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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
# SYNOPSIS

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>Dyax Corp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Finished Product:</td>
<td>DX-2930</td>
</tr>
<tr>
<td>Name of Active Ingredient:</td>
<td>DX-2930—a recombinant, Chinese hamster ovary cell-expressed, fully human immunoglobulin 1, kappa light chain, monoclonal antibody.</td>
</tr>
<tr>
<td>Study Title:</td>
<td>A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects</td>
</tr>
<tr>
<td>Investigators and Study Centers:</td>
<td>Multicenter; see Appendix 16.1.4</td>
</tr>
<tr>
<td>Publication (reference):</td>
<td>none</td>
</tr>
<tr>
<td>Studied Period:</td>
<td>14 May 2014 (first subject informed consent) to 18 May 2015 (last subject last visit completed)</td>
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<tr>
<td>Study Phase:</td>
<td>1b</td>
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<tr>
<td>Objectives:</td>
<td>The primary objective of this study was to assess the safety and tolerability of multiple, subcutaneous (SC) administrations of DX-2930 at different dose levels in hereditary angioedema (HAE) subjects. The secondary objective of this study was to characterize the pharmacokinetics (PK) of DX-2930 following multiple SC administrations at different dose levels. The tertiary objectives of this study were to:</td>
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<tr>
<td></td>
<td>• assess the immunogenicity of DX-2930</td>
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<td>• evaluate the pharmacodynamic (PD) effects of DX-2930 through exploratory biomarker assessments</td>
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<td></td>
<td>• conduct an exploratory assessment of the indirect effects of plasma kallikrein inhibition upon endogenous C1-inhibitor (C1-INH) activity</td>
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<td></td>
<td>• conduct exploratory assessments to characterize HAE attacks and acute attack therapy usage during the study</td>
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</table>
### Methodology:
This study was a Phase 1b, multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose trial of SC administrations of DX-2930 in HAE subjects. Eligible subjects were randomized in a 2:1 ratio to receive either active study drug or placebo within a cohort. The study consisted of 3 dose cohorts (30, 100, and 300 mg), with each cohort nominally consisting of 6 subjects. Cohorts were dosed in a staggered, dose-ascending fashion. In each dosing cohort, 4 subjects were to be randomized to receive active drug and 2 subjects were to be randomized to receive placebo. Each subject within a dosing cohort received 2 doses of study drug administered SC into the upper arm. The second dose was administered 14 days following the first dose. When a cohort had completed dosing, a review was conducted of the safety data through 14 days after the second dose. Cumulative safety data from any earlier cohort were also included in the review. This safety evaluation was conducted by a dose-escalation committee (DEC) and included a review of all adverse events (AEs), vital signs, physical examinations, laboratory results, and electrocardiograms (ECGs). Escalation to the next highest dosing cohort proceeded if there were no concerning safety signals.

A flexible dose-escalation scheme was used in this study that (based on review of safety data from previous cohorts) allowed for expansion of a current or prior cohort, or intermediate doses higher or lower than the preceding dose to be studied in a subsequent cohort. This resulted in the addition of 2 additional cohorts (Cohorts 4 and 5), in which subjects were randomized 2:1 to receive either placebo or 400 mg DX-2930.

Blood samples for the measurement of plasma DX-2930 concentration were obtained prior to administration of study drug and at specific time points following study drug administration. If subjects experienced acute HAE attacks during the study, they were permitted standard-of-care acute attack treatment, as prescribed by their physician. Any subject experiencing an HAE attack (even if resolving or limited to prodromal symptoms) on Day 1 had their scheduled visit postponed for at least 72 hours after their attack had resolved. An HAE attack after signing informed consent was considered an AE.

### Number of Subjects (Planned and Analyzed):
Approximately 18 to 36 HAE subjects were to be enrolled across multiple clinical sites according to the flexible dose-escalation scheme; 37 subjects (13 placebo, 24 DX-2930) were treated and analyzed for safety; 22 subjects (0 placebo, 22 DX-2930) were included in the PK analyses; 35 subjects (13 placebo, 22 DX-2930) were included in the PD analyses; and 26 subjects (11 placebo, 4 DX-2930 300 mg, and 11 DX-2930 400 mg) were included in the primary efficacy analyses.
**Diagnosis and Main Criteria for Inclusion:** Subjects at least 18 years of age with a documented diagnosis of HAE (Type I or II) based upon all of the following:

- Documented clinical history consistent with HAE (SC or mucosal, nonpruritic swelling episodes without accompanying urticaria).
- C1-INH antigen or functional level <40% of the normal level. Subjects with C1-INH antigen or functional level 40-50% of the normal level may have been enrolled if they also had a C4 level below the normal range and a family history consistent with HAE Type I or II. Test results must have been obtained within 5 years of enrollment.
- Age at reported onset of first angioedema symptoms ≤30 years or a family history consistent with HAE Type I or II.

Subjects must also have been experiencing ≥2 HAE attacks per year, with at least 1 attack in the past 6 months.

**Test Product, Dose and Mode of Administration, Lot Number:** DX-2930 solution for SC injection. Subjects randomized to receive active study drug received 1 of the following dose levels of DX-2930: 30, 100, 300, or 400 mg, from lot number [redacted].

**Duration of Treatment:** Subjects received 2 doses of study drug administered SC to the upper arm 14 days apart.

**Reference Therapy; Dose; and Mode of Administration:** Placebo consisted of the inactive formulation of the test product. Subjects randomized to receive placebo received study drug from lot number [redacted].

**Criteria for Evaluation:**

**Pharmacokinetic Variables:**

DX-2930 non-compartmental PK variable determinations included maximum concentration in plasma (C$_{\text{max}}$), time to maximum plasma concentration (t$_{\text{max}}$), and area under the concentration-time curve from time 0 to the last quantifiable concentration in plasma at time t (AUC$_{0-t}$). DX-2930 compartmental PK variable determinations included C$_{\text{max}}$, t$_{\text{max}}$, area under the plasma concentration-time curve (AUC), terminal elimination half-life (t$_{1/2}$), apparent volume of distribution during terminal phase after extravascular administration (Vd/F), and apparent total plasma clearance after extravascular administration (CL/F).

**Safety:**

Safety variables assessed were AEs, including serious adverse events (SAEs); vital signs, including sitting or supine blood pressure, heart rate, oral body temperature, and respiratory rate; physical examination; clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis); 12-lead ECG; and plasma anti-drug antibody testing.

**Pharmacodynamic Assessments:**

The ability of DX-2930 to inhibit plasma kallikrein was assessed ex vivo in plasma using 2 different exploratory biomarker assays: 1) a fluorogenic plasma kallikrein activity assay and 2) a Western blot assay for 2-chain high molecular weight kininogen (HMWK). In addition, exploratory biomarkers (% Functional C1-INH and C4) were measured.
**Statistical Methods:**

*Pharmacokinetics:* All PK parameters were estimated by non-compartmental and compartmental analysis of the plasma concentration versus time data using WinNonlin Enterprise (Version 6.2), Pharsight Corporation. Calculation of AUC was to be performed using the linear trapezoidal rule. Actual times relative to dosing rather than the nominal times were to be used in the computation with the exception of pre-dose samples, for which a nominal time of 0 hours was used. A minimum of 3 quantifiable concentration-time points was required for generation of an AUC_{0-t}.

*Efficacy:* Pre-specified efficacy analyses evaluated subjects treated with placebo, DX-2930 300 mg, and DX-2930 400 mg with a historical baseline attack rate of at least 2 attacks over the past 3 months prior to enrollment (Primary Efficacy Analysis Population). The primary efficacy endpoint was the number of HAE attacks per week from Day 8 to Day 50. Secondary efficacy endpoints were the number of HAE attacks per week from Days 1 to 50, from Days 8 to 64, and from Days 8 to 92.

The endpoints were repeated measures of the number of distinct HAE attacks reported in a 7-day period (168 hours) for each subject. All reports of HAE attacks on study and for the historical baseline rate were subject-provided. The last-observation-carried-forward method and imputation of missing data were not used in this analysis.

Generalized Estimating Equation (GEE) approach with Poisson distribution assumption was applied to the repeated-measures mixed model with independence working correlation structure. The treatment group was a fixed effect and the number of baseline HAE attacks per week was included as a covariate in the GEE. Subject was considered as a random effect. The baseline attack rate was calculated by dividing the number of HAE attacks within the past 3 months by 13 weeks.

The baseline attack rate was used as a covariate, but there may have been a small number of large potential outliers among reported baseline attack rates. To avoid any possible undue influence of a baseline attack rate outlier, any potential outliers were tested using the Dixon Gap test (with alpha=0.05) prior to performing any efficacy analyses. If an outlier was present by the Dixon Gap test, it was given the value of mean + 2 SD, where mean and SD were computed without the presence of the Dixon outlier.

The least-square mean (lsmean) (log of the mean event rate) for each dose level and its corresponding standard error was directly estimated from the GEE model. The mean event rate was estimated by transforming the above lsmeans by the exponential function.

The lsmean difference of the natural logarithms of attack rates between each dose level and placebo, which is also the regression coefficient for each treatment group effect, and its 95% confidence interval (CI) were directly estimated from the GEE model. The ratio of the mean event rate per week for each dose level versus placebo and its 95% CI were estimated by transforming the above lsmean difference and its 95% CI by the exponential function.

The percentage change in mean attack rate of each active treatment group from the attack rate of placebo, defined as 100%*(treatment attack rate – placebo attack rate)/placebo attack rate, was also displayed. The 95% CI for the percentage change in mean attack rate was also displayed. For cases in which there were no HAE attacks, an arbitrarily small value (0.000001) was imputed for the HAE occurrence variable to enable the GEE analyses to converge.
Statistical Methods (continued):  

Safety:  
All safety data were summarized in tabular format using descriptive statistics for continuous variables and frequency and percentages for discrete variables for each dose level, total DX-2930, and overall in the Safety Population (randomized subjects who received at least 1 dose of study drug).  
The Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 coding system was used for system organ class and preferred term classification of AEs. The proportion of subjects who experienced TEAEs, life-threatening TEAEs, SAEs, AEs leading to death, and AEs leading to early termination from the study were summarized. TEAEs were summarized by severity and relationship to study drug.  
Clinical laboratory tests were summarized descriptively. Observed values and change from baseline for numeric clinical laboratory data were summarized using descriptive statistics. Shift tables were provided for hematology, coagulation, and chemistry laboratory results only.  
For DX-2930 plasma anti-drug antibody testing, by-subject results were listed by time point. A shift table was provided for confirmed results and for neutralizing antibody results.  
Observed values and change from baseline in vital sign measurements were summarized descriptively.  
Physical examination was summarized descriptively by body system and time point.  
Observed values and change from baseline at each time point for ECG parameters were summarized descriptively. An ECG shift table was provided.  
Summaries of prior and concomitant therapies by medication class and preferred term were generated.  

Summary of Results  

Pharmacokinetics:  
DX-2930 levels were dose-dependent and exhibited a prolonged half-life, typical of a human monoclonal antibody. $C_{\text{max}}$ drug levels increased with increasing dose, as expected. In addition, data indicate sustained exposure, as quantifiable concentrations were observed through Day 120 following dosing in all cohorts. The $t_{\text{max}}$ was about 18 days (approximately 3 to 4 days following the dose administered on Day 15) and the half-life was approximately 14 days. These parameters are consistent with values obtained in Study DX-2930-01.  

Pharmacodynamics:  
Based on results from the fluorogenic assay, dose-dependent plasma kallikrein inhibition was evident in plasma samples collected from the 100, 300, and 400 mg dose groups. The amount of plasma kallikrein inhibition was similar in the 30 mg and placebo dose groups. Following the second dose of DX-2930 100, 300, and 400 mg, peak inhibition values of approximately 30%, 60%, and 70%, respectively, were observed. The observed inhibition was time-dependent and aligned closely with the observed DX-2930 plasma concentrations, suggesting that DX-2930 exposure correlates with its biological activity. Following the second dose of DX-2930, the 300 and 400 mg dose groups demonstrate levels of plasma kallikrein inhibition comparable to that observed with ecallantide, a plasma kallikrein inhibitor approved by the United States Food and Drug Administration for treatment of acute HAE attacks.
Summary of Results (Continued)
Pharmacodynamics (Continued):
The results from the Western blot assay corroborate the results from the fluorogenic assay. Unactivated, pre-dose plasma obtained from the HAE subjects in this study contained approximately 52% 2-chain HMWK. In contrast, unactivated, pre-dose plasma samples obtained from healthy subjects without HAE in the Phase 1a study (DX-2930-01) contained approximately 8% 2-chain HMWK. Therefore, HAE plasma exhibits abnormal behavior with high levels of 2-chain HMWK.

No statistically significant differences in mean 2-chain HMWK levels were observed in the 30 and 100 mg dose groups versus pre-dose levels at the time points tested. An evaluation of mean 2-chain HMWK levels in plasma demonstrated statistically significant reductions ($P < 0.05$, vs pre-dose levels) in the 300 mg and 400 mg dose groups for samples collected on Day 8 and 22. Maximum reductions in 2-chain levels for the 300 mg and 400 mg dose groups occurred at the Day 22 time point, which approximates the $t_{max}$ following the second DX-2930 administration. Furthermore, in these dose groups, the level of 2-chain HMWK approached that observed in healthy subjects, demonstrating the PD activity of DX-2930 and its ability to effectively normalize the instability of HAE plasma in this assay. There were no statistically significant differences versus pre-dose levels on Days 50, 64, 92, or 120.

Efficacy:
The baseline HAE attack rate was 0.33 attacks per week in the DX-2930 300 mg group, 0.55 attacks per week in the DX-2930 400 mg group, and 0.39 attacks per week in the placebo group. From Day 8 to Day 50, the HAE attack rate (adjusted for the baseline attack rate) was 0 in the DX-2930 300 mg group and 0.045 attacks per week in the DX-2930 400 mg group, compared to 0.371 attacks per week in the placebo group. This outcome resulted in a 100% reduction versus placebo for DX-2930 300 mg ($P < 0.0001$), an 88% reduction versus placebo for DX-2930 400 mg ($P = 0.0050$), and a 91% reduction versus placebo for DX-2930 300 mg and 400 mg combined ($P = 0.0012$).

From Day 1 to Day 50, Day 8 to Day 64, and Day 8 to Day 92, a 100% reduction versus placebo in the HAE attack rate (adjusted for the baseline attack rate) was observed for DX-2930 300 mg ($P < 0.0001$) during all 3 time periods and an 82% to 85% reduction versus placebo was observed for DX-2930 400 mg during these 3 time periods ($P = 0.0141$, $P < 0.0001$, and $P < 0.0001$, respectively).

Safety:
The percentage of subjects who experienced at least 1 TEAE was 58.3% among DX-2930 subjects and 76.9% among placebo subjects. The events in 29.2% of DX-2930 subjects and 38.5% of placebo subjects were considered to be related to study treatment by the blinded investigator. Severe TEAEs occurred in 25.0% of DX-2930 subjects and 38.5% of placebo subjects, with 2 DX-2930 subjects having severe TEAEs considered treatment-related by the blinded investigator.

No notable differences were apparent across dose cohorts. Treatment-emergent adverse events experienced by at least 5 subjects overall were hereditary angioedema, injection site pain, and headache. The rate of these TEAEs was not appreciably higher among subjects who received DX-2930 compared with subjects who received placebo.
Summary of Results (Continued)

Safety (Continued):

The most common study drug-related TEAEs were injection site pain (25.0% DX-2930, 23.1% placebo) and headache (8.3% DX-2930, 15.4% placebo).

The incidence of grade 3 (severe) TEAEs was 25.0% in DX-2930-treated subjects and 38.5% in placebo-treated subjects. The most common severe TEAE was hereditary angioedema, experienced by 3 (12.5%) DX-2930-treated subjects and 5 (38.5%) placebo-treated subjects.

Two subjects experienced TEAEs deemed related to treatment by the blinded investigator: injection site pain in 1 subject (DX-2930 30 mg), that was transient, resolving after 1 minute, and worsening headache and night sweats in another subject (DX-2930 400 mg). The worsening headache lasted 1 minute and the night sweats were noted as ongoing.

One placebo subject experienced a SAE (pneumonia) that was considered by the investigator to be mild in severity and not related to study drug. There were no deaths or discontinuations due to a TEAE.

There were no important safety signals identified by laboratory, vital sign, physical examination, or ECG evaluations.

A total of 3 out of 92 post-dose samples (3.3%), obtained from 2 out of 23 subjects (8.7%), were confirmed to be anti-drug antibody-positive. None of the positive anti-drug antibody samples were positive for neutralizing antibodies.

Based upon a review of the available safety data, no adverse drug reactions (events with a known or suspected causal relationship to DX-2930) were identified for DX-2930.