mg per kg per day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg per kg per day is recommended [see *Dosage and Administration (2.1)*].

**Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following EXJADE (5-30 mg per kg per day) in Study 1**




Study 2 was an open-label, noncomparative trial of efficacy and safety of Exjade given for 1 year to patients with chronic anemias and transfusional hemosiderosis. Similar to Study 1, patients received 5, 10, 20, or 30 mg per kg per day of Exjade based on baseline LIC.

A total of 184 patients were treated in this study: 85 patients with beta-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n=47; Diamond-Blackfan syndrome, n=30; other, n=22). 19% of patients were <16 years of age and 16% were ≥65 years of age. There was a reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).

Study 3 was a multicenter, open-label, randomized trial of the safety and efficacy of Exjade relative to deferoxamine given for 1 year in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to Exjade at doses of 5, 10, 20, or 30 mg per kg per day or subcutaneous deferoxamine at doses of 20-60 mg per kg per day for 5 days per week according to baseline LIC.

A total of 195 patients were treated in this study: 132 with Exjade and 63 with deferoxamine. 44% of patients were <16 years of age and 91% were black. At end of study, the mean change in LIC (as measured by magnetic susceptometry by a superconducting quantum interference device) in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving Exjade (n=113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n=54).

One-hundred five (105) patients with thalassemia major and cardiac iron overload were enrolled in a study assessing the change in cardiac MRI T2* value (measured in milliseconds, ms) before and after treatment with deferasirox. Cardiac T2* values at baseline ranged from 5 to <20 ms. The geometric mean of cardiac T2* in the 68 patients who completed 3 years of Exjade therapy increased from 11.98 ms at baseline to 17.12 ms at 3 years. Cardiac T2* values improved in patients with severe cardiac iron overload (<10 ms) and in those with mild to moderate cardiac iron overload (≥10 to <20 ms). The clinical significance of these observations is unknown.

Six hundred twenty-seven patients with MDS were enrolled across 5 uncontrolled trials. Two hundred thirty-nine of the 627 patients were enrolled in trials that limited enrollment to patients with IPSS Low or Intermediate 1 risk MDS and the remaining 388 patients were enrolled in trials that did not specify MDS risk stratification but required a life expectancy of greater than 1 year. Planned duration of treatment in these trials ranged from 1 year (365 patients) to 5 years (47 patients). These trials evaluated the effects of Exjade therapy on parameters of iron overload, including LIC (125 patients) and serum ferritin (627 patients). Percent of patients completing planned duration of treatment was 51% in the largest 1 year study, 52% in the 3-year study and 22% in the 5 year study. The major causes for treatment discontinuation were withdrawal of consent, adverse reaction, and death. Over 1 year of follow-up across these pooled studies, mean change in serum ferritin was -332.8 (±2615.59) mcg/L (n=593) and mean change in LIC was -5.9 (±8.32) mg Fe/g dw (n=68). Results of these pooled studies in 627 patients with MDS suggest a progressive decrease in serum ferritin and LIC beyond 1 year in those patients who are able to continue Exjade. No controlled trials have been performed to demonstrate that these reductions improve morbidity or mortality in patients with MDS. Adverse reactions with Exjade therapy occur more frequently in older patients [see *Use in Specific Populations (8.5)*]. In elderly patients, including those with MDS, individualize the decision to remove accumulated iron based on clinical circumstances and the anticipated clinical benefit and risks of Exjade therapy.

**Non-Transfusion Dependent Thalassemia**

Study 4 was a randomized, double-blind, placebo-controlled trial of treatment with Exjade for patients 10 years of age or older with NTDT syndromes and iron overload. Eligible patients had an LIC of at least 5 mg Fe/g dw measured by R2 MRI and a serum ferritin exceeding 300 mcg/L at screening (2 consecutive values at least 14 days apart from each other). A total of 166 patients were randomized, 55 to the Exjade 5 mg/kg/day dose group, 55 to the Exjade 10 mg/kg/day dose group, and 56 to placebo (28 to each matching placebo group). Doses could be increased after 6 months if the LIC exceeded 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The patients enrolled included 89 males and 77 females. The underlying disease was beta-thalassemia intermedia in 95 (57%) patients, HbE beta-thalassemia in 49 (30%) patients, and alpha-thalassemia in 22 (13%) patients. There were 17 pediatric patients in the study. Caucasians comprised 57% of the study population and Asians comprised 42%. The median baseline LIC (range) for all patients was 12.1 (2.6-49.1) mg Fe/g dw. Follow-up was for 1 year. The primary efficacy endpoint of change in LIC from baseline to Week 52 was statistically significant in favor of both Exjade dose groups compared with placebo ($p \leq 0.001$) (Table 5). Furthermore, a statistically significant dose effect of Exjade was observed in favor of the 10 mg/kg/day dose group (10 versus 5 mg/kg/day, p=0.009). In a descriptive analysis, the target LIC (less than 5 mg Fe/g dw) was reached by 15 (27%) of 55 patients in the 10 mg/kg/day arm, 8 (15%) of 55 patients in the 5 mg/kg/day arm and 2 (4%) of 56 patients in the combined placebo groups.

**Table 5. Absolute Change in LIC at Week 52 in NTDT Patients**

| | Starting Dose[1] | | | |
|---|---|---|---|---|
| | Placebo | EXJADE 5 mg/kg/day | EXJADE 10 mg/kg/day | EXJADE 20 mg/kg/day |
| **Study 4[2]** | | | | |
| Number of Patients | n=54 | n=51 | n=54 | - |
| Mean LIC at Baseline (mg Fe/g dw) | 16.1 | 13.4 | 14.4 | - |
| Mean Change (mg Fe/g dw) | +0.4 | -2.0 | -3.8 | - |
| (95% Confidence Interval) | (-0.6, +1.3) | (-2.9, -1.0) | (-4.8, -2.9) | - |
| **Study 5** | | | | |
| Number of Patients | - | n=8 | n=77 | n=43 |
| Mean LIC at Baseline (mg Fe/g dw) | - | 5.6 | 8.8 | 23.5 |
| Mean Change (mg Fe/g dw) | - | -1.5 | -2.8 | -9.1 |
| (95% Confidence Interval) | - | (-3.7, +0.7) | (-3.4, -2.2) | (-11.0, -7.3) |

[1]Randomized dose in Study 4 or assigned starting dose in Study 5

[2]Least square mean change for Study 4

Study 5 was an open-label trial of Exjade for the treatment of patients previously enrolled on Study 4, including cross-over to active treatment for those previously treated with placebo. The starting dose of Exjade in Study 5 was assigned based on the patient's LIC at completion of Study 4, being 20 mg/kg/day for an LIC exceeding 15 mg Fe/g dw, 10 mg/kg/day for LIC 3-15 mg Fe/g dw, and observation if the LIC was less than 3 mg Fe/g dw. Patients could continue on 5 mg/kg/day if they had previously exhibited at least a 30% reduction in LIC. Doses could be increased to a maximum of 20 mg/kg/day after 6 months if the LIC was more than 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The primary efficacy endpoint in Study 5 was the proportion of patients achieving an LIC less than 5 mg Fe/g dw. A total of 133 patients were enrolled. Twenty patients began Study 5 with an LIC less than 5 mg Fe/g dw. Of the 113 patients with a baseline LIC of at least 5 mg Fe/g dw in Study 5, the target LIC (less than 5 mg Fe/g dw) was reached by 39 (35%). The responders included 4 (10%) of 39 patients treated at 20 mg/kg/day for a baseline LIC exceeding 15 mg Fe/g dw, and 31 (51%) of 61 patients treated at 10 mg/kg/day for a baseline LIC between 5 and 15 mg Fe/g dw. The absolute change in LIC at Week 52 by starting dose is shown in Table 5 above.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Exjade is provided as 125 mg, 250 mg, and 500 mg tablets for oral suspension.

*125 mg*

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "125" on one side and "NVR" on the other.

Bottles of 30 tablets……(NDC 0078-0468-15)

*250 mg*

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "250" on one side and "NVR" on the other.

Bottles of 30 tablets……(NDC 0078-0469-15)

*500 mg*

Off-white, round, flat tablet with beveled edge and imprinted with "J" and "500" on one side and "NVR" on the other.

Bottles of 30 tablets.....(NDC 0078-0470-15)

Store Exjade tablets at 25°C (77°F); excursions are permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature]. Protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

- Advise patients to take Exjade once daily on an empty stomach at least 30 minutes prior to food, preferably at the same time every day. Instruct patients to completely disperse the tablets in water, orange juice, or apple juice, and drink the resulting suspension immediately. After the suspension has been swallowed, resuspend any residue in a small volume of the liquid and swallow [see *Dosage and Administration (2.3)*].
- Advise patients not to chew tablets or swallow them whole [see *Dosage and Administration (2.3)*].
- Caution patients not to take aluminum-containing antacids and Exjade simultaneously [see *Drug Interactions (7.1)*].
- Because auditory and ocular disturbances have been reported with Exjade, conduct auditory testing and ophthalmic testing before starting Exjade treatment and thereafter at regular intervals [see *Warnings and Precautions (5.9)*].
- Caution patients experiencing dizziness to avoid driving or operating machinery [see *Adverse Reactions (6.1)*].
- Caution patients about the potential for the development of GI ulcers or bleeding when taking Exjade in combination with drugs that have ulcerogenic or hemorrhagic potential, such as NSAIDs, corticosteroids, oral bisphosphonates, or anticoagulants [see *Warnings and Precautions (5.3)*].
- Caution patients about potential loss of effectiveness of drugs metabolized by CYP3A4 (e.g., cyclosporine, simvastatin, hormonal contraceptive agents) when Exjade is administered with these drugs [see *Drug Interactions (7.2)*].
- Caution patients about potential loss of effectiveness of Exjade when administered with drugs that are potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir). Based on serum ferritin levels and clinical response, consider increases in the dose of Exjade when concomitantly used with potent UGT inducers [see *Drug Interactions (7.5)*].
- Caution patients about potential loss of effectiveness of Exjade when administered with drugs that are bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol). Based on serum ferritin levels and clinical response, consider increases in the dose of Exjade when concomitantly used with bile acid sequestrants [see *Drug Interactions (7.6)*].
- Perform careful monitoring of glucose levels when repaglinide is used concomitantly with Exjade. An interaction between Exjade and other CYP2C8 substrates like paclitaxel cannot be excluded [see *Drug Interactions (7.3)*].
- Advise patients that blood tests will be performed because Exjade may affect your kidneys, liver, or blood cells. The blood tests will be performed every month or more frequently if you are at increased risk of complications (e.g., preexisting kidney condition, are elderly, have multiple medical conditions, or are taking medicine that affects your organs). There have been reports of severe kidney and liver problems, blood disorders, stomach hemorrhage and death in patients taking Exjade [see *Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5)*].
- Skin rashes may occur during Exjade treatment and if severe, interrupt treatment. Serious allergic reactions (which include swelling of the throat) have been reported in patients taking Exjade, usually within the first month of treatment. If reactions are severe, advise patients to stop taking Exjade and contact their doctor immediately [see *Warnings and Precautions (5.6, 5.7, 5.8)*].

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936



T2013-XX

## APPENDIX B: JADENU LABEL

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use JADENU safely and effectively. See full prescribing information for JADENU.**

**JADENU™ (deferasirox) tablets, for oral use**
**Initial U.S. Approval: 2005**

**WARNING: RENAL FAILURE, HEPATIC FAILURE, AND GASTROINTESTINAL HEMORRHAGE**

***See full prescribing information for complete boxed warning.***

**JADENU may cause serious and fatal:**
- **renal toxicity, including failure (5.1)**
- **hepatic toxicity, including failure (5.2)**
- **gastrointestinal hemorrhage (5.3)**

**JADENU therapy requires close patient monitoring, including laboratory tests of renal and hepatic function. (5)**

### INDICATIONS AND USAGE

JADENU is an iron chelator indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. This indication is approved under accelerated approval based on a reduction of liver iron concentrations and serum ferritin levels. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)

JADENU is 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 (Fe) concentration (LIC) of at least 5 mg Fe per gram of dry weight (Fe/g dw) and a serum ferritin greater than 300 mcg/L. This indication is approved under accelerated approval based on a reduction of liver iron concentrations (to less than 5 mg Fe/g dw) and serum ferritin levels. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.2)

Limitation of Use
Controlled clinical trials of JADENU in patients with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusion have not been performed. (1.3)

The safety and efficacy of JADENU when administered with other iron chelation therapy have not been established. (1.3)

### DOSAGE AND ADMINISTRATION

- Transfusional iron overload: Initial dose 14 mg/kg (calculated to nearest whole tablet) once daily. (2.1)
- NTDT syndromes: Initial dose 7 mg/kg (calculated to nearest whole tablet) once daily. (2.2)
- Monitor serum ferritin monthly and adjust dose accordingly. (2.1, 2.2)
- Monitor LIC every 6 months and adjust dose accordingly. (2.2)
- Take on an empty stomach or with a low-fat meal. (2.3)
- Reduce dose for moderate (Child-Pugh B) hepatic impairment by 50%. Avoid in patients with severe (Child-Pugh C) hepatic impairment. (2.4)
- Reduce dose by 50% in patients with renal impairment (CrCr 40–60 mL/min). (2.4)

### DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg, 180 mg, 360 mg. (3)

### CONTRAINDICATIONS

- Serum creatinine greater than 2 times the age-appropriate upper limit of normal (ULN) or creatinine clearance (CrCr) less than 40 mL/min. (4)
- Patients with poor performance status. (4)
- Patients with high-risk myelodysplastic syndromes (MDS). (4)
- Patients with advanced malignancies. (4)
- Patients with platelet counts <50 x $10^9$/L. (4)
- Known hypersensitivity to deferasirox or any component of JADENU. (4)

### WARNINGS AND PRECAUTIONS

- Bone marrow suppression: Neutropenia, agranulocytosis, worsening anemia, and thrombocytopenia, including fatal events; monitor blood counts during JADENU therapy. Interrupt therapy for toxicity. (5.4)
- Increased Toxicity in the Elderly: Monitor closely for toxicity. (5.5)
- Hypersensitivity Reactions: Discontinue JADENU for severe reactions and institute medical intervention. (5.6)
- Severe skin reactions including Stevens-Johnson syndrome: Discontinue JADENU and evaluate. (5.7)

### ADVERSE REACTIONS

In patients with transfusional iron overload, the most frequently occurring (>5%) adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine. In deferasirox-treated patients with NTDT syndromes, the most frequently occurring (>5%) adverse reactions are diarrhea, rash and nausea. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### DRUG INTERACTIONS

- Avoid the use of JADENU with aluminum-containing antacid preparations due to the mechanism of action of JADENU. (7.1)
- Deferasirox increases the exposure of the CYP2C8 substrate repaglinide. Consider repaglinide dose reduction and monitor blood glucose levels. (7.3)
- Avoid the use of JADENU with CYP1A2 substrate theophylline as theophylline levels could be increased. (7.4)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, may cause fetal harm. (8.1)
- Lactation: Discontinue drug or breastfeeding, taking into consideration importance of drug to mother. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 3/2015**

FULL PRESCRIBING INFORMATION: CONTENTS*



* Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**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.**
- **Measure serum creatinine and determine creatinine clearance (ClCr) in duplicate prior to initiation of therapy and monitor renal function at least monthly thereafter. For patients with baseline renal impairment or increased risk of acute renal failure, monitor creatinine weekly for the first month, then at least monthly. Consider dose reduction, interruption, or discontinuation based on increases in serum creatinine *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)]*.**

**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 *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*.**

**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 *[see Warnings and Precautions (5.3)]*.**

## 1 INDICATIONS AND USAGE

### 1.1 Treatment of Chronic Iron Overload Due to Blood Transfusions (Transfusional Iron Overload)

JADENU is indicated for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. This indication is approved under accelerated approval based on a reduction of liver iron concentrations and serum ferritin levels *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

### 1.2 Treatment of Chronic Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

JADENU is 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 greater than 300 mcg/L. This indication is approved under accelerated approval based on a reduction of liver iron concentrations (to less than 5 mg Fe/g dw) and serum ferritin levels *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

### 1.3 Limitation of Use

Controlled clinical trials of JADENU with myelodysplastic syndromes (MDS) and chronic iron overload due to blood transfusions have not been performed *[see Clinical Studies (14)]*.

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Transfusional Iron Overload

JADENU therapy should only be considered when a patient has evidence of chronic transfusional iron overload. The evidence should include the transfusion of at least 100 mL/kg of packed red blood cells (e.g., at least 20 units of packed red blood cells for a 40 kg person or more in individuals weighing more than 40 kg), and a serum ferritin consistently greater than 1000 mcg/L.

Prior to starting therapy, obtain:

- serum ferritin level
- baseline serum creatinine in duplicate (due to variations in measurements) and determine the ClCr (Cockcroft-Gault method) *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*
- serum transaminases and bilirubin *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*
- baseline auditory and ophthalmic examinations *[see Warnings and Precautions (5.8)]*

The recommended initial dose of JADENU for patients 2 years of age and older is 14 mg per kg body weight orally, once daily. Calculate doses (mg per kg per day) to the nearest whole tablet. Changes in weight of pediatric patients over time must be taken into account when calculating the dose.

After commencing therapy, monitor serum ferritin monthly and adjust the dose of JADENU, if necessary, every 3 to 6 months based on serum ferritin trends. Make dose adjustments in steps of 3.5 or 7 mg per kg and tailor adjustments to the individual patient's response and therapeutic goals. In patients not adequately controlled with doses of 21 mg per kg (e.g., serum ferritin levels persistently above 2500 mcg/L and not showing a decreasing trend over time), doses of up to 28 mg per kg may be considered. Doses above 28 mg per kg are not recommended.

If the serum ferritin falls consistently below 500 mcg/L, consider temporarily interrupting therapy with JADENU *[see Warnings and Precautions (5.9)]*.

### 2.2 Iron Overload in Non-Transfusion-Dependent Thalassemia Syndromes

JADENU therapy should only be considered when a patient with NTDT syndrome has an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L.

Prior to starting therapy, obtain:

- LIC by liver biopsy or by an FDA-cleared or approved method for identifying patients for treatment with deferasirox therapy
- Serum ferritin level on at least 2 measurements 1 month apart *[see Clinical Studies (14)]*
- Baseline serum creatinine in duplicate (due to variations in measurements) and determine the ClCr (Cockcroft-Gault method) *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*
- Serum transaminases and bilirubin *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*
- Baseline auditory and ophthalmic examinations *[see Warnings and Precautions (5.8)]*

Initiating therapy:

- The recommended initial dose of JADENU is 7 mg per kg body weight orally once daily. Calculate doses (mg per kg per day) to the nearest whole tablet.
- If the baseline LIC is greater than 15 mg Fe/g dw, consider increasing the dose to 14 mg/kg/day after 4 weeks.

During therapy:

- Monitor serum ferritin monthly. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw.
- Monitor LIC every 6 months.
- After 6 months of therapy, if the LIC remains greater than 7 mg Fe/g dw, increase the dose of deferasirox to a maximum of 14 mg/kg/day. Do not exceed a maximum of 14 mg/kg/day.
- If after 6 months of therapy, the LIC is 3 to 7 mg Fe/g dw, continue treatment with deferasirox at no more than 7 mg/kg/day.
- When the LIC is less than 3 mg Fe/g dw, interrupt treatment with deferasirox and continue to monitor the LIC.
- Monitor blood counts, hepatic function, and renal function *[see Warnings and Precautions (5.1, 5.2, 5.4)]*.

Restart treatment when the LIC rises again to more than 5 mg Fe/g dw.

**2.3 Administration**

JADENU tablets should be swallowed once daily with water or other liquids, preferably at the same time each day. JADENU tablets may be taken on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories). Examples of light meals include 1 whole wheat English muffin, 1 packet jelly (0.5 ounces), and skim milk (8 fluid ounces) or a turkey sandwich (2 oz. turkey on whole wheat bread w/ lettuce, tomato, and 1 packet mustard). Do not take JADENU with aluminum-containing antacid products *[see Drug Interactions (7.1)]*.

For patients who are currently on chelation therapy with Exjade tablets for oral suspension and converting to JADENU tablets, the dose of JADENU should be about 30% lower, rounded to the nearest whole tablet. The table below provides additional information on dosing conversion to JADENU tablets.

| | EXJADE Tablets for oral suspension (white round tablet) | JADENU Tablets (film coated blue oval tablet) |
|---|---|---|
| **Transfusion-Dependent Iron Overload** | | |
| Starting Dose | 20 mg/kg/day | 14 mg/kg/day |
| Titration Increments | 5–10 mg/kg | 3.5–7 mg/kg |
| Maximum Dose | 40 mg/kg/day | 28 mg/kg/day |
| **Non-Transfusion-Dependent Thalassemia Syndromes** | | |
| Starting Dose | 10 mg/kg/day | 7 mg/kg/day |
| Titration Increments | 5–10 mg/kg | 3.5–7 mg/kg |
| Maximum Dose | 20 mg/kg/day | 14 mg/kg/day |

For patients that have trouble swallowing JADENU tablets, consider the use of deferasirox tablets for oral suspension (see the deferasirox tablets for oral suspension prescribing information).

**2.4 Use in Patients with Baseline Hepatic or Renal Impairment**

*Patients with Baseline Hepatic Impairment*

Mild (Child-Pugh A) hepatic impairment: No dose adjustment is necessary.

Moderate (Child-Pugh B) hepatic impairment: Reduce the starting dose by 50%.

Severe (Child-Pugh C) hepatic impairment: Avoid JADENU *[see Warnings and Precautions (5.2), Use in Specific Populations (8.7)]*.

*Patients with Baseline Renal Impairment*

For patients with renal impairment (ClCr 40 to 60 mL/min), reduce the starting dose by 50% *[see Use in Specific Populations (8.6)]*. Do not use JADENU in patients with serum creatinine greater than 2 times the upper limit of normal (ULN) or ClCr less than 40 mL/min *[see Contraindications (4)]*.

**2.5 Dose Modifications for Increases in Serum Creatinine**

For serum creatinine increases while receiving JADENU *[see Warnings and Precautions (5.1)]* modify the dose as follows:

**Transfusional Iron Overload**

*Adults and Adolescents (ages 16 years and older):*

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, reduce the dose by 7 mg per kg.

*Pediatric Patients (ages 2 to 15 years):*

- Reduce the dose by 7 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate ULN.

*All Patients (regardless of age):*

- Discontinue therapy for serum creatinine greater than 2 times the age-appropriate ULN or for creatinine clearance less than 40 mL/min. *[see Contraindications (4)]*

**Non-Transfusion-Dependent Thalassemia Syndromes**

*Adults and Adolescents (ages 16 years and older):*

- If the serum creatinine increases by 33% or more above the average baseline measurement, repeat the serum creatinine within 1 week, and if still elevated by 33% or more, interrupt therapy if the dose is 3.5 mg per kg, or reduce by 50% if the dose is 7 or 14 mg per kg.

*Pediatric Patients (ages 10 to 15 years):*

- Reduce the dose by 3.5 mg per kg if serum creatinine increases to greater than 33% above the average baseline measurement and greater than the age appropriate ULN.

*All Patients (regardless of age):*

- Discontinue therapy for serum creatinine greater than 2 times the age-appropriate ULN or for creatinine clearance less than 40 mL/min *[see Contraindications (4)]*.

### 2.6 Dose Modifications Based on Concomitant Medications

*UDP-glucuronosyltransferases (UGT) Inducers*

Concomitant use of UGT inducers decreases JADENU systemic exposure. Avoid the concomitant use of potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) with JADENU. If you must administer JADENU with 1 of these agents, consider increasing the initial dose of JADENU by 50%, and monitor serum ferritin levels and clinical responses for further dose modification *[see Dosage and Administration (2.1, 2.2), Drug Interactions (7.5)]*.

*Bile Acid Sequestrants*

Concomitant use of bile acid sequestrants decreases JADENU systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with JADENU. If you must administer JADENU with 1 of these agents, consider increasing the initial dose of JADENU by 50%, and monitor serum ferritin levels and clinical responses for further dose modification *[see Dosage and Administration (2.1, 2.2), Drug Interactions (7.6)]*.

## 3 DOSAGE FORMS AND STRENGTHS

- 90 mg tablets

  Light blue oval biconvex film-coated tablet with beveled edges, debossed with 'NVR' on one side and '90' on a slight upward slope in between two debossed curved lines on the other side.

- 180 mg tablets

  Medium blue oval biconvex film-coated tablet with beveled edges, debossed with 'NVR' on one side and '180' on a slight upward slope in between two debossed curved lines on the other side.

- 360 mg tablets

  Dark blue oval biconvex film-coated tablet with beveled edges, debossed with 'NVR' on one side and '360' on a slight upward slope in between two debossed curved lines on the other side.

## 4 CONTRAINDICATIONS

JADENU is contraindicated in patients with:

- Serum creatinine greater than 2 times the age-appropriate ULN or ClCr less than 40 mL/min *[see Warning and Precautions (5.1)]*;
- Poor performance status;
- High-risk myelodysplastic syndromes;
- Advanced malignancies;
- Platelet counts $<50 \times 10^9$/L;
- Known hypersensitivity to deferasirox or any component of JADENU *[see Warnings and Precautions (5.6), Adverse Reactions (6.2)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Renal Toxicity, Renal Failure, and Proteinuria

JADENU can cause acute renal failure, fatal in some patients and requiring dialysis in others. Postmarketing experience showed that most fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. In the clinical trials, deferasirox-treated patients experienced dose-dependent increases in serum creatinine. In patients with transfusional iron overload, these increases in creatinine occurred at a greater frequency compared to deferoxamine-treated patients (38% versus 14%, respectively, in Study 1 and 36% versus 22%, respectively, in Study 3) *[see Adverse Reactions (6.1, 6.2)]*.

Measure serum creatinine in duplicate (due to variations in measurements) and determine the ClCr (estimated by the Cockcroft-Gault method) before initiating therapy in all patients in order to establish a reliable pretreatment baseline. Monitor serum creatinine weekly during the first month after initiation or modification of therapy and at least monthly thereafter. Monitor serum creatinine and/or ClCr more frequently if creatinine levels are increasing. Dose reduction, interruption, or discontinuation based on increases in serum creatinine may be necessary *[see Dosage and Administration (2.5)]*.

JADENU is contraindicated in patients with ClCr less than 40 mL/minute or serum creatinine greater than 2 times the age appropriate ULN.

Renal tubular damage, including Fanconi's Syndrome, has been reported in patients treated with deferasirox, most commonly in children and adolescents with beta-thalassemia and serum ferritin levels <1500 mcg/L.

Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of deferasirox-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1. In clinical trials in patients with transfusional iron overload, deferasirox was temporarily withheld until the urine protein/creatinine ratio fell below 0.6 mg/mg. Monthly monitoring for proteinuria is recommended. The mechanism and clinical significance of the proteinuria are uncertain *[see Adverse Reactions (6.1)]*.

### 5.2 Hepatic Toxicity and Failure

Deferasirox can cause hepatic injury, fatal in some patients. In Study 1, 4 patients (1.3%) 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 greater than 55 years of age. Hepatic failure was more common in patients with significant comorbidities, including liver cirrhosis and multiorgan failure *[see Adverse Reactions (6.1)]*.

Measure transaminases (AST and 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 *[see Dosage and Administration (2.4), Use in Specific Populations (8.7)]*. Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment may be at higher risk for hepatic toxicity.

### 5.3 Gastrointestinal (GI) Hemorrhage

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 *[see Adverse Reactions (6.1)]*. 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 event is suspected. The risk of gastrointestinal 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.

### 5.4 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 below $50 \times 10^9$/L.

### 5.5 Increased Risk of Toxicity in the Elderly

Deferasirox has been associated with serious and fatal adverse reactions in the postmarketing setting, predominantly in elderly patients. Monitor elderly patients treated with JADENU more frequently for toxicity *[see Use in Specific Populations (8.5)]*.

### 5.6 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 *[see Adverse Reactions (6.2)]*. If reactions are severe, discontinue JADENU and institute appropriate medical intervention. JADENU is contraindicated in patients with known hypersensitivity to JADENU.

### 5.7 Skin Toxicity

Severe skin reactions, including Stevens-Johnson syndrome (SJS) and erythema multiforme, have been reported during deferasirox therapy *[see Adverse Reactions (6.2)]*. If SJS or erythema multiforme is suspected, discontinue JADENU and evaluate.

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 in combination with a short period of oral steroid administration *[see Adverse Reactions (6.1)]*.

### 5.8 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. 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.

**5.9 Overchelation**

For patients with transfusional iron overload, measure serum ferritin monthly to assess for possible overchelation of iron. If the serum ferritin falls below 500 mcg/L, consider interrupting therapy with JADENU, since overchelation may increase JADENU toxicity *[see Dosage and Administration (2.1)]*.

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 *[see Clinical Studies (14)]*.

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. JADENU was evaluated in healthy volunteer trials. Currently, there are no clinical data in patients with JADENU tablets. JADENU contains the same active ingredient as Exjade (deferasirox) tablets for oral suspension. The following adverse reactions have been reported with Exjade tablets for oral suspension.

The following adverse reactions are also discussed in other sections of the labeling:

- Renal Toxicity, Renal Failure, and Proteinuria *[see Warnings and Precautions (5.1)]*
- Hepatic Toxicity and Failure *[see Warnings and Precautions (5.2)]*
- Gastrointestinal (GI) Hemorrhage *[see Warnings and Precautions (5.3)]*
- Bone Marrow Suppression *[see Warnings and Precautions (5.4)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*
- Skin Toxicity *[see Warnings and Precautions (5.7)]*
- Auditory and Ocular Abnormalities *[see Warnings and Precautions (5.8)]*

**Transfusional Iron Overload**

A total of 700 adult and pediatric patients were treated with deferasirox for 48 weeks in premarketing studies. These included 469 patients with beta-thalassemia, 99 with rare anemias, and 132 with sickle cell disease. Of these patients, 45% were male, 70% were Caucasian and 292 patients were <16 years of age. In the sickle cell disease population, 89% of patients were black. Median treatment duration among the sickle cell patients was 51 weeks. Of the 700 patients treated, 469 (403 beta-thalassemia and 66 rare anemias) were entered into extensions of the original clinical protocols. In ongoing extension studies, median durations of treatment were 88 to 205 weeks.

Six hundred twenty-seven patients with MDS were enrolled across 5 uncontrolled trials. These studies varied in duration from 1 to 5 years. The discontinuation rate across studies in the first year was 46% (AEs 20%, withdrawal of consent 10%, death 8%, other 4%, lab abnormalities 3%, and lack of efficacy 1%). Among 47 patients enrolled in the study of 5-year duration, 10 remained on deferasirox at the completion of the study.

Table 1 displays adverse reactions occurring in >5% of deferasirox-treated beta-thalassemia patients (Study 1), sickle cell disease patients (Study 3), and patients with MDS (MDS pool). Abdominal pain, nausea, vomiting, diarrhea, skin rashes, and increases in serum creatinine were the most frequent adverse reactions reported with a

suspected relationship to deferasirox. Gastrointestinal symptoms, increases in serum creatinine, and skin rash were dose related.

**Table 1. Adverse Reactions* Occurring in >5% of Deferasirox-treated Patients in Study 1, Study 3, and MDS Pool**

| | Study 1 (Beta-thalassemia) | | Study 3 (Sickle Cell Disease) | | MDS Pool |
|---|---|---|---|---|---|
| Preferred Term | Deferasirox N=296 n (%) | Deferoxamine N=290 n (%) | Deferasirox N=132 n (%) | Deferoxamine N=63 n (%) | Deferasirox N=627 n (%) |
| Abdominal Pain** | 63 (21) | 41 (14) | 37 (28) | 9 (14) | 145 (23) |
| Diarrhea | 35 (12) | 21 (7) | 26 (20) | 3 (5) | 297 (47) |
| Creatinine Increased*** | 33 (11) | 0 (0) | 9 (7) | 0 | 89 (14) |
| Nausea | 31 (11) | 14 (5) | 30 (23) | 7 (11) | 161 (26) |
| Vomiting | 30 (10) | 28 (10) | 28 (21) | 10 (16) | 83 (13) |
| Rash | 25 (8) | 9 (3) | 14 (11) | 3 (5) | 83 (13) |

*Adverse reaction frequencies are based on adverse events reported regardless of relationship to study drug.
**Includes 'abdominal pain', 'abdominal pain lower', and 'abdominal pain upper' which were reported as adverse events.
***Includes 'blood creatinine increased' and 'blood creatinine abnormal' which were reported as adverse events. Also see Table 2.

In Study 1, a total of 113 (38%) patients treated with deferasirox had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) and 25 (8%) patients required dose reductions. Increases in serum creatinine appeared to be dose related *[see Warnings and Precautions (5.1)]*. In this study, 17 (6%) patients treated with deferasirox developed elevations in SGPT/ALT levels >5 times the ULN at 2 consecutive visits. Of these, 2 patients had liver biopsy proven drug-induced hepatitis and both discontinued deferasirox therapy *[see Warnings and Precautions (5.2)]*. An additional 2 patients, who did not have elevations in SGPT/ALT >5 times the ULN, discontinued deferasirox because of increased SGPT/ALT. Increases in transaminases did not appear to be dose related. Adverse reactions that led to discontinuations included abnormal liver function tests (2 patients) and drug-induced hepatitis (2 patients), skin rash, glycosuria/proteinuria, Henoch Schönlein purpura, hyperactivity/insomnia, drug fever, and cataract (1 patient each).

In Study 3, a total of 48 (36%) patients treated with deferasirox had increases in serum creatinine >33% above baseline on 2 separate occasions (Table 2) *[see Warnings and Precautions (5.1)]*. Of the patients who experienced creatinine increases in Study 3, 8 deferasirox-treated patients required dose reductions. In this study, 5 patients in the deferasirox group developed elevations in SGPT/ALT levels >5 times the ULN at 2 consecutive visits and 1 patient subsequently had deferasirox permanently discontinued. Four additional patients discontinued due to adverse reactions with a suspected relationship to study drug, including diarrhea, pancreatitis associated with gallstones, atypical tuberculosis, and skin rash.

In the MDS pool, in the first year, a total of 229 (37%) patients treated with deferasirox had increases in serum creatinine >33% above baseline on 2 consecutive occasions (Table 2) and 8 (3.5%) patients permanently discontinued *[see Warnings and Precautions (5.1)]*. A total of 5 (0.8%) patients developed SGPT/ALT levels >5 times the ULN at 2 consecutive visits. The most frequent adverse reactions that led to discontinuation included increases in serum creatinine, diarrhea, nausea, rash, and vomiting. Death was reported in the first year in 52 (8%) of patients *[see Clinical Studies (14)]*.

**Table 2. Number (%) of Patients with Increases in Serum Creatinine or SGPT/ALT in Study 1, Study 3, and MDS Pool**

| | Study 1 (Beta-thalassemia) | | Study 3 (Sickle Cell Disease) | | MDS Pool |
|---|---|---|---|---|---|
| Laboratory Parameter | Deferasirox N=296 n (%) | Deferoxamine N=290 n (%) | Deferasirox N=132 n (%) | Deferoxamine N=63 n (%) | Deferasirox N=627 n (%) |
| **Serum Creatinine** | | | | | |
| Creatinine increase >33% at 2 consecutive postbaseline visits | 113 (38) | 41 (14) | 48 (36) | 14 (22) | 229 (37) |
| Creatinine increase >33% and >ULN at 2 consecutive postbaseline visits | 7 (2) | 1 (0) | 3 (2) | 2 (3) | 126 (20) |
| **SGPT/ALT** | | | | | |
| SGPT/ALT >5 x ULN at 2 postbaseline visits | 25 (8) | 7 (2) | 2 (2) | 0 | 9 (1) |
| SGPT/ALT >5 x ULN at 2 consecutive postbaseline visits | 17 (6) | 5 (2) | 5 (4) | 0 | 5 (1) |

**Non-Transfusion-Dependent Thalassemia Syndromes**

In Study 4, 110 patients with NTDT received 1 year of treatment with deferasirox 5 or 10 mg/kg/day and 56 patients received placebo in a double-blind, randomized trial. In Study 5, 130 of the patients who completed Study 4 were treated with open-label deferasirox at 5, 10, or 20 mg/kg/day (depending on the baseline LIC) for 1 year *[see Clinical Studies (14)]*. Table 3 displays adverse reactions occurring in >5% in any group. The most frequent adverse reactions with a suspected relationship to study drug were nausea, rash, and diarrhea.

**Table 3. Adverse Reactions Occurring in >5% in NTDT Patients**

| | Study 4 | | Study 5 |
|---|---|---|---|
| | Deferasirox | Placebo | Deferasirox |
| | N=110 | N=56 | N=130 |
| | n (%) | n (%) | n (%) |
| **Any adverse reaction** | **31 (28)** | **9 (16)** | **27 (21)** |
| Nausea | 7 (6) | 4 (7) | 2 (2) |
| Rash | 7 (6) | 1 (2) | 2 (2) |
| Diarrhea | 5 (5) | 1 (2) | 7 (5) |

In Study 4, 1 patient in the placebo 10 mg/kg/day group experienced an ALT increase to >5 times ULN and >2 times baseline (Table 4). Three deferasirox-treated patients (all in the 10 mg/kg/day group) had 2 consecutive serum creatinine level increases >33% from baseline and >ULN. Serum creatinine returned to normal in all 3 patients (in 1 spontaneously and in the other 2 after drug interruption). Two additional cases of ALT increase and 2 additional cases of serum creatinine increase were observed in the 1-year extension of Study 4.

**Table 4. Number (%) of NTDT Patients with Increases in Serum Creatinine or SGPT/ALT**

| | Study 4 | | Study 5 |
|---|---|---|---|
| | Deferasirox | Placebo | Deferasirox |
| | N=110 | N=56 | N=130 |
| **Laboratory Parameter** | **n (%)** | **n (%)** | **n (%)** |
| Serum creatinine (>33% increase from baseline and >ULN at ≥2 consecutive postbaseline values) | 3 (3) | 0 | 2 (2) |
| SGPT/ALT (>5 x ULN and >2 x baseline) | 1 (1) | 1 (2) | 2 (2) |

*Proteinuria*

In clinical studies, urine protein was measured monthly. Intermittent proteinuria (urine protein/creatinine ratio >0.6 mg/mg) occurred in 18.6% of deferasirox-treated patients compared to 7.2% of deferoxamine-treated patients in Study 1 *[see Warnings and Precautions (5.1)]*.

*Other Adverse Reactions*

In the population of more than 5,000 patients with transfusional iron overload who have been treated with deferasirox during clinical trials, adverse reactions occurring in 0.1% to 1% of patients included gastritis, edema, sleep disorder, pigmentation disorder, dizziness, anxiety, maculopathy, cholelithiasis, pyrexia, fatigue, pharyngolaryngeal pain, early cataract, hearing loss, gastrointestinal hemorrhage, gastric ulcer (including multiple ulcers), duodenal ulcer, and renal tubulopathy (Fanconi's syndrome). Adverse reactions occurring in 0.01% to 0.1% of patients included optic neuritis, esophagitis, and erythema multiforme. Adverse reactions which most frequently led to dose interruption or dose adjustment during clinical trials were rash, gastrointestinal disorders, infections, increased serum creatinine, and increased serum transaminases.

### 6.2 Postmarketing Experience

The following adverse reactions have been spontaneously reported during post-approval use of deferasirox in the transfusional iron overload setting. Because these reactions are reported voluntarily from a population of uncertain size, in which patients may have received concomitant medication, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), leukocytoclastic vasculitis, urticaria, alopecia

Immune system disorders: hypersensitivity reactions (including anaphylaxis and angioedema)

Renal and urinary disorders: acute renal failure, tubulointerstitial nephritis

Hepatobiliary disorders: hepatic failure

Gastrointestinal disorders: gastrointestinal hemorrhage

Blood and lymphatic system disorders: worsening anemia

## 7 DRUG INTERACTIONS

### 7.1 Aluminum Containing Antacid Preparations

The concomitant administration of JADENU and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, avoid use of JADENU with aluminum-containing antacid preparations due to the mechanism of action of JADENU.

### 7.2 Agents Metabolized by CYP3A4

Deferasirox may induce CYP3A4 resulting in a decrease in CYP3A4 substrate concentration when these drugs are coadministered. Closely monitor patients for signs of reduced effectiveness when deferasirox is administered with drugs metabolized by CYP3A4 (e.g., alfentanil, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, hormonal contraceptive agents, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, tolvaptan, tipranavir, triazolam, ticagrelor, and vardenafil) *[see Clinical Pharmacology (12.3)]*.

### 7.3 Agents Metabolized by CYP2C8

Deferasirox inhibits CYP2C8 resulting in an increase in CYP2C8 substrate (e.g., repaglinide and paclitaxel) concentration when these drugs are coadministered. If JADENU and repaglinide are used concomitantly, consider decreasing the dose of repaglinide and perform careful monitoring of blood glucose levels. Closely monitor patients for signs of exposure related toxicity when JADENU is coadministered with other CYP2C8 substrates *[see Clinical Pharmacology (12.3)]*.

### 7.4 Agents Metabolized by CYP1A2

Deferasirox inhibits CYP1A2 resulting in an increase in CYP1A2 substrate (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, theophylline, tizanidine) concentration when these drugs are coadministered. An increase in theophylline plasma concentrations could lead to clinically significant theophylline induced CNS or other adverse reactions. Avoid the concomitant use of theophylline or other CYP1A2 substrates with a narrow therapeutic index (e.g., tizanidine) with JADENU. Monitor theophylline concentrations and consider theophylline dose modification if you must coadminister theophylline with JADENU. Closely monitor patients for signs of exposure related toxicity when JADENU is coadministered with other drugs metabolized by CYP1A2 *[see Clinical Pharmacology (12.3)]*.

### 7.5 Agents Inducing UDP-glucuronosyltransferase (UGT) Metabolism

Deferasirox is a substrate of UGT1A1 and to a lesser extent UGT1A3. The concomitant use of JADENU with potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in JADENU efficacy due to a possible decrease in deferasirox concentration. Avoid the concomitant use of potent UGT inducers with JADENU. Consider increasing the initial dose of JADENU if you must coadminister these agents together *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

### 7.6 Bile Acid Sequestrants

Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with JADENU due to a possible decrease in deferasirox concentration. If you must coadminister these agents together, consider increasing the initial dose of JADENU *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Risk Summary*

There are no adequate and well-controlled studies with JADENU in pregnant women. Administration of deferasirox to animals during pregnancy and lactation resulted in decreased offspring viability and an increase in renal anomalies in male offspring at exposures that were less than the recommended human exposure. JADENU should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

*Animal Data*

In embryo-fetal developmental studies, pregnant rats and rabbits received oral deferasirox during the period of organogenesis at doses up to 100 mg/kg/day in rats and 50 mg/kg/day in rabbits (1.2 times the maximum recommended human dose (MRHD) on a mg/m$^2$ basis). These doses resulted in maternal toxicity but no fetal harm was observed.

In a prenatal and postnatal developmental study, pregnant rats received oral deferasirox daily from organogenesis through lactation day 20 at doses of 10, 30, and 90 mg/kg/day (0.1, 0.3, and 1.0 times the MRHD on a mg/m$^2$ basis). Maternal toxicity, loss of litters, and decreased offspring viability occurred at 90 mg/kg/day (1.0 times the MRHD on a mg/m$^2$ basis), and increases in renal anomalies in male offspring occurred at 30 mg/kg/day (0.3 times the MRHD on a mg/m$^2$ basis).

**8.2 Lactation**

*Risk Summary*

It is not known whether JADENU is excreted in human milk. Deferasirox and its metabolites were excreted in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from deferasirox and its metabolites, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

**8.4 Pediatric Use**

Of the 700 patients with transfusional iron overload who received deferasirox during clinical studies, 292 were pediatric patients 2 to <16 years of age with various congenital and acquired anemias, including 52 patients age 2 to <6 years, 121 patients age 6 to <12 years and 119 patients age 12 to <16 years. Seventy percent of these patients had beta-thalassemia. Children between the ages of 2 to <6 years have a systemic exposure to deferasirox approximately 50% of that of adults *[see Clinical Pharmacology (12.3)]*. However, the safety and efficacy of deferasirox in pediatric patients was similar to that of adult patients, and younger pediatric patients responded similarly to older pediatric patients. The recommended starting dose and dosing modification are the same for children and adults *[see Clinical Studies (14), Indications and Usage (1), Dosage and Administration (2.1)]*.

Growth and development in patients with chronic iron overload due to blood transfusions were within normal limits in children followed for up to 5 years in clinical trials.

Sixteen pediatric patients (10 to <16 years of age) with chronic iron overload and NTDT were treated with deferasirox in clinical studies. The safety and efficacy of deferasirox in these children was similar to that seen in the adults. The recommended starting dose and dosing modification are the same for children and adults with chronic iron overload in NTDT *[see Clinical Studies (14), Indications and Usage (1.2), Dosage and Administration (2.2)]*.

Safety and effectiveness have not been established in pediatric patients with chronic iron overload due to blood transfusions who are less than 2 years of age or pediatric patients with chronic iron overload and NTDT who are less than 10 years of age.

### 8.5 Geriatric Use

Four hundred thirty-one patients ≥65 years of age were studied in clinical trials of deferasirox in the transfusional iron overload setting. Two hundred twenty-five of these patients were between 65 and 75 years of age while 206 were ≥75 years of age. The majority of these patients had myelodysplastic syndrome (MDS) (n=393). In these trials, elderly patients experienced a higher frequency of adverse reactions than younger patients. Monitor elderly patients for early signs or symptoms of adverse reactions that may require a dose adjustment. Elderly patients are at increased risk for toxicity due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

### 8.6 Renal Impairment

For patients with renal impairment (ClCr 40 to 60 mL/min), reduce the starting dose by 50% *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*. JADENU is contraindicated in patients with a ClCr <40 mL/min or serum creatinine >2 times the age-appropriate ULN *[see Contraindications (4)]*.

JADENU can cause renal failure. Monitor serum creatinine and calculate ClCr (using Cockcroft-Gault method) during treatment in all patients. Reduce, interrupt or discontinue JADENU dosing based on increases in serum creatinine *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.1)]*.

### 8.7 Hepatic Impairment

In a single dose (20 mg/kg) study in patients with varying degrees of hepatic impairment, deferasirox exposure was increased compared to patients with normal hepatic function. The average total (free and bound) AUC of deferasirox increased 16% in 6 patients with mild (Child-Pugh A) hepatic impairment, and 76% in 6 patients with moderate (Child-Pugh B) hepatic impairment compared to 6 patients with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only 1 patient.

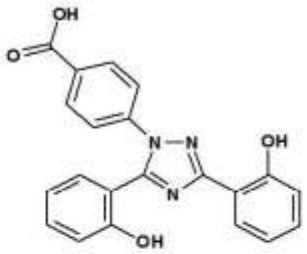
Avoid the use of JADENU in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, the starting dose should be reduced by 50%. Closely monitor patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment for efficacy and adverse reactions that may require dose titration *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*.

## 10 OVERDOSAGE

Cases of overdose (2 to 3 times the prescribed dose for several weeks) have been reported. In 1 case, this resulted in hepatitis which resolved without long-term consequences after a dose interruption. Single doses of deferasirox up to 80 mg per kg per day with the tablet for oral suspension formulation in iron overloaded beta-thalassemic patients have been tolerated with nausea and diarrhea noted. In healthy subjects, single doses of up to 40 mg per kg per day with the tablet for oral suspension formulation were tolerated. There is no specific antidote for JADENU. In case of overdose, induce vomiting and employ gastric lavage.

## 11 DESCRIPTION

JADENU (deferasirox) is an iron chelating agent provided as a tablet for oral use. Deferasirox is designated chemically as 4-[3,5-bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid and has the following structural formula:



Deferasirox is a white to slightly yellow powder. It has a molecular formula $C_{21}H_{15}N_3O_4$ and molecular weight of 373.4.

JADENU tablets contain 90 mg, 180 mg, or 360 mg deferasirox. Inactive ingredients include microcrystalline cellulose, crospovidone, povidone (K30), magnesium stearate, colloidal silicon dioxide, and poloxamer (188). The film coating contains opadry blue.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

JADENU (deferasirox) is an orally active chelator that is selective for iron (as $Fe^{3+}$). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

### 12.2 Pharmacodynamics

Pharmacodynamic effects tested in an iron balance metabolic study with the tablet for oral suspension formulation showed that deferasirox (10, 20, and 40 mg per kg per day) was able to induce a mean net iron excretion (0.119, 0.329, and 0.445 mg Fe/kg body weight per day, respectively) within the clinically relevant range (0.1 to 0.5 mg per kg per day). Iron excretion was predominantly fecal.

*Cardiac Electrophysiology*

The effect of 20 and 40 mg per kg per day of deferasirox (tablets for oral suspension) on the QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg), parallel group study in 182 healthy male and female subjects age 18 to 65 years. No evidence of prolongation of the QTc interval was observed in this study.

### 12.3 Pharmacokinetics

*Absorption*

Based on studies in patients with the tablet for oral suspension, deferasirox is absorbed following oral administration with median times to maximum plasma concentration ($t_{max}$) of about 1.5 to 4 hours. In healthy subjects, JADENU showed comparable $t_{max}$. The $C_{max}$ and AUC of deferasirox increase approximately linearly with dose after both single administration and under steady-state conditions. Exposure to deferasirox increased by an accumulation factor of 1.3 to 2.3 after multiple doses with the tablet for oral suspension formulation.

The absolute bioavailability (AUC) of deferasirox tablets for oral suspension is 70% compared to an intravenous dose. The bioavailability (AUC) of JADENU was 36% greater than with deferasirox tablets for oral suspension. After strength-adjustment, JADENU (i.e., 360 mg strength) was equivalent to deferasirox tablets for oral suspension (i.e., 500 mg strength) with respect to the mean AUC under fasting conditions, however the

mean $C_{max}$ was increased by 30%. The exposure-response analysis for safety indicated that 30% increase in JADENU $C_{max}$ is not clinically meaningful.

A food-effect study involving administration of JADENU to healthy subjects under fasting conditions and with a low-fat (fat content <7% of total calories) or high-fat (fat content >50% of total calories) meal indicated that the AUC and $C_{max}$ were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and $C_{max}$ were increased by 18% and 29%, respectively. The increases in $C_{max}$ due to the change in formulation and due to the effect of a high-fat meal may be additive and therefore, it is recommended that JADENU should be taken on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories) *[see Dosage and Administration (2.3)]*.

*Distribution*

Deferasirox is highly (~99%) protein bound almost exclusively to serum albumin. The percentage of deferasirox confined to the blood cells was 5% in humans. The volume of distribution at steady state ($V_{ss}$) of deferasirox is 14.37 ± 2.69 L in adults.

*Metabolism*

Glucuronidation is the main metabolic pathway for deferasirox, with subsequent biliary excretion. Deconjugation of glucuronidates in the intestine and subsequent reabsorption (enterohepatic recycling) is likely to occur. Deferasirox is mainly glucuronidated by UGT1A1 and to a lesser extent UGT1A3. CYP450-catalyzed (oxidative) metabolism of deferasirox appears to be minor in humans (about 8%). Deconjugation of glucuronide metabolites in the intestine and subsequent reabsorption (enterohepatic recycling) was confirmed in a healthy subjects study in which the administration of cholestyramine 12 g twice daily (strongly binds to deferasirox and its conjugates) 4 and 10 hours after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure (AUC) by interfering with the enterohepatic recycling of deferasirox.

*Excretion*

Deferasirox and metabolites are primarily (84% of the dose) excreted in the feces. Renal excretion of deferasirox and metabolites is minimal (8% of the administered dose). The mean elimination half-life ($t_{1/2}$) ranged from 8 to 16 hours following oral administration.

*Drug Interactions*

Midazolam: In healthy subjects, the concomitant administration of deferasirox tablets for oral suspension and midazolam (a CYP3A4 probe substrate) resulted in a decrease of midazolam peak concentration by 23% and exposure by 17%. In the clinical setting, this effect may be more pronounced. The study was not adequately designed to conclusively assess the potential induction of CYP3A4 by deferasirox *[see Drug Interactions (7.2)]*.

Repaglinide: In a healthy volunteer study, the concomitant administration of deferasirox tablets for oral suspension (30 mg per kg/day for 4 days) and the CYP2C8 probe substrate repaglinide (single dose of 0.5 mg) resulted in an increase in repaglinide systemic exposure (AUC) to 2.3-fold of control and an increase in $C_{max}$ of 62% *[see Drug Interactions (7.3)]*.

Theophylline: In a healthy volunteer study, the concomitant administration of deferasirox tablets for oral suspension (repeated dose of 30 mg per kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an approximate doubling of the theophylline AUC and elimination half-life. The single dose $C_{max}$ was not affected, but an increase in theophylline $C_{max}$ is expected to occur with chronic dosing *[see Drug Interactions (7.4)]*.

Rifampicin: In a healthy volunteer study, the concomitant administration of deferasirox tablets for oral suspension (single dose of 30 mg per kg) and the potent UDP-glucuronosyltransferase (UGT) inducer

rifampicin (600 mg/day for 9 days) resulted in a decrease of deferasirox systemic exposure (AUC) by 44% *[see Drug Interactions (7.5)]*.

Cholestyramine: The concomitant use of deferasirox with bile acid sequestrants may result in a decrease in deferasirox efficacy. In healthy subjects, the administration of cholestyramine after a single dose of deferasirox tablets for oral suspension resulted in a 45% decrease in deferasirox exposure (AUC) *[see Drug Interactions (7.6)]*.

In vitro studies:

- Cytochrome P450 Enzymes: Deferasirox inhibits human CYP3A4, CYP2C8, CYP1A2, CYP2A6, CYP2D6, and CYP2C19 in vitro.
- Transporter Systems: The addition of cyclosporin A (PgP/MRP1/MRP2 inhibitor) or verapamil (PgP/MRP1 inhibitor) did not influence ICL670 permeability in vitro.

*Pharmacokinetics in Specific Populations*

Pediatric: Following oral administration of single or multiple doses, systemic exposure of adolescents and children to deferasirox was less than in adult patients. In children <6 years of age, systemic exposure was about 50% lower than in adults.

Geriatric: The pharmacokinetics of deferasirox have not been studied in elderly patients (65 years of age or older).

Gender: Females have a moderately lower apparent clearance (by 17.5%) for deferasirox compared to males.

Renal Impairment: Compared to patients with MDS and ClCr >60 mL/min, patients with MDS and ClCr 40 to 60 mL/min (n=34) had approximately 50% higher mean deferasirox trough plasma concentrations.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week oral carcinogenicity study in Wistar rats showed no evidence of carcinogenicity from deferasirox at doses up to 60 mg/kg/day (0.7 times the MRHD on a mg/m$^2$ basis). A 26-week oral carcinogenicity study in p53 (+/-) transgenic mice has shown no evidence of carcinogenicity from deferasirox at doses up to 200 mg/kg/day (1.2 times the MRHD on a mg/m$^2$ basis) in males and 300 mg/kg/day (1.7 times the MRHD on a mg/m$^2$ basis) in females.

Deferasirox was negative in the Ames test and chromosome aberration test with human peripheral blood lymphocytes. It was positive in 1 of 3 *in vivo* oral rat micronucleus tests.

Deferasirox at oral doses up to 75 mg/kg/day (0.9 times the MRHD on a mg/m$^2$ basis) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

## 14 CLINICAL STUDIES

JADENU was evaluated in healthy subjects. There are no clinical data in patients with JADENU. JADENU contains the same active ingredient as Exjade (deferasirox) tablets for oral suspension. The following information is based on clinical trials conducted with Exjade tablets for oral suspension.

**Transfusional Iron Overload**

The primary efficacy study, Study 1, was a multicenter, open-label, randomized, active-comparator control study to compare deferasirox tablets for oral suspension and deferoxamine in patients with beta-thalassemia and transfusional hemosiderosis. Patients ≥2 years of age were randomized in a 1:1 ratio to receive either oral deferasirox tablets for oral suspension at starting doses of 5, 10, 20, or 30 mg per kg once daily or subcutaneous

Desferal (deferoxamine) at starting doses of 20 to 60 mg per kg for at least 5 days per week based on LIC at baseline (2 to 3, >3 to 7, >7 to 14, and >14 mg Fe/g dry weight). Patients randomized to deferoxamine who had LIC values <7 mg Fe/g dry weight were permitted to continue on their prior deferoxamine dose, even though the dose may have been higher than specified in the protocol.

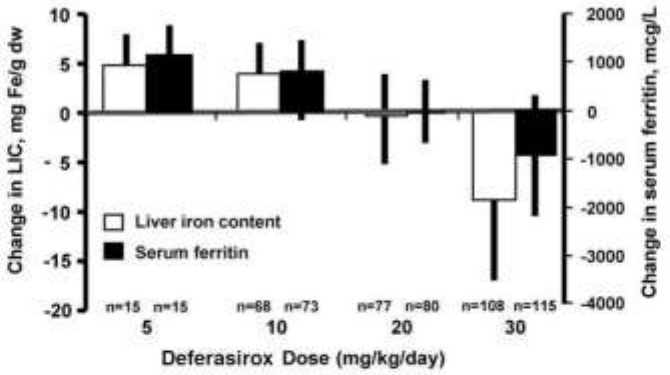
Patients were to have a liver biopsy at baseline and end of study (after 12 months) for LIC. The primary efficacy endpoint was defined as a reduction in LIC of ≥3 mg Fe/g dry weight for baseline values ≥10 mg Fe/g dry weight, reduction of baseline values between 7 and <10 to <7 mg Fe/g dry weight, or maintenance or reduction for baseline values <7 mg Fe/g dry weight.

A total of 586 patients were randomized and treated, 296 with deferasirox tablets for oral suspension and 290 with deferoxamine. The mean age was 17.1 years (range, 2 to 53 years); 52% were females and 88% were Caucasian. The primary efficacy population consisted of 553 patients (deferasirox tablets for oral suspension n=276; deferoxamine n=277) who had LIC evaluated at baseline and 12 months or discontinued due to an adverse event. The percentage of patients achieving the primary endpoint was 52.9% for deferasirox tablets for oral suspension and 66.4% for deferoxamine. The relative efficacy of deferasirox to deferoxamine cannot be determined from this study.

In patients who had an LIC at baseline and at end of study, the mean change in LIC was -2.4 mg Fe/g dry weight in patients treated with deferasirox tablets for oral suspension and -2.9 mg Fe/g dry weight in patients treated with deferoxamine.

Reduction of LIC and serum ferritin was observed with deferasirox tablet for oral suspension doses of 20 to 30 mg per kg per day. Deferasirox tablets for oral suspension doses below 20 mg per kg per day failed to provide consistent lowering of LIC and serum ferritin levels (Figure 1). Therefore, a starting dose of 20 mg per kg per day is recommended *[see Dosage and Administration (2.1)]*.

**Figure 1. Changes in Liver Iron Concentration and Serum Ferritin Following Deferasirox tablets for oral suspension (5 to 30 mg per kg per day) in Study 1**




Study 2 was an open-label, noncomparative trial of efficacy and safety of deferasirox tablets for oral suspension given for 1 year to patients with chronic anemias and transfusional hemosiderosis. Similar to Study 1, patients received 5, 10, 20, or 30 mg per kg per day of deferasirox tablets for oral suspension based on baseline LIC.

A total of 184 patients were treated in this study: 85 patients with beta-thalassemia and 99 patients with other congenital or acquired anemias (myelodysplastic syndromes, n=47; Diamond-Blackfan syndrome, n=30; other,

n=22). 19% of patients were <16 years of age and 16% were ≥65 years of age. There was a reduction in the absolute LIC from baseline to end of study (-4.2 mg Fe/g dry weight).

Study 3 was a multicenter, open-label, randomized trial of the safety and efficacy of deferasirox tablets for oral suspension relative to deferoxamine given for 1 year in patients with sickle cell disease and transfusional hemosiderosis. Patients were randomized to deferasirox tablets for oral suspension at doses of 5, 10, 20, or 30 mg per kg per day or subcutaneous deferoxamine at doses of 20-60 mg per kg per day for 5 days per week according to baseline LIC.

A total of 195 patients were treated in this study: 132 with deferasirox tablets for oral suspension and 63 with deferoxamine. Forty-four percent of patients were <16 years of age and 91% were black. At end of study, the mean change in LIC (as measured by magnetic susceptometry by a superconducting quantum interference device) in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox tablets for oral suspension (n=113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n=54).

One-hundred five (105) patients with thalassemia major and cardiac iron overload were enrolled in a study assessing the change in cardiac MRI T2* value (measured in milliseconds, ms) before and after treatment with deferasirox. Cardiac T2* values at baseline ranged from 5 to <20 ms. The geometric mean of cardiac T2* in the 68 patients who completed 3 years of deferasirox tablets for oral suspension therapy increased from 11.98 ms at baseline to 17.12 ms at 3 years. Cardiac T2* values improved in patients with severe cardiac iron overload (<10 ms) and in those with mild to moderate cardiac iron overload (≥10 to <20 ms). The clinical significance of these observations is unknown.

Six hundred twenty-seven patients with MDS were enrolled across 5 uncontrolled trials. Two hundred thirty-nine of the 627 patients were enrolled in trials that limited enrollment to patients with IPSS Low or Intermediate 1 risk MDS and the remaining 388 patients were enrolled in trials that did not specify MDS risk stratification but required a life expectancy of greater than 1 year. Planned duration of treatment in these trials ranged from 1 year (365 patients) to 5 years (47 patients). These trials evaluated the effects of deferasirox tablets for oral suspension therapy on parameters of iron overload, including LIC (125 patients) and serum ferritin (627 patients). Percent of patients completing planned duration of treatment was 51% in the largest 1 year study, 52% in the 3-year study and 22% in the 5 year study. The major causes for treatment discontinuation were withdrawal of consent, adverse reaction, and death. Over 1 year of follow-up across these pooled studies, mean change in serum ferritin was -332.8 (±2615.59) mcg/L (n=593) and mean change in LIC was -5.9 (±8.32) mg Fe/g dw (n=68). Results of these pooled studies in 627 patients with MDS suggest a progressive decrease in serum ferritin and LIC beyond 1 year in those patients who are able to continue deferasirox tablets for oral suspension. No controlled trials have been performed to demonstrate that these reductions improve morbidity or mortality in patients with MDS. Adverse reactions with deferasirox tablets for oral suspension therapy occur more frequently in older patients *[see Use in Specific Populations (8.5)]*. In elderly patients, including those with MDS, individualize the decision to remove accumulated iron based on clinical circumstances and the anticipated clinical benefit and risks of deferasirox tablets for oral suspension therapy.

**Non-Transfusion-Dependent Thalassemia**

Study 4 was a randomized, double-blind, placebo-controlled trial of treatment with deferasirox tablets for oral suspension for patients 10 years of age or older with NTDT syndromes and iron overload. Eligible patients had an LIC of at least 5 mg Fe/g dw measured by R2 MRI and a serum ferritin exceeding 300 mcg/L at screening (2 consecutive values at least 14 days apart from each other). A total of 166 patients were randomized, 55 to the deferasirox tablets for oral suspension 5 mg/kg/day dose group, 55 to the deferasirox tablets for oral suspension 10 mg/kg/day dose group, and 56 to placebo (28 to each matching placebo group). Doses could be increased after 6 months if the LIC exceeded 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The

patients enrolled included 89 males and 77 females. The underlying disease was beta-thalassemia intermedia in 95 (57%) patients, HbE beta-thalassemia in 49 (30%) patients, and alpha-thalassemia in 22 (13%) patients. There were 17 pediatric patients in the study. Caucasians comprised 57% of the study population and Asians comprised 42%. The median baseline LIC (range) for all patients was 12.1 (2.6 to 49.1) mg Fe/g dw. Follow-up was for 1 year. The primary efficacy endpoint of change in LIC from baseline to Week 52 was statistically significant in favor of both deferasirox dose groups compared with placebo ($p \leq 0.001$) (Table 5). Furthermore, a statistically significant dose effect of deferasirox was observed in favor of the 10 mg/kg/day dose group (10 versus 5 mg/kg/day, p=0.009). In a descriptive analysis, the target LIC (less than 5 mg Fe/g dw) was reached by 15 (27%) of 55 patients in the 10 mg/kg/day arm, 8 (15%) of 55 patients in the 5 mg/kg/day arm and 2 (4%) of 56 patients in the combined placebo groups.

**Table 5. Absolute Change in LIC at Week 52 in NTDT Patients**

| | Deferasirox tablets for oral suspension Starting Dose[1] | | | |
|---|---|---|---|---|
| | **Placebo** | **5 mg/kg/day** | **10 mg/kg/day** | **20 mg/kg/day** |
| **Study 4[2]** | | | | |
| Number of Patients | n=54 | n=51 | n=54 | - |
| Mean LIC at Baseline (mg Fe/g dw) | 16.1 | 13.4 | 14.4 | - |
| Mean Change (mg Fe/g dw) | +0.4 | -2.0 | -3.8 | - |
| (95% Confidence Interval) | (-0.6, +1.3) | (-2.9, -1.0) | (-4.8, -2.9) | - |
| **Study 5** | | | | |
| Number of Patients | - | n=8 | n=77 | n=43 |
| Mean LIC at Baseline (mg Fe/g dw) | - | 5.6 | 8.8 | 23.5 |
| Mean Change (mg Fe/g dw) | - | -1.5 | -2.8 | -9.1 |
| (95% Confidence Interval) | - | (-3.7, +0.7) | (-3.4, -2.2) | (-11.0, -7.3) |

[1]Randomized dose in Study 4 or assigned starting dose in Study 5
[2]Least square mean change for Study 4

Study 5 was an open-label trial of deferasirox tablets for oral suspension for the treatment of patients previously enrolled on Study 4, including cross-over to active treatment for those previously treated with placebo. The starting dose of deferasirox tablets for oral suspension in Study 5 was assigned based on the patient's LIC at completion of Study 4, being 20 mg/kg/day for an LIC exceeding 15 mg Fe/g dw, 10 mg/kg/day for LIC 3 to 15 mg Fe/g dw, and observation if the LIC was less than 3 mg Fe/g dw. Patients could continue on 5 mg/kg/day if they had previously exhibited at least a 30% reduction in LIC. Doses could be increased to a maximum of 20 mg/kg/day after 6 months if the LIC was more than 7 mg Fe/g dw and the LIC reduction from baseline was less than 15%. The primary efficacy endpoint in Study 5 was the proportion of patients achieving an LIC less than 5 mg Fe/g dw. A total of 133 patients were enrolled. Twenty patients began Study 5 with an LIC less than 5 mg Fe/g dw. Of the 113 patients with a baseline LIC of at least 5 mg Fe/g dw in Study 5, the target LIC (less than 5 mg Fe/g dw) was reached by 39 (35%). The responders included 4 (10%) of 39 patients treated at 20 mg/kg/day for a baseline LIC exceeding 15 mg Fe/g dw, and 31 (51%) of 61 patients treated at 10 mg/kg/day for a baseline LIC between 5 and 15 mg Fe/g dw. The absolute change in LIC at Week 52 by starting dose is shown in Table 5.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

JADENU 90 mg tablets are light blue in color, film-coated, oval biconvex tablets with beveled edges, debossed with 'NVR' on one side and '90' on a slight upward slope in between two debossed curved lines on the other side. They are available in bottles of 30 tablets (NDC 0078-0654-15).

JADENU 180 mg tablets are medium blue in color, film-coated, oval biconvex tablet with beveled edges, debossed with 'NVR' on one side and '180' on a slight upward slope in between two debossed curved lines on the other side. They are available in bottles of 30 tablets (NDC 0078-0655-15).

JADENU 360 mg tablets are dark blue in color, film-coated, oval biconvex tablet with beveled edges, debossed with 'NVR' on one side and '360' on a slight upward slope in between two debossed curved lines on the other side. They are available in bottles of 30 tablets (NDC 0078-0656-15).

Store JADENU tablets at 25°C (77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

- Advise patients to take JADENU once daily, on an empty stomach or with a light meal, (contains less than 7% fat content and approximately 250 calories) preferably at the same time every day *[see Dosage and Administration (2.3)]*. Examples of light meals include 1 whole wheat English muffin, 1 packet jelly (0.5 ounces), and skim milk (8 fluid ounces) or a turkey sandwich (2 oz. turkey on whole wheat bread w/ lettuce, tomato, and 1 packet mustard).
- Advise patients to take the tablet with water or other liquids *[see Dosage and Administration (2.3)]*.
- Advise patients to store JADENU in a dry, room-temperature environment *[see How Supplied/Storage and Handling (16)]*.
- Caution patients not to take aluminum-containing antacids and JADENU simultaneously *[see Drug Interactions (7.1)]*.
- Because auditory and ocular disturbances have been reported with deferasirox, conduct auditory testing and ophthalmic testing before starting JADENU treatment and thereafter at regular intervals *[see Warnings and Precautions (5.8)]*.
- Caution patients experiencing dizziness to avoid driving or operating machinery *[see Adverse Reactions (6.1)]*.
- Caution patients about the potential for the development of GI ulcers or bleeding when taking JADENU in combination with drugs that have ulcerogenic or hemorrhagic potential, such as NSAIDs, corticosteroids, oral bisphosphonates, or anticoagulants *[see Warnings and Precautions (5.3)]*.
- Caution patients about potential loss of effectiveness of drugs metabolized by CYP3A4 (e.g., cyclosporine, simvastatin, hormonal contraceptive agents) when JADENU is administered with these drugs *[see Drug Interactions (7.2)]*.
- Caution patients about potential loss of effectiveness of JADENU when administered with drugs that are potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir). Based on serum ferritin levels and clinical response, consider increases in the dose of JADENU when concomitantly used with potent UGT inducers [see *Drug Interactions (7.5)*].

- Caution patients about potential loss of effectiveness of JADENU when administered with drugs that are bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol). Based on serum ferritin levels and clinical response, consider increases in the dose of JADENU when concomitantly used with bile acid sequestrants *[see Drug Interactions (7.6)]*.
- Perform careful monitoring of glucose levels when repaglinide is used concomitantly with JADENU. An interaction between JADENU and other CYP2C8 substrates like paclitaxel cannot be excluded *[see Drug Interactions (7.3)]*.
- Advise patients that blood tests will be performed because JADENU may affect your kidneys, liver, or blood cells. The blood tests will be performed every month or more frequently if you are at increased risk of complications (e.g., preexisting kidney condition, are elderly, have multiple medical conditions, or are taking medicine that affects your organs). There have been reports of severe kidney and liver problems, blood disorders, stomach hemorrhage and death in patients taking JADENU *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5)]*.
- Skin rashes may occur during JADENU treatment and if severe, interrupt treatment. Serious allergic reactions (which include swelling of the throat) have been reported in patients taking JADENU, usually within the first month of treatment. If reactions are severe, advise patients to stop taking JADENU and contact their doctor immediately *[see Warnings and Precautions (5.6, 5.7)]*.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936



T2015-XX
Month Year

Reference ID: 3723516

## APPENDIX C: ECOG PERFORMANCE STATUS

| ECOG Performance Status Scale | |
|---|---|
| **Grade** | **Descriptions** |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655.

## APPENDIX D: SICT QUESTIONNAIRE

**The combination of scores for each domain, as well as disease (Thalassemia having the worst adherence), age, missed doses have a high correlation with Non-Compliance.**

**SICT item Satisfaction domain**

All SICT Item responses are averaged along the response scale from 1 to 5 such that a higher satisfaction domain score indicates a high level of satisfaction.

**Perceived Effectiveness of ICT (6 items)** (lower scores in this domain indicative of non-compliance)

**Acceptance of ICT (5 items)** (higher scores in this domain indicative of non-compliance)

**Burden of ICT (5 items)** (higher scores in this domain indicative of non-compliance)

**Side Effects of ICT (3 items)** (higher scores in this domain indicative of non-compliance)

**The SICT used here is modified to exclude questions where there was no significant association, above**.

**Scoring:**

1. A total score for <u>each domain</u> would be calculated using an adjusted mean % score, compared to the total possible score of 100%.
2. Consideration for age is judgmental – adolescents suggested with lower compliance.
3. Higher number of missed doses is suggestive of non-compliance.

DisperSol Technologies, LLC
Protocol Number: DST-0509-201 Subject Initials:_____Subject #: _____ Date: _____

## Eligibility Visit
## SICT Questionnaire

**Instruction:**
**This questionnaire is intended to assess your Satisfaction with Iron Chelation Therapy (SICT) Quality of Life (QoL). Please rate the following questions on a scale of 1 – 5 as best as you can. Additional details regarding the scale are included within each section. Please only answer each question once.**

### Group 1:
### Perception of Health

| | < Strongly Disagree……Neutral……Strongly agree><br>1 2 3 4 5 | Patient Rating |
|---|---|---|
| 1. | In the past three months, did you feel your current chelation therapy would help with a longer life? | |
| 2. | In the past three months, did you feel your current chelation therapy would reduce your excess iron? | |
| 3. | In the past three months did you feel your chelation therapy would stop your condition from getting worse? | |
| 4. | In the past three months, did you think your chelation therapy was actually working? | |
| 5. | In the past three months, did you feel that chelation therapy was worthwhile? | |

### Group 2:
### Acceptance of Therapy

| | | Patient Rating |
|---|---|---|
| 1. | In the past three months, how would you rate the ease for you to take your chelation therapy?<br><Easy……Difficult><br>1 2 3 4 5 | |
| 2. | In the past three months, did you think chelation therapy was as difficult as you expected?<br>< Easy……Difficult><br>1 2 3 4 5 | |
| 3. | How would you rate how convenient it was to take chelation therapy?<br>< Convenient……Inconvenient><br>1 2 3 4 5 | |
| 4. | In the past three months, did chelation therapy meet your expectations?<br>< Fully Met……Not Met><br>1 2 3 4 5 | |

| | | |
|---|---|---|
| 5. | Were you satisfied or dissatisfied with the form of your chelation therapy (oral pill/capsules or pump)?<br><Satisfied.....Dissatisfied><br>1 2 3 4 5 | |

## Group 3:
## Burden of Therapy

| | < Never.....Always><br>1 2 3 4 5 | Patient Rating |
|---|---|---|
| 1. | In the past three months, how frequently did your chelation therapy limit your after-hours or night-time activities? | |
| 2. | In the past three months, did you feel that your chelation therapy limited your daytime activities or routine? | |
| 3. | How often did you feel your that your chelation therapy prevented you from getting a good night sleep? | |
| 4. | How often do you feel that chelation therapy made you depend on others? | |
| 5. | How disturbed were you with how much time it took to take your chelation therapy? | |

## Group 4:
## Side Effects of ICT

| | < Never.....Always><br>1 2 3 4 5 | Patient Rating |
|---|---|---|
| 1. | In the past three months, how frequently were you concerned about the side effects of your chelation therapy (e.g., pain, nausea)? | |
| 2. | How often did you feel that chelation therapy had a bad effect on your personal appearance? | |
| 3. | Did you feel pain because of your chelation therapy? | |

## To be Completed by the Site Staff:

| | |
|---|---|
| **Patient Disease: (Thalassemia, SCD, MDS)** | |
| **Number of doses missed in last 7 days** | |

The Following references were used in the development of the SICT questionnaire:

1. Development and Scoring of the Satisfaction with Iron Chelation Therapy Instrument for Patients with Iron Overload
Rofail D[1],Viala M[2], Abetz L[3], Gait C[4]
[1]Mapi Values Limited, Macclesfield, UK, [2]Mapi Values France, Lyon, France, [3]Mapi Values Limited, Bollington, UK, [4]Mapi Values Ltd, Macclesfield, UK

2. Satisfaction with iron chelation therapy and its impact on adherence in patients with Beta Thalassemia Major: Results From the Ithaca Study
Rofail D[1], Ravera S[2], Scalone L[3], Cappellini M[4], Mantovani LG[5]
[1]Mapi Values Limited, Macclesfield, UK, [2]Center of Pharmacoeconomics, University of Milan, Milan, Italy, [3]University of Milan, Milan, Italy, [4]Congenital Anemia Center, IRCSS Foundation Policlinico, Mangiagalli, Regina Elena Hospitals and University of Milan, Milan, Italy, [5]University of Naples, Federico II, Naples, Italy

3. An Instrument Assessing Satisfaction with Iron Chelation Therapy: Psychometric Testing From an Open-Label Clinical Trial
Diana Rofail · Muriel Viala · Adam Gater · Linda Abetz‑Webb · Jean‑Francois Baladi · Maria Domenica Cappellini
Received: May 10, 2010 / Published online: July 20, 2010© Springer Healthcare 2010

4. Impact of medication adherence on the effectiveness of deferasirox for the treatment of transfusional iron overload in myelodysplastic syndrome
V. Escudero-Vilaplana* PharmD PhD, X. Garcia-Gonzalez* PharmD, S. Osorio-Prendes† MD, R. M. Romero-Jimenez* PharmD PhD and M. Sanjurjo-Saez* PharmD, *Pharmacy Department, Gregorio Marañon University General Hospital, Madrid, and †Hematology Department, Gregorio Marañon University General Hospital, Madrid, Spain
Received 27 September 2015, Accepted 7 December 2015

5. Compliance and satisfaction with deferasirox (Exjade) compared with deferoxamine in patients.
Article in Hematology (Amsterdam, Netherlands) September 2013.
DOI: 10.1179/1607845413Y.0000000121 Source: PubMed

6. Compliance and satisfaction with deferasirox (Exjade®) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia.
Haghpanah S, Zarei T, Zahedi Z, Karimi M.
2014 Jun;19(4):187-91. doi: 10.1179/1607845413Y.0000000121. Epub 2013 Nov 25.

7. Satisfaction and Adherence in Patients with Iron Overload Receiving Iron Chelation Therapy as Assessed by a Newly Developed Patient Instrument
Diana Rofail, MSc,1 Linda Abetz, MA,1 Muriel Viala, MSc,2 Claire Gait, MPhil,1 Jean-Francois Baladi, MBA.3Krista Payne, MEd4, 1 Mapi Values, Cheshire, UK; 2Mapi Values, Lyon, France; 3Novartis Pharmaceuticals Corporation, East Hanovc,r, NJ, USA; •caro Research Institute, Montreal, QC, Canada