STUDY SYNOPSIS:

Protocol number:	CDX1135-01
Title:	A Pilot, Open-label, Multicenter Clinical Trial of CDX-1135 in Pediatric and Adult Patients with Dense Deposit Disease
Investigators	Carla Nester, Richard Smith Additional investigators from other centers based on patient enrollment
Investigational Treatment:	CDX-1135 (also known as TP10): Soluble form of human complement receptor type 1 (sCR1)
Indication:	Pediatric and Adult Patients with Dense Deposit Disease (DDD)
Number of Patients:	Five patients will be enrolled.
Number of Study Centers:	TBD
Study Period:	Estimated first date of enrollment: June, 2012 Estimated last patient completed: June, 2014
Objectives:	Primary: • To evaluate the safety of repeated CDX-1135 dosing in pediatric and adult patients with Dense Deposit Disease. • To evaluate the activity of CDX-1135 in pediatric and adult patients with Dense Deposit Disease, as measured by the proportion of patients with normalization of serum C3 or serum C3 breakdown products. Secondary: • To determine the appropriate dose range and regimen for CDX-1135 in Dense Deposit Disease based on biologic parameters including serum levels of C3 and C3 breakdown products, assays of alternative pathway activity, and dose-limiting toxicities. • To further assess the activity of CDX-1135 in pediatric and adult patients with Dense Deposit Disease as measured by: 1) duration of normalization of serum levels of C3 or C3 breakdown products; 2) normalization of assays of alternative pathway activity; 3) time to these events; 4) stabilization or improvement in renal function (as measured by serum creatinine and proteinuria) and improvement on renal biopsy (as measured by reduction in C3 deposition in the glomerular basement membrane). • To determine the immunogenicity of repeat CDX-1135 administration Exploratory: • To evaluate the correlation between pharmacokinetic (PK) parameters and pharmacodynamics (PD) of CDX-1135 in pediatric and adult patients with Dense Deposit Disease.
Overview of study design:	This study is an open-label, non-randomized, single-arm, multicenter clinical trial of CDX-1135 in up to 5 patients with DDD, aged 4 years or older. There are two periods in this study. (See Schedule of Events, Table 1.) • 4-week Screening Period

	• 52-week Treatment Period
	  o Induction Period (Week 0 to Week 4)
	  o Maintenance Period (Week 5 to Week 52)
	Enrollment: Patients will be enrolled through the University of Iowa. All enrolled patients will complete the CDX-1135 Induction Period at the University of Iowa. The Maintenance Period will be completed at the home institution.
	Safety Data: Safety data for this trial will be reviewed by an independent Data Monitoring and Safety Committee (DMSC). If at any time any of the criteria for halting of the trial are met (see below), OR if the DMSC identifies a potential safety concern requiring further discussion, an ad hoc meeting will be called. If a safety concern is confirmed, the DMSC may recommend modifying the protocol, or halting or permanently stopping the trial.
	Study Stopping Rules**:**
	If any of the following criteria are met, further enrollment into the trial will be halted and the data reviewed with the DMSC. The trial will only be reopened after a mutually agreed plan is defined with the DMSC.
	• Futility in the first three patients. Futility is defined as:
	  o Failure during the Induction Period to normalize C3, C3 breakdown products or alternative pathway complement activity
	• Toxicity in more than one patient
	  o Dose-limiting toxicity (DLT), defined as any Grade 3 or higher drug-related adverse event
	  o Grade 3 or higher infection caused by encapsulated bacteria not responsive to appropriate medical intervention within 24 hours
	• Drug-related death

Investigational Product Dosing and Administration	Each CDX-1135 administration will consist of a 30-minute intravenous drip. Administered doses will range from 5 mg/kg to 60 mg/kg, once or twice weekly, as determined by patient-specific dose-escalation and adjustment. To determine the effect of CDX-1135 on complement and C3 convertase inhibition, complement studies will be performed twice-weekly during the Induction Period, weekly until week 26 of the Maintenance Period, and then biweekly from weeks 27-52 of the Maintenance Period. The complement studies will include measuring serum levels of C3 and C3 breakdown products and assays of alternative pathway function. Testing will be done on serum and plasma samples obtained prior to and ~60 minutes after dosing. All complement studies will be performed at the University of Iowa. The following treatment plan will be followed for each patient: Induction Period (at University of Iowa) The Induction Period will utilize twice weekly dosing (Mon-Thur or Tues-Fri), based on the estimated half-life of ~48 hours for CDX-1135. The first dose will be 5 mg/kg, with intrapatient dose-escalation in 5-10 mg/kg increments for each subsequent dose, up to a maximum dose of 60 mg/kg. Up to six escalating doses over three weeks may be administered in the Induction Period. The dose will be escalated until any of the following criteria are met:

	• Normalization of C3, C3 breakdown products or alternative pathway complement activity. Thereafter, the patient will receive two additional infusions on the same twice-weekly schedule at the same dose and then transition to Maintenance Period. • If the maximum dose level (60 mg/kg) is reached without normalization of C3, C3 breakdown products or alternative pathway complement activity, the patient will receive one additional week of therapy at the same twice-weekly schedule (two additional doses of CDX-1135). If normalization of C3, C3 breakdown products or alternative pathway complement activity fails to occur, treatment will be discontinued. If normalization of C3, C3 breakdown products or alternative pathway complement activity occurs, the patient will enter the Maintenance Period and follow rules for Maintenance Period dose adjustments. • Any additional criteria for discontinuation of study therapy (see below) are met. <u>Maintenance Period (at home institution)</u> CDX-1135 Maintenance will begin with weekly dosing. The first Maintenance dose will be given at University of Iowa, one week after the last Induction dose. The remaining Maintenance doses will be given at the referring/home institution. Dose-level for each Maintenance dose will be determined based on the following criteria: • If C3 levels have NOT dropped more than 25% (compared to the last time point), C3 breakdown products are absent (<=+1) and alternative pathway complement activity is normal, the next Maintenance dose will be the same as the prior dose. • If C3 levels have dropped more than 25% (compared to the last time point) or C3 breakdown products are present (+1 or greater) or alternative pathway complement activity is abnormal, the next Maintenance dose will be increased by 5 mg/kg. In the event the patient is already receiving 60 mg/kg per week as a single dose, the dosing schedule will be increased to 60 mg/kg twice weekly for 1-2 weeks based on pharmacokinetic data. The Maintenance Period will be continued until either 1) the study treatment period of 52 weeks has lapsed, OR 2) normalization of C3, C3 breakdown products or alternative pathway complement activity cannot be achieved despite escalation to a twice weekly dose of 60 mg/kg for a two week continuous interval, or 3) any additional criteria for discontinuation of study therapy (see below) are met. <u>Criteria for treatment discontinuation</u> At any point during the study, treatment may be discontinued for any of the following reasons: • Decrease in renal function, defined by: an increase in serum creatinine by 50% over baseline at enrollment, persistent for 4 weeks. • Development of dose-limiting toxicity (DLT), defined as any Grade 3 or higher drug-related adverse event, or Grade 3 infection not responsive to appropriate medical intervention within 24 hours. Patients who experience DLT or Grade 3 infection but who are considered by the treating investigator to be potentially appropriate for further CDX-1135 treatment may be retreated only after consultation with, and agreement by,

	the DMSC; • Request of the patient or the patient's legal representative; • Non-compliance; • If, in the Investigator's medical judgment, further participation would be injurious to the patient's health or well being; • The study is terminated (see early stopping rules).
Concomitant Treatment:	Palliative and supportive care is permitted during the course of the study for underlying conditions. The following concurrent medications are prohibited during the study: • IVIg • Rituximab • mTOR inhibitors • Calcineurin inhibitors • Use of any other investigational drug or device as part of a clinical trial is prohibited beginning 4 weeks prior to screening and throughout the entire trial The following concomitant medications and therapy during the study are allowed under certain circumstances and restrictions: • Patients receiving steroids therapy for a condition other than DDD, such as asthma, as reviewed by the investigators. • The use of anti-proteinuric medications (ACEI, ARB, etc) is permitted but should remain at a stable or decreasing dose for four weeks prior to initiation of study treatment, and should not be increased during the course of the trial.
Eligibility Criteria	Inclusion Criteria**:** 1. Patient and/or parent/legal guardian (as appropriate) must be willing and able to give written informed consent and the patient must be willing to give written informed assent, if applicable 2. Patient must be 4 years of age or older 3. Patient must have DDD as confirmed by renal biopsy within six months of enrollment (confirmation by University of Iowa investigators is required) 4. C3 serum must be less than 50% of the low limit of normal 5. Signs of alternative pathway dysregulation must be present. C3 breakdown products or C3Nef activity must be detectable in plasma using assays we have described and validated (Zhang et al, 2012) 6. Serum creatinine level must be abnormal (>97 percentile for age or <80 ml/min using the Cockroft Gault equation for adults) 7. Either 24 hour urine protein >1000 mg/day or urine protein:creatinine ratio >1.0 8. Screening laboratory values must meet the following criteria: a. hemoglobin ≥ 9.0 g/dL b. platelet count ≥ 100,000/mm^3 c. alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 3.0 x

	ULN 9. Female patients of childbearing age must be practicing an effective, reliable and medically approved contraceptive regimen 10. Patient must be willing and able to comply with study procedures including vaccination against meningitis, hemophilus and pneumococci at least 2 weeks prior to starting the Induction Period and agree to a renal biopsy at the conclusion of the 52-week Maintenance Period. 11. Patient must wear an ID bracelet that warns of possibly overwhelming infection with encapsulated organisms. 12. Any anti-proteinuric medications (ACEI, ARB, etc) must be at a stable dose for at least four weeks prior to initiation of study <u>Exclusion Criteria</u>: 1. Chronic dialysis or patients with an eGFR of less than 30 ml/min/1.73 m^2 for over a four-week period prior to the Screening Period 2. Presence or suspicion of active or untreated systemic bacterial infection that in the opinion of the investigator precludes treatment with CDX-1135 3. Pregnancy or lactation 4. Rituximab therapy, unless discontinued with B cell levels and immunoglobulin levels normalized by study entry 5. Patients receiving immunosuppressive therapies (except for low dose steroids given for non-DDD related conditions such as asthma) 6. Receipt of any other investigational drug or device or experimental procedures beginning four weeks prior to study enrollment 7. Prior renal transplant 8. A preexisting condition with a reported association as a potential cause of DDD (i.e. Monoclonal Gammopathy of Undetermined Significance, MGUS) or an alternate glomerular disease that may interfere with the interpretation of study results 9. Malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated in situ disease, or other cancer from which the patient has been disease-free for ≥ 5 years 10. Patients with myocardial infarction within 1 year of screening, congestive heart failure, arrhythmia persistent on medication at screening or clinically evident chronic lung disease 11. Known Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C infection 12. Any medical or psychological condition that, in the opinion of the investigator, would increase the patient's risk by participation in this study or would interfere with interpretation of the study

Criteria for Evaluation	Safety: Safety will be assessed by vital sign measurements, clinical laboratory tests, and routine physical examinations including physical growth for children up to 18 years old and the incidence and severity of adverse events (graded according to CTCAE v 4.0). Activity: Activity of CDX-1135 in DDD will be assessed by measuring serum C3, C3 breakdown products, alternative pathway complement activity and CKD stage and renal function (proteinuria, serum creatinine). Immunogenicity: Patients will be monitored for the development of antibodies to CDX-1135. Pharmacokinetics (PK): A limited PK assessment will be made by measuring serum concentrations of CDX-1135 concurrently with serum C3, C3 breakdown levels and alternative pathway activity. These samples are taken immediately before and ~60 minutes after CDX-1135 infusion to approximate peak and trough levels of CDX-1135. No additional PK parameters will be determined in this study. Pharmacodynamics (PD): Pharmacodynamics of CDX-1135 will be assayed by changes in serum C3, C3 breakdown products and alternative pathway complement activity. Pharmacogenomics: Patients will undergo: genetic testing of *CFH*, *C3*, *CFB* and *CFHR5*; assays for C3Nef activity; and screening for factor H autoantibodies (FHAA) and factor B autoantibodies (FBAA).
Statistical Methods	The planned number of patients to be enrolled in this trial is based on feasibility considerations and reflects the extremely low prevalence of DDD (an ultra disease that affects ~2 persons per million). The safety, efficacy, pharmacokinetic, pharmacodynamic and immunologic outcomes for patients enrolled in this trial will be summarized using descriptive statistics, and will include tabulation according to presence or absence of *CFH*, *C3*, *CFB* and *CFHR5* mutations, C3Nefs types and titers/levels, FHAAs and FBAAs, and measures of complement activity. Narratives will be provided for each patient. The narratives will describe the diagnosis, treatment history, doses of CDX-1135, and overall response to therapy, including status of serum C3, C3 breakdown products and alternative pathway activity. Adverse events will be summarized, including a description of any major infections, infusion related reactions, and antibody development.

1. SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Events

Visit[1]	Screening Period[2,3]	Treatment Period			Extension Period[6]	Study Completion / Termination[7]	
		Induction[4]		Maintenance[5]			
Visit Window	Day -28 to Day -1	Week 1, 2, 3		Up to Week 26	Week 27, 28, 29….	Within 5 days of last dose	30 +/- 3 days after last dose
		Wk n, Day 1	Wk n, Day 4 +/- 1 day	Wk n, Day 1 +/- 1 day	Wk n, Day 1 +/- 2 days		
Informed Consent/Assent	X			X[8]	X[8]		
Medical History	X						
Physical Exam (including growth chart for children up to 18 years old)	X	X		X	X[9]		X
Opthalmic exam[11]	X[11]				X[11]	X[11]	
Renal Biopsy	X[10]				X[10]	X[10]	
CFH mutation status, C3Nef status and factor H autoantibody (FHAA) status	X						
Chest radiography	X						
ECG[12]	X						
Routine laboratory assessments/ urinalysis[13]	X[13]	X[13]		X[13]	X[13]	X[13]	X[13]
Complement specific labs[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]
Vaccinations (MCV4, Hib, PCV13)	X[15]						
CDX-1135 Serum Levels		X		X	X[9]	X	X
Immunogenicity[16]		X[16]		X[16]	X[16]	X[16]	X[16]
Assessment of Opsonin Function[17]		X[17]			X[17]		
CDX-1135 Treatment[4,5,6]		X	X	X	X		
Concomitant medication review	X	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X	X

Footnotes provided on next page.

Table 1: Footnotes

1. The Induction Phase and the first Maintenance dose must be conducted/administered at the University of Iowa; all other study Phases may be conducted at either University of Iowa or the referring/home institution. Referring/home institutions will be required to obtain IRB approval and appropriate patient consent/assent before conducting any study-specific patient assessments.
2. No study procedures will be performed prior to receipt of signed Informed Consent/Assent. However, assessments performed according to standard of care prior to receipt of Informed Consent/Assent may be utilized to fulfill the screening requirement, if completed within the required window for screening.
3. Review of screening data and approval for study enrollment will be performed by University of Iowa in consultation with Celldex.
4. During the Induction Phase, each patient will receive up to a maximum of six twice-weekly doses of CDX-1135, over up to three weeks. Dose escalation shall proceed as described in Section XXX.
5. The first Maintenance dose will be given one week after the last Induction dose. Maintenance dosing shall continue as described in Section XXX, for a maximum of a 26-week treatment period (for the Induction and Maintenance Phases combined).
6. After completion of the Maintenance Phase, patients who continue with normalization of C3 and/or C3c and who do not show worsening of renal function or pathology will be eligible to transition into the Extension Treatment Period, in which CDX-1135 will be received in an uninterrupted fashion following conclusion of the 26 week study treatment period until either 1) any criteria for discontinuation of study therapy are met , OR 2) availability of CDX-1135 through an alternative route, such as a compassionate use trial or market approval, OR 3) decision of the study sponsor.
7. Patients who complete the Treatment Period and then discontinue CDX-1135 will be followed for one month after termination of therapy.
8. Informed Consent/Assent will be re-reviewed and continuing consent obtained upon transition to the referring/home institution for the Maintenance Phase and upon entry into the Extension Phase.
9. Obtained on a monthly basis during the Extension Period.
10. Renal biopsy done per standard of care within six months of enrollment may be used for confirmation of diagnosis (renal pathology review) at screening. Repeat renal biopsy will be performed at the end of the Maintenance Phase (as soon as possible after the last CDX-1135 dose or upon entry into the Extension Phase) or upon discontinuation of study treatment at any time during the study (as soon as possible after the last CDX-1135 dose). If renal biopsy is abnormal at end of the Maintenance Phase, an additional biopsy at the end of the Extension Phase may also be performed.
11. Opthalmic (fundoscopic) exam to be done during the physical exam at screening, upon entry to the Extension Phase, and upon discontinuation of study treatment at any time during the study (as soon as possible after the last CDX-1135 dose). If abnormalities are detected, further evaluation by an ophthalmologist should be performed.
12. ECG only required for patients 35 years of age or older.
13. General laboratory assessments will be performed weekly during the Induction Phase, monthly during the Maintenance Phase, and every two months during the Extension Phase. General laboratory assessments will include the following:

Hematology:	**Clinical Chemistry:**	**Urinalysis**:
Hemoglobin	Sodium	PH
Hematocrit	Potassium	Protein
Mean corpuscular volume (MCV)	Chloride	Glucose
	Bicarbonate	Ketones
Erythrocyte count (RBC)	Glucose (nonfasting)	Blood
Leukocytes (WBC)	Blood urea nitrogen (BUN)	Nitrite
Platelets	Creatinine	Urine protein:creatinine ratio (or 24-hour urine protein)
Differential (percent):	Calcium	*Microscopic examination should be performed if indicated*
Neutrophils	Phosphate	
Lymphocytes	Alkaline phosphatase	
Monocytes	Alanine transaminase (ALT/SGPT)	
	Aspartate transaminase (AST/SGOT)	
	Total protein	
	Albumin	
	Lactate Dehydrogenase (LDH)	
	Total Bilirubin	
	C-Reactive Protein	

14. Complement specific labs include serum C3 levels, plasma C3c levels, and C3Nef levels. All complement studies will be performed centrally, at the University of Iowa. Complement studies (drawn prior to and ~60 minutes after dosing) will be performed biweekly during the Induction Period, weekly during the Maintenance Period, every two weeks during the first year of the Extension Period, and monthly thereafter.
15. Vaccinations must be completed at least 14 days before beginning treatment (i.e. before beginning the Induction Period). The patient will be vaccinated against meningitis (Meningococcal conjugate vaccine, quadrivalent (MCV4)), hemophilus (Haemophilus influenzae type b conjugate vaccine (Hib)) and pneumococci (13-valent pneumococcal conjugate vaccine (PCV13)) if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer.
16. CDX-1135 antibodies will be performed prior to dosing on Week 1, and then repeated at the beginning and end of the Maintenance Phase and at the end of the Extension Phase, or upon treatment discontinuation. Immunogenicity should also be determined when complement levels, previously normalized, fall outside the normal range.
17. This assay will be performed Iowa University on plasma and serum from pre-treatment blood draws and Maintenance Period blood draws. The assay measures phagocytosis – results appear as cell-associated fluorescence, with the fluorescence derived from ingested GFP-expressing Staphylococcus.