Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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TABLE OF CONTENTS

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FULL STUDY METHODS

STUDY DESIGN

This was a phase 1b, multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose trial of subcutaneous (SC) administrations of DX-2930 in patients with hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency (HAE-C1-INH). The objectives were to assess safety and tolerability, characterize the pharmacokinetics (PK) and pharmacodynamics (PD), and evaluate the immunogenicity of multiple SC DX-2930 administrations. In addition, the reduction of frequency of HAE attacks and on-demand attack therapy was determined in higher-dose groups. If patients experienced HAE attacks during the study, they followed standard-of-care HAE on-demand attack treatment as prescribed by their physician. HAE attack history and attacks during the study were self-reported; however, the investigative sites had frequent and extensive contact with the study patients between and during site visits.

There were four dose groups (30, 100, 300, and 400 mg), administered in a staggered, dose-escalating fashion. Eligible patients were randomized in a 2:1 ratio (done for ethical reasons to maximize patients' chances of assignment to a treatment to prevent a potentially fatal disease and to obtain additional safety data[1,2]) to receive active medication or placebo within a dose group on days 1 and 15, for a total of two SC injections. Recruitment was sequential and assignment of participants to specific dosing groups was not based upon past HAE attack frequency or severity. The study drug/placebo was delivered as one (30- or 100-mg groups) or two (300- and 400-mg groups) SC injections into the upper arm. The second dose was given 14 days after the first dose.

DX-2930 is a sterile, preservative-free solution (pH 6.0). The active ingredient, DX-2930 (100 mg/ml), is formulated in 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, and 0.01% Tween 80. The placebo consists of the inactive formulation containing 30 mM sodium phosphate, 8.6 mM citric acid, 50 mM histidine, 90 mM sodium chloride, and 0.01% Tween 80. For the 30-mg group, each patient received 0.3 ml of DX-2930 or placebo in a single SC injection per dose. For the 100-mg group, each patient received 1.0 ml of DX-2930 or placebo in a single SC injection per dose. For the 300-mg group, each patient received 3.0 ml of DX-2930 or placebo in two separate SC injections of 1.5 ml each per dose. For the 400-mg group, each patient received 4.0 ml of DX-2930 or placebo in two separate SC injections of 2.0 ml each per dose.

The sponsor (Dyax Corp.), with input from all authors of the manuscript, designed the study. The protocol (available with the full text of this manuscript at NEJM.org) was approved by the institutional review boards or ethics committees of the participating institutions. All patients provided written informed consent before enrollment. Data were gathered by study investigators and staff in collaboration with the sponsor. The first and subsequent drafts of the manuscript were written by the co-first authors. All the authors reviewed and edited the manuscript, and approved submission for publication. Editorial and technical support in the preparation of the manuscript was provided by a professional medical writer at Dyax Corp. (S.C.). All the authors contributed to the interpretation of the data and had access to the full data (nondisclosure agreements were in place). The authors vouch for the integrity and completeness of the data and all analyses. Statistical analyses were performed by ICON plc (Marlborough, MA).

PATIENT RECRUITMENT

Patients were at least 18 years of age with a documented diagnosis of HAE-C1-INH (type I or II) based upon all the following criteria: (1) a clinical history consistent with HAE-C1-INH, (2) C1-INH protein or functional level less than 40% of the normal level (patients with C1-INH antigen or functional level 40 to 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-C1-INH type I or II), and (3) 30 years of age or less at reported onset of first angioedema symptoms or a family history consistent with HAE-C1-INH type I or II. Patients must have experienced two or more HAE-C1-INH attacks per year, with at least one attack in the past 6 months. Patients were excluded if they received long-term prophylactic medications for HAE-C1-INH in the past 90 days, used C1-INH within 7 before study enrollment, had participated in another investigational study in the past 90 days, or had a prior exposure within the past 5 years to a monoclonal antibody or recombinant protein bearing an Fc domain.

BLOOD SAMPLING

To avoid artificial activation of the contact pathway system during blood collection, plasma was collected from patients with HAE and healthy controls by means of a clean venipuncture and removal of the tourniquet upon blood flow to decrease stasis. The first tube of blood was discarded to minimize activation caused by the initial needle puncture injury. Samples to measure C4 levels and C1-INH protein and functional level were collected in a no additive blood collection tube. For the PK and antidrug antibody (ADA) analysis, samples were collected in a plastic evacuated tube containing 0.5 ml of a 10× concentrated mixture composed of the following reagents: 100 mM benzamidine, 400 μg/ml polybrene, 2 mg/ml soybean trypsin

inhibitor, 20 mM EDTA, 263 µM leupeptin, and 20 mM 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) dissolved in acid citrate dextrose (100 mM trisodium citrate, 67 mM citric acid, and 2% dextrose [pH 4.5]).

For PD assays (to measure plasma kallikrein [pKal] inhibition by DX-2930), samples were collected in polypropylene sodium citrate tubes (BD Biosciences, San Jose, CA, USA; 3.8% sodium citrate [0.109 M]). All samples were centrifuged within 30 minutes, plasma removed and divided into aliquots, and stored at –80°C until processing. All sites performed collection and processing in a standardized fashion and protease inhibitors were added to the plasma before measurement of cleaved high-molecular-weight kininogen (cHMWK) to decrease further cleavage, as done by other groups.[3,4]

Normal control citrated plasma (n = 32) was obtained from healthy volunteers recruited from the phase 1a study of DX-2930 and was collected at a single clinical site (Vince and Associates Clinical Research, Overland Park, KS, USA) following the same blood collection protocol.[5]

PHARMACOKINETICS AND PHARMACODYNAMICS

PK and PD samples were obtained before administration of each dose of study drug/placebo (days 1 and 15) and at days 2, 4, 8, 16, 18, 22, 29, 36, 50, 64, 92, and 120 for all four dose groups. DX-2930 compartmental analysis using a one-compartment model provided PK parameters, including maximum concentration in plasma, time to maximum plasma concentration, area under the plasma concentration–time curve (AUC), and terminal elimination half-life. The PD effect of DX-2930 was evaluated using two exploratory biomarker assays. The first assay was a Western blot assay for the cHMWK in inactivated and activated factor XII

(FXIIa) citrated plasma samples. FXIIa rapidly converts prekallikrein to active pKal and is an in vitro model of the biochemical events triggering an HAE attack. The PD also was measured using a synthetic peptide fluorogenic assay for pKal activity.

PK Methods

DX-2930 drug levels were measured in plasma using a sandwich enzyme-linked immunosorbent assay using an anti-idiotypic antibody against DX-2930 (M293-D02). The M293-D02 antibody is a fully human antibody discovered using phage display. Briefly, plasma was diluted 10-fold in phosphate-buffered saline (PBS) with 0.05% Tween 20 and 0.1% bovine serum albumin (BSA) and added to a 96-well microtiter plate containing the recombinant Fab fragment of M293-D02 (1 µg/ml) as a capture antibody that was passively immobilized on the plate surface. Following sample addition, the plate was washed with PBS with 0.05% Tween 20 and 0.1% BSA and biotinylated M293-D02 as an immunoglobulin G (IgG; 0.5 µg/ml) was added and incubated for approximately 60 minutes. Before adding (14 ng/ml) streptavidin conjugated to horseradish peroxidase (ThermoFisher Scientific, Waltham, MA, USA), the plate was again washed with PBS with 0.01% Tween 20. Absorbance was measured at 450 nm following the addition of Ultra TMB substrate (ThermoFisher Scientific) and stop with acid solution. The lower limit of quantification for the PK assay was 31.3 ng/ml.

Western Blotting Methods

Samples were diluted to approximately 5% plasma and analyzed under reduced conditions using 1× Tris-buffered saline (TBS). There was 5 µl of an 10× anti-protease inhibitor cocktail consisting of 100 mM benzamidine, 400 µg/ml polybrene, 2 mg/ml soybean trypsin inhibitor, 20 mM EDTA, 263 µM leupeptin, and 20 mM AEBSF dissolved in acid citrate dextrose (100 mM

trisodium citrate, 67 mM citric acid, and 2% dextrose [pH 4.5]) was added immediately upon thawing of frozen plasma samples to prevent ex vivo cleavage of HMWK. The percent cHMWK was assessed by means of sodium dodecyl sulphate-polyacrylamide gel electrophoresis using a precast 4 to 12% acrylamide gradient gel using the MES SDS (2-(N-morpholino) ethanesulfonic acide sodium dodecyl sulfate) buffer system (Life Technologies Corporation, Carlsbad, CA, USA). After electrophoretic separations, proteins were transferred from the gel to a nitrocellulose membrane (Life Technologies Corporation). The membranes were blocked in Odyssey blocking buffer (LI-COR Biosciences, Lincoln, NE, USA) containing 0.2% Tween 20 and incubated for 1 hour at room temperature (RT) with a mouse monoclonal antibody that specifically binds the light chain of HMWK (mouse monoclonal anti-LC HMWK antibody clone, Clone 11H05; generated by Maine Biotechnology Services, Portland, ME, USA) diluted to 1 µg/ml in Odyssey blocking buffer. Goat anti-mouse IRDye680 was prepared at a 1:15,000 dilution (goat anti-Mouse IRDye 680RD, category #926-68070; LI-COR Biosciences) and membrane incubated for 1 hour at RT. After PBS rinse, membranes were read on a LI-COR Odyssey buffer (LI-COR Biosciences). The percent cHMWK was calculated from the fluorescent intensities of Western blot bands attributed to the cHMWK band compared with total HMWK in each sample. The effect of DX-2930 on the inhibition of FXIIa activity was measured in the Western blot assay following incubation of the plasma with FXIIa (Enzyme Research Laboratories, South Bend, IN, USA) at a final concentration of 2.5 nM for 10 minutes at 37°C. The FXIIa-treated sample was then treated with the above protease inhibitor cocktail and analyzed by Western blot as described above.

Fluorogenic Assay for pKal Activity

Plasma samples were diluted 1:40 in assay buffer (20 mmol/l of Tris-HCl [pH 7.5]; 150 mmol/l of NaCl, 1 mmol/l of EDTA, 0.1% polyethylene glycol 8000, and 0.1% Triton X-100) at RT (21°C) and aliquoted in duplicate to a 96-well microplate. The pKal-kinin pathway in the dilute plasma was activated by the addition of 10 nmol/l of FXIIa (Enzyme Research Laboratories) for 2 minutes and subsequently quenched by the addition of 100 nmol/l of corn trypsin inhibitor (Enzyme Research Laboratories), a specific FXIIa inhibitor. Activated plasma was diluted nine-fold into a replicate microplate containing assay buffer prewarmed to 30°C. The activity of generated pKal was assessed by adding 10 µmol/l final of fluorogenic substrate H-Pro-Phe-Arg-AMC (catalog number P9273; Sigma-Aldrich Co. LLC, St. Louis, MO, USA), and measuring fluorescence changes in a SpectraMax plate reader (Molecular Devices, LLC, Sunnyvale, CA, USA), with excitation and emission wavelengths at 360 and 480 nm, respectively. The final "neat" plasma dilution was 400-fold. However, reported DX-2930 concentrations refer to the concentration in 100% plasma. The initial rate of the fluorescence increase over 10 minutes was recorded and converted to percentage of inhibition relative to the individual patient's predose control plasma by the following equation: inhibition of pKal activity (%) = $(1 - [V_{obs} / V_{max}]) \times 100$, where V_{max} is the average rate of pKal activity obtained for the predose plasma sample and V_{obs} is the average rate obtained for the experimental postdose DX-2930 or placebo plasma samples. The percent inhibition for each postdose plasma sample was calculated using the initial rates of pKal-mediated substrate hydrolysis (equation used: percent inhibition = 100 – [postdose rate / predose rate] × 100).

EFFICACY

Prespecified efficacy analyses were performed in patients treated with the higher doses of DX-2930 (300 and 400 mg) versus placebo; these patients had a higher historical baseline frequency of two or more attacks over the 3 months before enrollment (primary efficacy analysis population). This allowed patients a reasonable probability to have one or more attacks during the day 8 to 50 (6-week) time interval. We prospectively selected a primary assessment period of days 8 to 50 based upon PK modeling from the prior phase 1a study.[5]

A post hoc modified intention-to-treat efficacy analysis also was conducted, removing 2 patients from the 400-mg dosing group to more meaningfully evaluate the data (Table S1). One patient prematurely discontinued the study after one dose (relocating out of state for reasons unrelated to treatment) and was subsequently lost to follow-up. Another patient did not meet criteria for HAE-C1-INH (C1-INH testing during the study revealed that this patient did not have a valid diagnosis of HAE-C1-INH type I or II despite a historical laboratory test result indicating otherwise) after study enrollment. Both patients (assigned to the 400-mg group) were included in the safety and primary efficacy intention-to-treat analyses, but were removed from the PK and PD analyses.

SAFETY

Safety variables were adverse events (AEs), including serious AEs; vital signs (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 electrocardiogram; and plasma ADA testing. A safety evaluation was conducted by a dose-escalation committee after each group completed dosing. Escalation to the next dosing group

proceeded if there were no concerning safety signals. Any HAE attack after signing the informed consent was considered an AE. Clinical laboratory tests were summarized descriptively. Observed values and changes from baseline for numeric clinical data were summarized using descriptive statistics.

ADA Methods

Plasma samples were collected on days 1 (before dosing), 36, 64, 92, and 120 for the analysis of ADAs. The ADA analysis strategy was previously described[5] and is based upon validated methodology[6,7] that involved an initial screening step for the presence of ADAs using an assay that detects all Ig classes in plasma, followed by confirmation, titer determination (if antibodies were detected), and further characterization in neutralizing antibody (nAb) assays. To prevent a false-positive ADA signal in the solid-phase extraction, acid dissociation (SPEAD) electrochemiluminescent (ECL) assay from any active pKal present in the samples, plasma was collected into evacuated blood collections containing protease inhibitors (0.5 ml of 100 mM benzamidine, 400 µg/ml polybrene, 2 mg/ml soybean trypsin inhibitor, 20 mM EDTA, 263 µM leupeptin, and 20 mM AEBSF dissolved in acid citrate dextrose (100 mM trisodium citrate, 67 mM citric acid, and 2% dextrose [pH 4.5]). The plasma collected from these evacuated blood collection tubes containing inhibitors are hereon referred to as "SCAT169 plasma."

Briefly, the ADA assay involved a SPEAD procedure whereby potential anti–DX-2930 antibodies from each patient's plasma sample were extracted using a biotininlyated DX-2930 on the surface of a microtiter plate followed by the addition of ruthenium-labeled DX-2930 to generate an ECL signal. This assay detects all classes of antibody as a bridge between biotinylated DX-2930 on the plate surface and ruthenium-labeled DX-2930. The positive control

for the assay was a fully human anti–DX-2930 IgG antibody generated by Dyax Corp. using a phage display human Fab fragment library.[8] The anti–DX-2930 positive control was spiked into pooled normal human SCAT169 plasma at three concentrations (5000, 1000 and 250 ng/ml). The negative control was pooled human SCAT169 plasma to represent the background signal of the assay. Controls and samples were diluted 10-fold in assay buffer (Casein in TBS; Surmodics, Inc., Eden Prairie, MN, USA). The plate was incubated overnight at RT with gentle shaking.

The next day, a streptavidin-coated microtiter plate was blocked with a commercially available buffer containing an undisclosed percentage of Casein in TBS (Surmodics, Inc. or ThermoFisher Scientific) for 10 minutes at RT with gentle shaking. The blocking solution was discarded and controls and samples from the polypropylene dilution plate were transferred and loaded onto the streptavidin-coated plate and incubated with gentle shaking at RT for approximately 2 hours. After washing the plate, an acetic acid solution (300 mmol/l), which dissociates captured antibodies from the bound complexes, was added. Acidified samples were next transferred to a new polypropylene dilution plate containing a neutralizing solution (1 mol/l Tris-HCL [pH 9.5]) and briefly incubated. The samples were then transferred from the dilution plate and coated onto a bare 96-well stand bind MSD Imager plate (Meso Scale Diagnostics, Rockville, MD, USA) for 1 hour. After washing, sulfo-tagged DX-2930 (2 µg/ml) was added (to detect anti–DX-2930 antibodies bound to the plate) for 1 hour at RT. After another wash, an ECL read buffer was added to the plate, which was analyzed using a MSD Sector Imager 6000 reader (Meso Scale Diagnostics). The sulfo tag–labeled drug bound to the anti–DX-2930 antibodies emitted light at electrochemical stimulation from the electrode surface on the plate. The intensity of the light emitted was proportional to the amount of anti–DX-2930 antibodies present in the sample. ADA assay sensitivity towards the positive control is 36.45 ng/ml and the

assay tolerates DX-2930 plasma concentrations up to 250 µg/ml at the low control concentration (250 ng/ml).

A floating screening cutpoint with a 5% false-positive rate was established during assay validation as previously described.[6,7] Samples that screened positive were tested in a confirmatory assay that added excess unlabeled DX-2930 as an inhibitor. Signals for confirmed positive samples were inhibited to a greater extent than immunodepletion cutpoint (25.9%; 0.1% false-positive rate), which was established during assay validation. Confirmed positive samples were titered and tested for the presence of nAb activity. We have previously shown using X-ray crystallography that DX-2930 binds the active site of pKal.[9] A nAb against DX-2930 prevents DX-2930 from binding and inhibiting pKal.[9] Consequently, nAbs were detected using a binding assay that consisted of the same procedure as the ADA assay with the expectation that the catalytic domain of pKal was substituted for the unlabeled DX-2930 in the immunodepletion confirmatory step. If the addition of pKal inhibited the binding of the anti–DX-2930 antibody, the ADA had neutralizing activity. Samples with signals inhibited above both the immunodepletion and specificity cutpoint were considered indeterminate (due to pKal interference).

Presumptive positive samples from screening then underwent confirmatory testing by inhibition with DX-2930 and a subsequent titer was performed. To perform the titer, the sample was serially diluted four-fold using the negative control pool before analysis in the assay. After titer analysis, ADA-positive samples were subsequently tested in the nAb assay. Samples with a percent neutralization greater than the 38.8% cutpoint (0.1% false-positive rate) were considered positive for the presence of nAbs. Drug tolerance was determined using the nAb-positive control, which was detected at a concentration of 250 ng/ml in the presence of DX-2930 250 µg/ml.

STATISTICAL ANALYSIS

Statistical analysis and programming of tables and listings were conducted using SAS® Release 9.3 or higher (SAS Institute Inc., Cary, NC, USA). Continuous data were summarized with descriptive statistics and categorical data were summarized with frequencies (number of patients in category) and percentages. Percentages were computed using the number of patients with available data. Missing data were not imputed.

Pharmacokinetics

All PK parameters were estimated by noncompartmental and compartmental analysis of the plasma concentration versus time data using WinNonlin Enterprise (version 6.2; Pharsight Corporation, Mountain View, CA, USA). 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 predose samples, for which a nominal time of 0 hours was used. A minimum of three quantifiable concentration–time points was required for generation of an AUC over the dosing interval.

Efficacy Analysis

The primary efficacy endpoint was the number of HAE attacks per week from days 8 to 50. The endpoint was a repeated measure of the number of distinct HAE attacks reported in a 7-day period (168 hours) for each patient. All reports of HAE attacks during the study and for the historical baseline rate were patient provided. Last observation carried forward and imputation of missing data were not used in this analysis.

The generalized estimating equation (GEE) approach with Poisson distribution assumption was applied to the repeated-measures mixed model with independence working

correlation structure.[10] The baseline attack rate was used as a covariate. To avoid any possible undue influence of a baseline attack rate outlier, any potential outliers were tested using the Dixon gap test (with $\alpha = 0.05$) before 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-squares (LS) mean (log of the mean event rate) for each dose level and its corresponding SE was directly estimated from the GEE model. The mean event rate was estimated by transforming the LS means by the exponential function. The ratio of the mean event rate per week for each dose level versus placebo and its 95% confidence intervals (CIs) were estimated by transforming the LS mean 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, also was 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.

SUPPLEMENTARY FIGURES AND TABLES

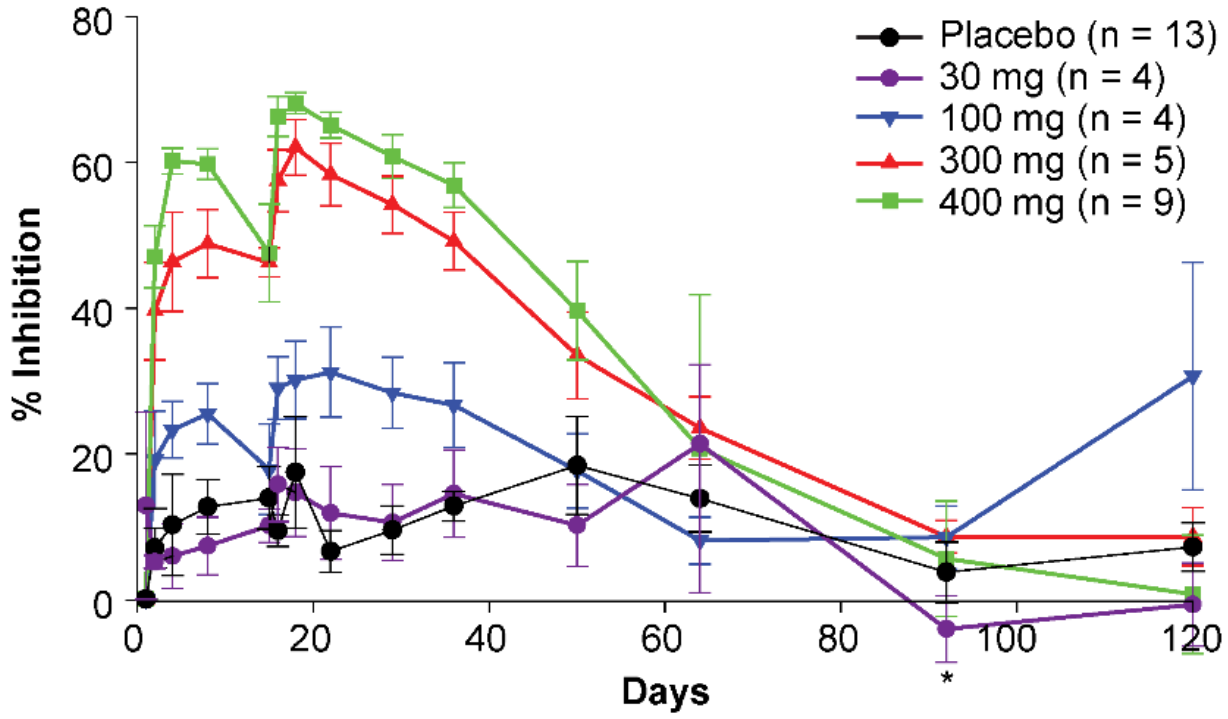

Figure S1. DX-2930 Inhibits Plasma Kallikrein Activity in Patients with HAE-C1-INH Measured by a Fluorogenic Assay.

Percent inhibition of plasma kallikrein activity in hereditary angioedema with C1 inhibitor deficiency (HAE-C1-INH) patient plasma activated with activated coagulation factor XII using a fluorogenic substrate. Patients were administered DX-2930 at the indicated dosage on days 1 and 15. Data presented are mean percent inhibition for each dose group at each time point (see Supplementary Methods). Error bars represent SEM. *The negative mean percent inhibition observed for the 30-mg dose at days 92 (–4.1%) and 120 (–0.8%) may be attributed to a slight

elevation in the plasma kallikrein substrate hydrolysis rate in these postdose samples, the extent of which is within the error of the measurement.

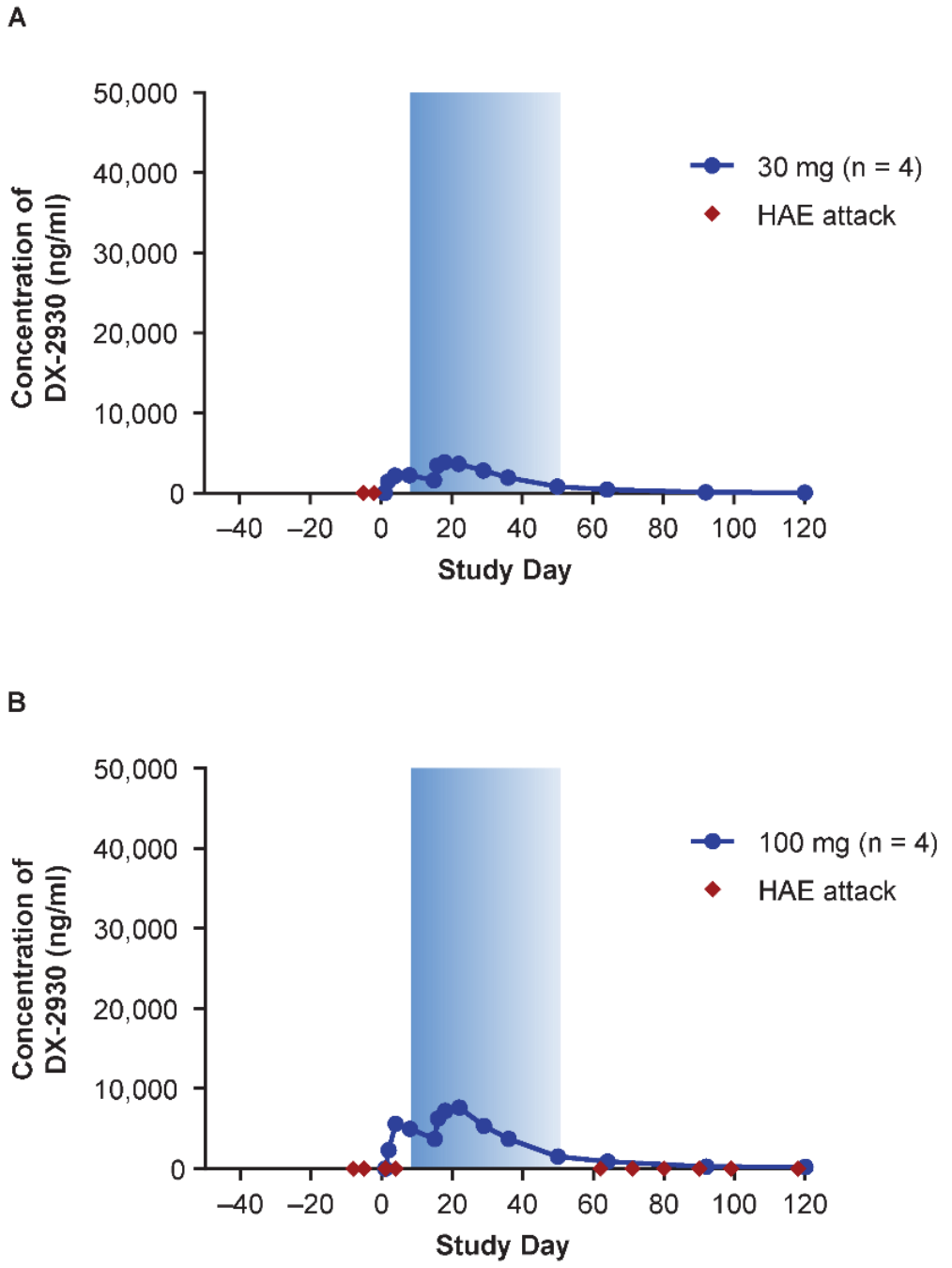

Figure S2. Mean Pharmacokinetic Plots and Reduction in Attack Frequency between Days 8 and 50.

Panels A and B are graphs of mean plasma concentration of DX-2930 (blue circles) in patients overlaid with the incidence of attacks in the DX-2930 30- or 100-mg dose groups. HAE denotes hereditary angioedema.

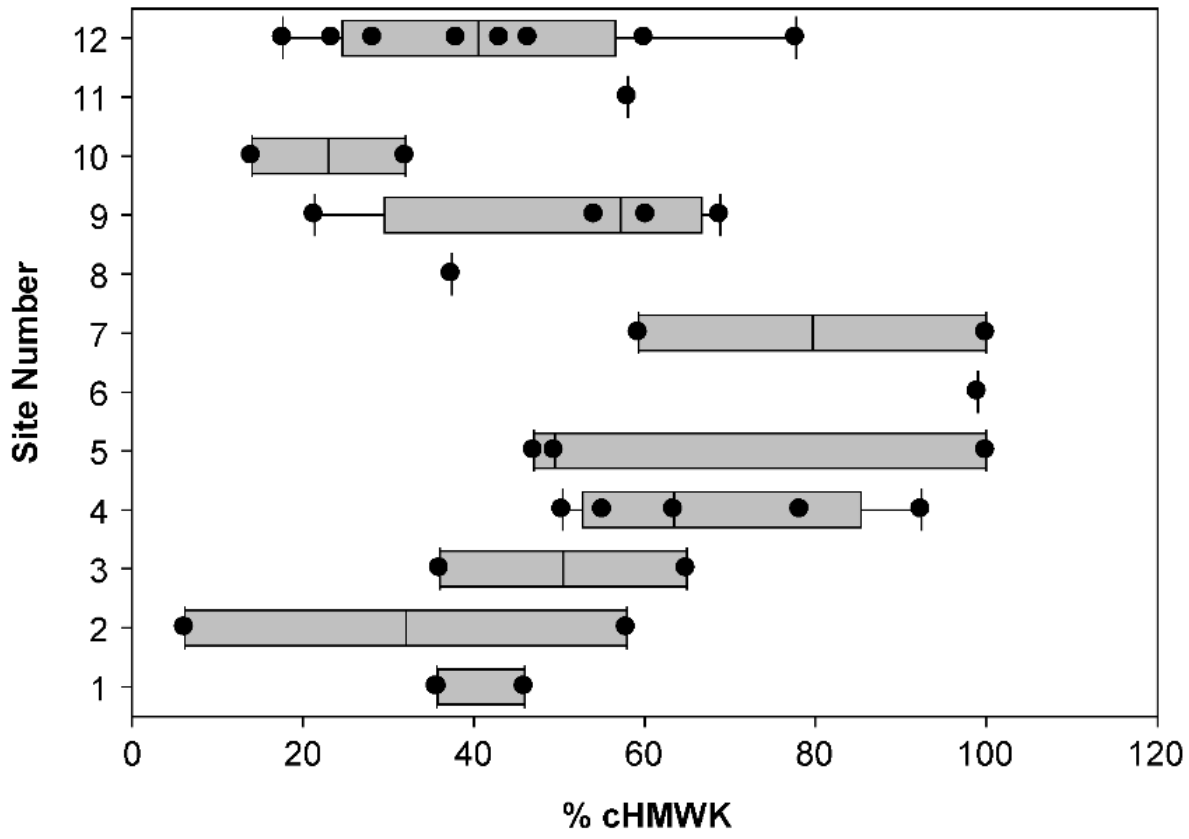

Figure S3. Comparison of Predose cHMWK Levels in Citrated Plasma Obtained from Patients, Collected at Different Clinical Sites.

Mean two-chain (cleaved high-molecular-weight kininogen; cHMWK) predose levels for patients in all dosing groups are shown. There were 12 sites recruiting patients; each site number is represented on the y-axis and each recruited between 1 and 8 patients. Results are reported as median with interquartile range confidence interval. The graph demonstrates that the interpatient variability appears to mask intersite variability.

Table S1. Number of Patients in the PK, PD, and Efficacy Assessments.

Population	DX-2930 Dose Group				Total DX-2930	Placebo	All Patients
	30 mg	100 mg	300 mg	400 mg			
Safety*	4	4	5	11	24	13	37
PK†	4	4	5	9	22	—	22
PD‡	4	4	5	9	22	13	35
Primary efficacy analysis§	—	—	4	11	15	11	26
Modified primary efficacy analysis¶	—	—-	4	9	13	11	24

*All randomized patients with HAE-C1-INH who received at least one dose of study drug.

†All randomized patients with HAE-C1-INH who received at least one dose of DX-2930 and who had sufficient blood samples for the pharmacokinetic (PK) analyses. Excludes two patients in the 400-mg dose group: one patient who only received one dose of study drug, was subsequently lost to follow-up, and did not have sufficient blood samples for the PK analyses, and one patient who did not have HAE-C1-INH type I or II.

‡All randomized patients with HAE-C1-INH who received at least one dose of study drug and who had sufficient blood samples for the pharmacodynamic (PD) analyses. Excludes two patients in the 400-mg dose group: one subject who only received one dose of study drug, was subsequently lost to follow-up, and did not have sufficient blood samples for the PK analyses, and one patient who did not have HAE-C1-INH type I or II.

§All randomized patients with HAE-C1-INH in the 300-mg, 400-mg, and placebo groups who received two doses of study drug and had a historical baseline attack rate of at least two attacks in the 3 months before enrollment.

¶All randomized patients with HAE-C1-INH in the 300-mg, 400-mg, and placebo groups who received two doses of study drug and had a historical baseline attack rate of at least two attacks in the 3 months before enrollment. Excludes two patients in the 400-mg dose group: one patient who only received one dose of study drug and was subsequently lost to follow-up, and one patient who did not have HAE-C1-INH type I or II.

Table S2. Characteristics of HAE Attacks (Days 8 to 50).

Characteristic	DX-2930 300 mg (n = 4)	DX-2930 400 mg (n = 11)	Placebo (n = 11)
Attacks*	0	3	24
Primary attack location		3	
Peripheral	0	0	10
Abdominal	0	0	13
Laryngeal	0		1
Attack severity			
Mild	0	1	8
Moderate	0	1	6
Severe	0	1	10
Acute attacks requiring treatment	0	2	22

*Represents the number of hereditary angioedema (HAE) attacks, not the number of patients having episodes.

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