Human Placenta-derived Cells (PDA-001) for the Treatment of Moderate-to-severe Crohn's Disease: A Phase 1b/2a Study

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Background: PDA-001 (cenplacel-L), a preparation of placenta-derived mesenchymal-like adherent cells with immunomodulatory effects, previously demonstrated safety and tolerability in an open-label Crohn's disease (CD) study. The current phase 1b/2a study evaluated the safety and efficacy of PDA-001 in subjects with moderate-to-severe CD.

Methods: Subjects had active inflammation on colonoscopy or elevated fecal calprotectin and inadequate response to conventional therapy. Concomitant therapy with stable doses of immunomodulators and/or biologics was permitted. Subjects received 8 units of PDA-001 (1.5×10^8 cells per unit) in the phase 1b open-label study. In the phase 2a double-blind study, subjects were randomly assigned placebo, 1 unit, or 4 units of PDA-001 (2 infusions 1 wk apart). The primary endpoint was induction of clinical response (≥100 points and/or 25% decrease in Crohn's Disease Activity Index) at 4 and 6 weeks.

Results: Fifty subjects were enrolled (safety analysis, 50 subjects; efficacy analysis, 48 subjects). Four subjects received 8 units of PDA-001 (phase 1b study); 46 subjects were subsequently randomized to 1 or 4 units of PDA-001 or placebo (phase 2a study). The primary endpoint was achieved in 10/28 (36%) of PDA-001 subjects compared with placebo (0%, $P = 0.026$). Clinical remission was achieved in 4/28 (14%) of PDA-001 subjects compared with placebo (0%, $P = 0.3$). One treatment-related serious adverse event occurred (systemic hypersensitivity reaction at 8 units). In the phase 2a study, serious adverse events occurred in 9/28 (32%) of PDA-001 subjects and 1/16 (7%) of placebo subjects.

Conclusions: A 2-infusion regimen of PDA-001 induced clinical response in subjects with moderate-to-severe CD. Additional studies are warranted.

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Key Words: Crohn's disease, PDA-001, immunomodulation, cell therapy

Crohn's disease (CD) is thought to result from aberrant intestinal mucosal inflammation triggered by commensal bacteria in a genetically susceptible host.[1,2] Subjects affected by CD experience significant intestinal and extraintestinal symptoms, increased risk for hospitalization and surgery and have significantly impaired quality of life.[3] Medical therapies for CD have traditionally involved immunosuppressive agents or selective biological inhibitors of inflammatory pathways including tumor necrosis factor α (TNF-α). However, there is a need for alternative pharmacological modalities for individuals intolerant of or refractory to currently available treatments.

Cell-based therapy has been investigated as a means to modulate inflammation. Both hematopoietic and mesenchymal cells have been studied in vivo and have been assessed for therapeutic potential in a variety of human immune-mediated conditions including CD.[4,5] PDA-001 (cenplacel-L) is a mesenchymal-like cell preparation derived from full term human placenta and is in clinical development for a variety of autoimmune and inflammatory diseases.[6] The cells display immunomodulatory, anti-inflammatory, proregenerative, neuroprotective, and angiogenic properties both in vitro and in animal models.[7–9] PDA-001 has been shown to modulate

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inflammation through various mechanisms including suppression of interleukin (IL)-6, TNF-α, and proliferation of activated T cells.[7,8]

An open-label study demonstrated the safety and tolerability of PDA-001 at 1 unit (1.5×10^8 cells) and 4 units (6×10^8 cells) in 12 subjects with CD.[6] In this study, we aimed to further assess the safety and efficacy of PDA-001 in subjects with moderate-to-severe CD in a multicenter placebo-controlled phase 1b/2a study.

MATERIALS AND METHODS

Study Design

A multicenter, adaptive, phase 1b/2a dose-ranging placebo-controlled study was performed to evaluate the safety and efficacy of PDA-001 in subjects with moderate-to-severe CD between August 2010 and November 2011. The first 4 subjects were enrolled into the 1b study and were assigned to receive 8 units (1.2×10^9 cells) of open-label PDA-001 at each of 2 infusions, which were administered at days 0 and 7. After completing enrollment of the phase 1b study, a safety analysis was conducted by an independent Data Monitoring Committee. Subsequent subjects were enrolled into the phase 2a study and were randomly assigned to receive placebo, 1 unit (1.5×10^8 cells), or 4 units (6×10^8 cells) of PDA-001 in a double-blinded fashion. Safety and efficacy assessments were performed at baseline and weeks 1, 2, 4, 6, 12, and 24. Subsequently, subjects returned for 3 additional 6-month visits for a total of 24 months. The study is registered at Clinical Trials.gov (identification number NCT01155362; http://clinicaltrials.gov/ct2/show/NCT01155362?term=celgene+crohn%27s&rank=2).[10]

Subject Selection

Male and nonpregnant nonlactating female subjects aged 18 to 75 years with a history of CD for at least 6 months were eligible for participation, provided they previously had an inadequate response, loss of response, or intolerance to therapy with 5-aminosalicylates, corticosteroids, immunomodulators (6-mercaptopurine, azathioprine, or methotrexate), anti–TNF-α (infliximab, adalimumab, or certolizumab), or other biological (natalizumab and ustekinumab) therapy. Subjects were required to have active CD (Crohn's Disease Activity Index [CDAI] between 220 and 450) at enrollment and visual evidence of mucosal inflammation within 3 months of enrollment by colonoscopy. An elevated fecal calprotectin (>162.9 μg/g) could also serve as evidence of mucosal inflammation, but no patients were enrolled based on this criterion. Subjects were not eligible for the study if they started or had a change in immunomodulator or biological response modulator dosing within 3 months, 5-aminosalicylates within 4 weeks, or corticosteroids within 4 weeks of study treatment. Additional exclusion criteria included those with serious comorbidities (including cardiac, neurological, hepatic, or renal disease), malignancy within 5 years (excluding basal cell carcinoma of the skin), hospitalization for stricturing disease or bowel surgery within 6 months, any surgery within 28 days or anticipated surgery within 3 months, weight below 50 kg, active infection requiring antibiotics within 4 weeks, active infection with *Clostridium difficile*, receipt of other investigational agents within 90 days (or 5 half-lives), known allergy to bovine or porcine products, anticipated surgery within 90 days, and any previous exposure to cell therapy.

Study Treatment

All active and placebo subjects received hydrocortisone (50 mg, intravenously) and diphenhydramine (50 mg, intravenously) 15 to 30 minutes before infusion of investigational product (IP). Subjects in the phase 2a randomized study also received oral hydrocortisone (100 mg) the night before or up to 4 hours before infusion of IP. Dosing with IP was performed on days 0 and 7 using identical procedures. Cryopreserved units of PDA-001 (1.5×10^8 cells per unit) and placebo (vehicle control without cells) were provided and stored at −120°C until thawing, dilution, and administration. Open-label phase 1b study subjects received 8 units of thawed PDA-001 plus sufficient diluent (infusion grade dextran 40) for a total of 240 mL per infusion. Subjects in the randomized, double-blind phase 2b study received either 1 or 4 units of thawed PDA-001 plus sufficient diluent (infusion grade dextran 40) for a total of 240 mL per infusion or vehicle control consisting of 4 units of thawed vehicle control plus sufficient diluent (infusion grade dextran 40) for a total of 240 mL per infusion. IP was covered with an opaque bag to maintain blinding and administered peripherally through a volumetric pump over 2 hours. Vital signs were monitored every 15 minutes during the infusion, and subjects were observed for 2 hours after infusion (during which time vital signs monitoring continued).

Concomitant Therapy

Concomitant treatment with stable doses of 5-aminosalicylates (for at least 8 wk before study dosing), corticosteroids (for at least 4 wk before study dosing), immunomodulators, and biologics (for at least 3 mo before study dosing) was permitted. Dosing changes for these therapies were not allowed during the 12-week study period.

Safety

Safety evaluations were performed throughout the study and continued for a total of 24 months. These included assessments of clinical parameters, laboratory abnormalities, and annual cross-sectional imaging of the chest, abdomen, and pelvis with either computed tomography or magnetic resonance imaging.

Efficacy

The primary endpoint was induction of clinical response (defined as a decrease in CDAI score of ≥100 points and/or 25% from baseline) at both week 4 (d 29) and week 6 (d 43). For the primary analysis, the proportion of responders at weeks 4 and 6 was compared between each of the treatment arms and placebo. Secondary endpoints included induction of clinical remission (defined as CDAI ≤150) at weeks 4 and 6. Exploratory endpoints

included assessments of clinical response and remission at each scheduled visit, time to flare (defined as an increase in CDAI score of ≥100 points and/or 25% above the CDAI scores at both wk 4 and 6 and a total CDAI score of ≥220 points) among subjects meeting criteria for clinical response and remission, fistula closure among subjects with baseline fistulae, improvement in C-reactive protein (CRP) and fecal calprotectin, and improvement in disease-specific health-related quality of life measured by the Inflammatory Bowel Disease Questionnaire. Finally, serum for measurements of chemokine ligands 5 and 16, eotaxin, growth-regulated protein alpha, granulocyte chemotactic protein 2, interferon γ, IL-1β, IL-10, IL-12 p70, IL-17, IL-23, IL-6, IL-8, and IL-1 receptor antagonist, and TNF-α was obtained at baseline, day 7, and weeks 2, 4, 6, and 12.

Sample Size Justification

To adequately power the randomized, double-blind phase 2a study, we considered a treatment response rate of 75% in the pooled active treatment arms and a placebo response rate between 25% and 50%. To achieve power of at least 80% at a significance level of 0.05, 16 subjects for each of 3 arms (assuming study of 1 and 4 units of PDA-001 and placebo) were required, for a total of 48 subjects.

Statistical Analysis

All randomized subjects who initiated at least one study infusion were included in the safety analysis. Efficacy analyses included all subjects who received at least 1 dose of PDA-001 or placebo and had a week 4 efficacy assessment (modified intention-to-treat population). Secondary and exploratory endpoints of proportions of response and remission were compared at all time points. Values of inflammatory markers (CRP, calprotectin) were compared across study groups using descriptive statistics, and changes in Inflammatory Bowel Disease Questionnaire scores were assessed, based on the assumption that an improvement of 16 points is clinically meaningful.[11,12] We also explored whether a center effect or sequence of enrollment was associated with response rates.

Ethical Considerations

The protocol was approved by the institutional review boards at all study sites. All subjects provided written informed consent. The study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final article.

RESULTS

Four subjects were enrolled in the open-label phase 1b study, and 46 of 48 planned subjects were randomized in the phase 2a, randomized placebo-controlled study (Fig. 1). The study was suspended before the last 2 enrolled subjects were randomized because of safety events (see Discussion section) in a separate PDA-001 study for a different indication (rheumatoid arthritis). The 50 subjects were included in the safety analysis. Forty-four of the 46 randomized subjects were included in the modified intention-to-treat efficacy analysis of the phase 2a study (the 2 excluded subjects completed both infusions;

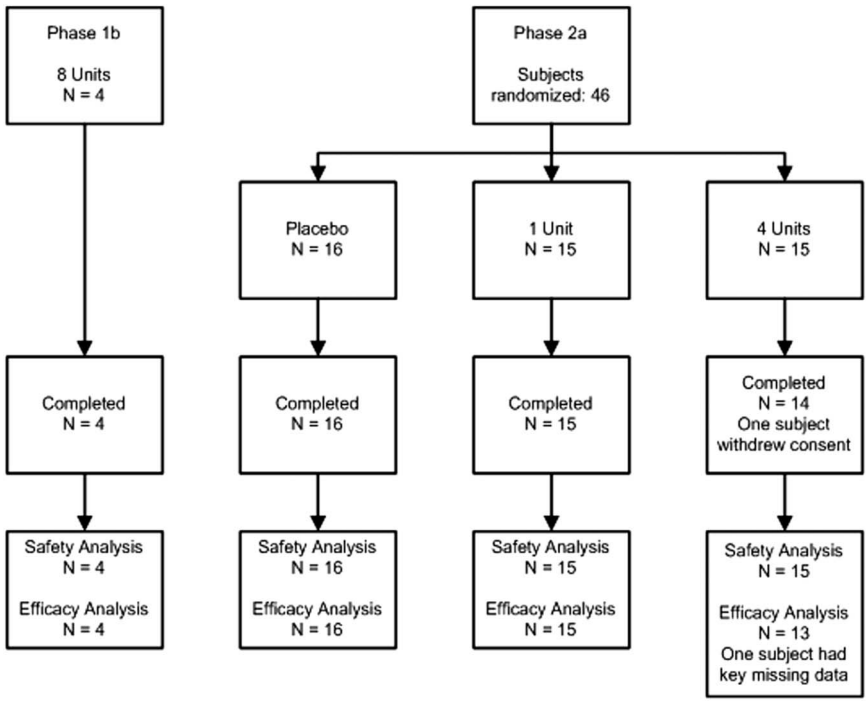

FIGURE 1. Study flow diagram.

TABLE 1. Clinical Characteristics at Baseline

	1 Unit (n = 15)	4 Units (n = 15)	8 Units (n = 4)	Placebo (n = 16)
Age, mean ± SD, yr	35.3 ± 14.0	36.2 ± 11.6	32.3 ± 10.9	36.5 ± 7.3
Male, n (%)	53.3	33.3	75.0	43.8
White, n (%)	100.0	93.3	100	93.8
Disease duration, mean ± SD, yr	18.5 ± 13.8	10.4 ± 10.7	13.5 ± 12.6	16.2 ± 9.4
CDAI score, mean ± SD	303.5 ± 66.8	323.0 ± 61.5	299.0 ± 61.8	329.9 ± 116.1
IBDQ score, mean ± SD	127.1 ± 36.5	111.9 ± 38.2	127.5 ± 46.7	129.4 ± 26.7
CRP, mean ± SD, mg/dL	1.3 ± 1.0	3.0 ± 4.1	1.1 ± 1.9	2.5 ± 4.4
Fecal calprotectin, median, μg/g	824	856	380	790
No. of subjects on concomitant therapy				
Steroids	0	1	0	4
Immunomodulators	2	6	2	4
Anti-TNF therapy	7	7	1	6

IBDQ, Inflammatory Bowel Disease Questionnaire.

however, one subject withdrew consent before the wk 4 efficacy endpoint, and a second subject did not provide the efficacy assessment at wk 4).

Phase 1b Study: 8-Unit PDA-001 Dose

Four subjects (3 male) were enrolled in the open-label phase 1b study and received 8 units (1.2×10^9 cells) of PDA-001. At baseline, these subjects had a mean CDAI of 299 (±62) points and a mean duration of disease of 13.5 years (Table 1). Two subjects experienced 1 significant adverse event each. Both adverse events were suspected to be related to PDA-001. One subject experienced a grade 3 hypersensitivity reaction, and the other experienced venous thrombosis at the infusion site. Based on these events, it was determined that the phase 2a randomized double-blind study would include 3 arms: 1 unit and 4 units of PDA-001 and placebo.

Phase 2a Study

Baseline Measures

Forty-six subjects were randomized into 1 of 3 arms (1 unit PDA-001, 4 units PDA-001, or placebo) in a 1:1:1 ratio. Baseline characteristics were similar across study groups with respect to age, gender, race, disease activity, health-related quality of life, inflammatory markers, and concomitant therapies (Table 1). Mean disease duration was numerically shorter among those who received 4 units of PDA-001 (10.4 yr) relative to those who received placebo (16.2 yr) or 1 unit of PDA-001 (18.5 yr).

Efficacy

Response and Remission

The primary efficacy endpoint of clinical response at both weeks 4 and 6 was achieved in 38.5% of subjects who received 4 units of PDA-001, 33.3% who received 1 unit of PDA-001, and 0% who received placebo ($P = 0.013$ [4 units versus placebo]; $P = 0.042$ [1 unit versus placebo]) (Table 2). There were placebo patients who had a reduction in CDAI of 100 points at either weeks 4 or 6, but none demonstrated this reduction at both weeks 4 and 6. Overall, subjects who received PDA-001 at any dose had significantly greater response than placebo ($P = 0.026$). The secondary endpoint of remission was achieved in 15.4% of those who received 4 units of PDA-001, 13.3% who received 1 unit of PDA-001, and 0% who received placebo (Table 2). Similarly, higher response rates were seen among PDA-001–treated subjects at weeks 4 and 6 than in those who received placebo (Fig. 2). Of 7 subjects in the phase 2a study who responded but later fulfilled the criteria for flare, the median time to flare was 115 days. Eight subjects had 1 or more perianal fistulae at baseline across all treatment groups; 1 fistula closed in 1 subject, and 1 fistula opened in each of 3 subjects.

Health-related Quality of Life

Improvements in scores on the Inflammatory Bowel Disease Questionnaire at weeks 4, 6, and 12 were greater among PDA-001–

TABLE 2. Primary Efficacy Endpoint: Clinical Response[a]

Outcome, n (%)	1 Unit (n = 15)	4 Units (n = 13)	Placebo (n = 16)
Response	5 (33.3)[b]	5 (38.5)[c]	0 (0)
Remission	2 (13.3)	2 (15.4)	0 (0)

[a]CDAI improvement of 100 points or 25% from baseline at both weeks 4 and 6.
[b]$P = 0.042$, 1 unit versus placebo.
[c]$P = 0.013$, 4 units versus placebo.

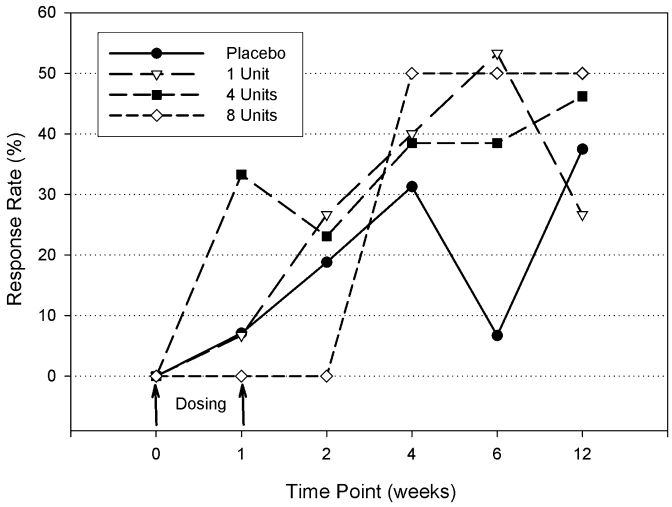

FIGURE 2. Clinical response at each visit.

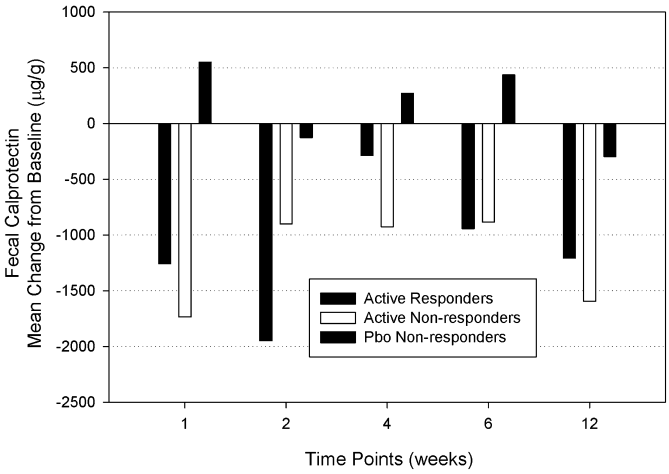

FIGURE 4. Mean change from baseline in fecal calprotectin for placebo (nonresponders), PDA-001 responders, and PDA-001 nonresponders.

treated subjects compared with those who received placebo. At week 6, both the 1- and 4-unit treatment groups experienced a 16-point increase (Fig. 3), considered clinically significant.[11]

Inflammatory Parameters

Changes in mean CRP were not consistently different across treatment groups, and baseline CRP levels did not distinguish responders from nonresponders. Similarly, changes in mean fecal calprotectin were not consistently different across treatment groups (Fig. 4). However, when analyzed by response status, subjects receiving any dose of PDA-001 showed a decrease in mean fecal calprotectin, whereas those receiving placebo showed either no change or a small increase (Fig. 5). There were no clear differences for other cytokines when stratified by treatment group or by responder status.

Center and Sequence Effects

Thirteen centers participated in the study. The proportion of responders was similar at each center. Furthermore, the sequence of subject enrollment was not associated with the likelihood of response.

Safety and Tolerability

Nonserious adverse events were seen in multiple body systems. Events judged at least possibly related to treatment included (all PDA-001 doses): pyrexia, headache; (1 unit): noncardiac chest pain, migraine, pain in extremity, leukopenia, neutropenia, respiratory disorder, hemoglobin decreased; (4 units): infusion-site pain, edema peripheral, infusion-site swelling, infusion-site mass, migraine, thrombophlebitis superficial, phlebitis, venous thrombosis limb, erythema, pruritus,

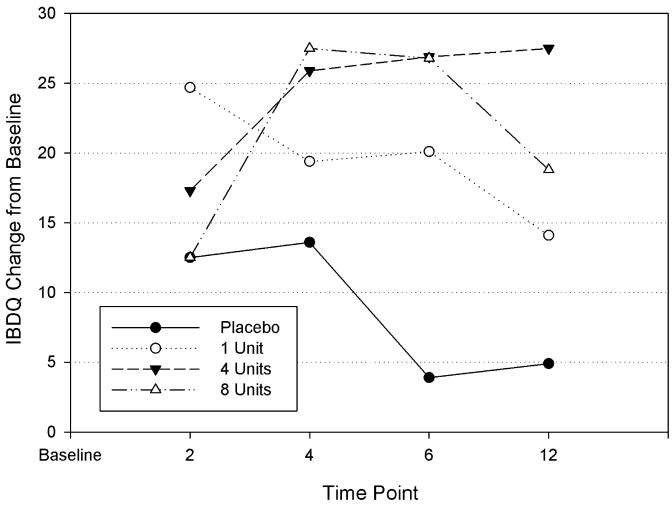

FIGURE 3. Inflammatory Bowel Disease Questionnaire mean change from baseline.

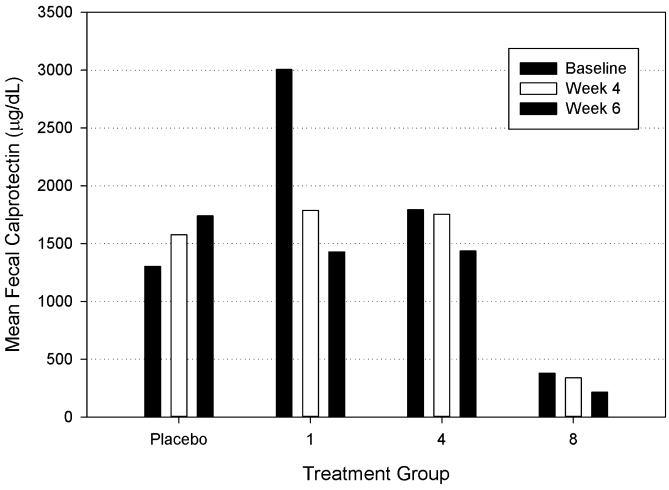

FIGURE 5. Fecal calprotectin levels at baseline and at weeks 4 and 6 by treatment group.

arthralgia, joint swelling, tachycardia, early menarche, and infusion-site infection; (8 units): nodule, venous thrombosis, erythema, pain in extremity, and lymphadenopathy; (placebo): flushing, erythema, urticaria, palpitations, throat irritation, and vision blurred. The most commonly reported adverse events overall (whether or not related to treatment) included anemia, CD flare, abdominal pain, nausea, pyrexia, headache, and erythema (6, 16, 9, 6, 16, 11, and 5 subjects each, respectively) (Table 3).

TABLE 3. Most Frequently Reported (≥3 Subjects) Treatment-emergent Adverse Events

		PDA-001 Dose[a]				
System Organ Class/Preferred Term, n (%)	Placebo (n = 9)	1 Unit (n = 19)	4 Units (n = 18)	8 Units (n = 4)	PDA-001 (n = 41)	All Subjects (N = 50)
Blood and lymphatic system disorders						
Anemia	1 (11.1)	2 (10.5)	2 (11.1)	1 (25.0)	5 (12.2)	6 (12.0)
Gastrointestinal disorders						
CD	1 (11.1)	8 (42.1)	6 (33.3)	1 (25.0)	15 (36.6)	16 (32.0)
Abdominal pain	0 (0)	4 (21.1)	4 (22.2)	1 (25.0)	9 (22.0)	9 (18.0)
Nausea	0 (0)	2 (10.5)	4 (22.2)	0 (0)	6 (14.6)	6 (12.0)
Anal fistula	0 (0)	0 (0)	2 (11.1)	2 (50.0)	4 (9.8)	4 (8.0)
Gastroesophageal reflux disease	1 (11.1)	1 (5.3)	1 (5.6)	1 (25.0)	3 (7.3)	4 (8.0)
Hematochezia	0 (0)	2 (10.5)	2 (11.1)	0 (0)	4 (9.8)	4 (8.0)
General disorders and administration site conditions						
Pyrexia	1 (11.1)	5 (26.3)	9 (50.0)	1 (25.0)	15 (36.6)	16 (32.0)
Infusion-site pain	0 (0)	1 (5.3)	3 (16.7)	0 (0)	4 (9.8)	4 (8.0)
Edema peripheral	0 (0)	1 (5.3)	2 (11.1)	1 (25.0)	4 (9.8)	4 (8.0)
Fatigue	1 (11.1)	1 (5.3)	1 (5.6)	0 (0)	2 (4.9)	3 (6.0)
Infections and infestations						
Urinary tract infection	0 (0)	1 (5.3)	2 (11.1)	1 (25.0)	4 (9.8)	4 (8.0)
Pneumonia	1 (11.1)	1 (5.3)	1 (5.6)	0 (0)	2 (4.9)	3 (6.0)
Sinusitis	1 (11.1)	0 (0)	2 (11.1)	0 (0)	2 (4.9)	3 (6.0)
Vulvovaginal mycotic infection	0 (0)	1 (5.3)	2 (11.1)	0 (0)	3 (7.3)	3 (6.0)
Investigations						
Aspartate aminotransferase increased	1 (11.1)	0 (0)	2 (11.1)	1 (25.0)	3 (7.3)	4 (8.0)
Alanine aminotransferase increased	1 (11.1)	0 (0)	1 (5.6)	1 (25.0)	2 (4.9)	3 (6.0)
Hematocrit decreased	1 (11.1)	1 (5.3)	1 (5.6)	0 (0)	2 (4.9)	3 (6.0)
Metabolism and nutrition disorders						
Dehydration	0 (0)	2 (10.5)	1 (5.6)	0 (0)	3 (7.3)	3 (6.0)
Musculoskeletal and connective tissue disorders						
Pain in extremity	0 (0)	2 (10.5)	0 (0)	2 (50.0)	4 (9.8)	4 (8.0)
Arthralgia	1 (11.1)	0 (0)	2 (11.1)	0 (0)	2 (4.9)	3 (6.0)
Back pain	1 (11.1)	2 (10.5)	0 (0)	0 (0)	2 (4.9)	3 (6.0)
Nervous system disorders						
Headache	1 (11.1)	3 (15.8)	5 (27.8)	2 (50.0)	10 (24.4)	11 (22.0)
Migraine	0 (0)	1 (5.3)	3 (16.7)	0 (0)	4 (9.8)	4 (8.0)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (11.1)	0 (0)	2 (11.1)	0 (0)	2 (4.9)	3 (6.0)
Skin and subcutaneous tissue disorders						
Erythema	1 (11.1)	0 (0)	2 (11.1)	2 (50.0)	4 (9.8)	5 (10.0)
Pruritus	0 (0)	1 (5.3)	2 (11.1)	0 (0)	3 (7.3)	3 (6.0)
Vascular disorders						
Phlebitis	0 (0)	0 (0)	2 (11.1)	1 (25.0)	3 (7.3)	3 (6.0)

[a]Treatment columns represent the maximum dose level the subject received during the study.

TABLE 4. Frequency of Local and Systemic Infusion Reactions Observed in PDA-001 Studies Across All Indications[a]

Event Category, n (%)	Placebo (N = 16)	1 Unit (N = 55)	4 Units (N = 32)	8 Units (N = 4)
Infusion reaction—local	0 (0)	5 (9.1)	14 (43.8)	1 (25.0)
Infusion reaction—systemic[b]	4 (25.0)	9 (16.4)	9 (28.1)	3 (75.0)
Phlebitis	0 (0)	1 (1.8)	3 (9.4)	1 (25.0)
Thrombophlebitis superficial	0 (0)	0 (0)	3 (9.4)	0 (0)

[a]Presented as subjects with events observed within the first 5 weeks after initial dose regardless of number of doses (1 or 2). The event categories contain collections of adverse event terms that are significantly overlapping and are not independent. Source: Celgene Cellular Therapeutics, data on file.
[b]Included in this category are these events: pruritus, dyspnea, flushing, rash, chills, hypersensitivity, and urticaria.

Fourteen subjects experienced 1 or more serious adverse events (SAEs). Three SAEs (hypersensitivity reaction [8-unit dose], gastric ulcer perforation [1-unit dose], and anal cancer [1-unit dose]) were judged possibly related to treatment. SAEs judged unrelated to treatment included CD flare, abdominal adhesions, ileus, small intestinal obstruction, perirectal abscess, pneumonia, colon cancer, anemia, intestinal anastomosis, peripheral arterial occlusive disease, and Takayasu's arteritis. The colon and anal cancers occurred 74 days and 8.5 months (during long-term follow-up) after PDA-001 administration, respectively. The colon and anal cancer subjects were 33.4 and 46.8 years from the initial CD diagnosis upon randomization into the study. There were no deaths.

DISCUSSION

In this Phase 1b/2a study of a novel cell-based therapy for the treatment of CD, the primary endpoint of clinical response at weeks 4 and 6 was achieved in significantly more subjects treated with either 1 unit or 4 units of PDA-001 than with placebo. In addition, clinically significant improvement in health-related quality of life was seen among PDA-001–treated subjects. However, corresponding decreases in CRP and fecal calprotectin were not observed. A hypothesis for this, which will be tested in a subsequent study, is that repeated doses of PDA-001 leading to longer term exposure is necessary to achieve reductions in these inflammatory biomarkers. The secondary endpoint of clinical remission at weeks 4 and 6 was not significantly greater for PDA-001–treated subjects compared with placebo, although placebo rates of remission were 0% at both time points. The efficacy of PDA-001 for maintenance of response beyond 12 weeks was not assessed.

Adverse events at the site of infusion were seen in 5 subjects, all of whom received PDA-001. The rate of these events (12.2%) was related to the infused dose and is consistent with that seen in the data from 91 subjects (12.1%) who have received PDA-001 across all indications (Table 4). These infusion-site events may be due to the expression of tissue factor (CD142) on the surface of mesenchymal-like cells, which can be prothrombotic.[13,14] Two SAEs were seen in a study of rheumatoid arthritis and led to the suspension of enrollment in this study. These SAEs, which will be described in detail in a separate article, included a case of acute myocardial infarction and a case of retinal artery spasm. Reduction of the dose and modification of the method of administration of PDA-001 including premedication with low molecular weight heparin might mitigate these events. A study to evaluate these strategies is currently ongoing.

Limitations to this study include a relatively small number of subjects, many of whom had a long duration of disease and over half of whom had previously been exposed to anti-TNF therapies, suggesting a medically resistant population. In addition, we did not account for potential confounding effects related to the timing of administration of permitted concomitant biological therapies.

In conclusion, this study showed that a 2-infusion regimen of either 1 unit or 4 units of PDA-001 can induce clinical response in subjects with moderate-to-severe CD. Additional studies are warranted to assess optimal dosing, effects of retreatment, and safety parameters.

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REFERENCES

1. Mayer L. Evolving paradigms in the pathogenesis of IBD. *J Gastroenterol.* 2010;45:9–16.
2. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. *Nat Rev Immunol.* 2003;3:521–533.
3. Podolsky DK. Inflammatory bowel disease. *N Engl J Med.* 2002;347:417–429.
4. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood*. 2005;105:1815–1822.
5. Gonzalez MA, Gonzalez-Rey E, Rico L, et al. Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses. *Gastroenterology*. 2009; 136:978–989.
6. Mayer L, Pandak WM, Melmed GY, et al. Safety and tolerability of human placenta-derived cells (PDA001) in treatment-resistant Crohn's disease: a phase 1 study. *Inflamm Bowel Dis.* 2013;19:754–760.
7. He S, Khan J, Gleason J, et al. Placenta-derived adherent cells attenuate hyperalgesia and neuroinflammatory response associated with perineural inflammation in rats. *Brain Behav Immun.* 2013;27:185–192.
8. Liu W, Morschauser A, Zhang X, et al. Human placenta-derived adherent cells induce tolerogenic immune responses. *Clin Translat Immunol.* 2014; 3:e14.
9. Shehadah A, Chen J, Pal A, et al. Human placenta-derived adherent cell treatment of experimental stroke promotes functional recovery after stroke in young adult and older rats. *PLoS One.* 2014;9:e86621.
10. A multi-center study to evaluate the safety and efficacy of intravenous infusion of human placenta-derived cells (PDA001) for the treatment of adults with moderate-to-severe Crohn's disease [ClinStudys.gov Web site]. 2011. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01155362?term=celgene+crohn%27s&rank=1. Accessed April 6, 2015.
11. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical studies in inflammatory bowel disease. *Gastroenterology*. 1989; 96:804–810.
12. Higgins PD, Schwartz M, Mapili J, et al. Subject defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut*. 2005;54:782–788.
13. Moll G, Rasmusson-Duprez I, von Bahr L, et al. Are therapeutic human mesenchymal stromal cells compatible with human blood? *Stem Cells.* 2012;30:1565–1574.
14. Tatsumi K, Ohashi K, Matsubara Y, et al. Tissue factor triggers procoagulation in transplanted mesenchymal stem cells leading to thromboembolism. *Biochem Biophys Res Commun.* 2013;431:203–209.