Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis

Duncan B. Richards,[1] Louise M. Cookson,[1] Sharon V. Barton,[1] Lia Liefaard,[1] Thirusha Lane,[2] David F. Hutt,[2] James M. Ritter,[3] Marianna Fontana,[2] James C. Moon,[4] Julian D. Gillmore,[2] Ashutosh Wechalekar,[2] Philip N. Hawkins,[2] Mark B. Pepys[2,5]*

[1]GlaxoSmithKline Research and Development, Stevenage, Herts SG1 2NY, UK. [2]National Health Service National Amyloidosis Centre, Centre for Amyloidosis and Acute Phase Proteins, University College London and Royal Free Hospital, London NW3 2PF, UK. [3]Quintiles Drug Research Unit, Guy's Hospital, London SE1 1YR, UK. [4]University College London Institute of Cardiovascular Science and Barts Heart Centre, St Bartholomew's Hospital, London EC1A 7BE, UK. [5]Wolfson Drug Discovery Unit, Centre for Amyloidosis and Acute Phase Proteins, University College London, London NW3 2PF, UK.

*Corresponding author. Email: m.pepys@ucl.ac.uk

ABSTRACT

Systemic amyloidosis is a fatal disorder caused by pathological extracellular deposits of amyloid fibrils that are always coated with the normal plasma protein, serum amyloid P component (SAP). The small-molecule drug, miridesap, [(R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC)] depletes circulating SAP but leaves some SAP in amyloid deposits. This

residual SAP is a specific target for dezamizumab, a fully humanized monoclonal IgG1 anti-SAP antibody that triggers immunotherapeutic clearance of amyloid. We report the safety, pharmacokinetics, and dose-response effects of up to three cycles of miridesap followed by dezamizumab in 23 adult subjects with systemic amyloidosis (ClinicalTrials.gov identifier: NCT01777243). Amyloid load was measured scintigraphically by amyloid-specific radioligand binding of ^{123}I-labeled SAP or of ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid. Organ extracellular volume was measured by equilibrium magnetic resonance imaging and liver stiffness by transient elastography. The treatment was well tolerated with the main adverse event being self-limiting early onset rashes after higher antibody doses related to whole body amyloid load. Progressive dose-related clearance of hepatic amyloid was associated with improved liver function tests. ^{123}I-SAP scintigraphy confirmed amyloid removal from the spleen and kidneys. No adverse cardiac events attributable to the intervention occurred in the six subjects with cardiac amyloidosis. Amyloid load reduction by miridesap treatment followed by dezamizumab has the potential to improve management and outcome in systemic amyloidosis.

INTRODUCTION

The extracellular accumulation of amyloid fibrils disrupts the architecture and function of affected tissues and organs in systemic amyloidosis, causing fatal disease (*1*). Systemic amyloid deposits usually do not elicit inflammation or the physiological phagocytic mechanisms that normally clear extracellular protein and cellular debris. Current management of systemic amyloidosis comprises support for damaged amyloidotic organs, coupled with attempts to reduce production of amyloidogenic proteins. Even if fibril

precursor abundance is sufficiently reduced, thereby arresting new amyloid accumulation, existing amyloid is cleared slowly and variably. Efforts to develop targeted immunotherapeutic clearance of amyloid are therefore underway (*2*, *3*).

Human serum amyloid P component (SAP) from the plasma is present in all human amyloid deposits due to its avid but reversible binding to amyloid fibrils of all types (*4*). Our small-molecule drug, miridesap [(R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid], previously known as CPHPC, swiftly depletes circulating SAP (*5*) but leaves some SAP in amyloid deposits (*6*). The residual SAP acts as a specific antigen target for therapeutic anti-SAP antibodies that can bind to it and thereby trigger amyloid removal (*2*, *3*). Plasma SAP depletion by miridesap is essential before anti-SAP antibody administration to avoid formation of potentially proinflammatory circulating immune complexes. In humanized murine models, binding of anti-SAP antibodies to amyloid activates the classical complement pathway and opsonizes the deposits with fixed complement C3, attracting and engaging macrophages that fuse into multinucleated giant cells uniquely able to surround, engulf, and destroy large complement opsonized objects (*2*, *7*).

We have recently reported safety and clinical proof-of-concept results for miridesap followed by the fully humanized monoclonal anti-human SAP antibody, dezamizumab, in patients with different forms of systemic amyloidosis, including the following types: monoclonal immunoglobulin light chain (AL), reactive systemic amyloid A protein (AA), apolipoprotein AI (AApoAI), and fibrinogen A α-chain (AFib) (*3*). Infusion of anti-SAP antibody triggered transient early inflammatory cytokine production and an acute phase response, followed by substantial plasma C3 depletion, but there was no new or increased renal or other organ dysfunction (*3*). Amyloid clearance from the liver was associated with improved liver function tests (*3*). However, maximal removal of amyloid from all organs and tissues, which will be required for optimal clinical efficacy, was not achieved with just

a single dose of anti-SAP antibody. Here, we investigated the safety, tolerability, and efficacy of up to three cycles of treatment with miridesap followed by dezamizumab in 23 adult subjects with systemic amyloidosis (15 participated in the previous study, whereas 8 were new subjects).

RESULTS

Patient characteristics, trial design, and safety data

We conducted the second part, designated part B, of an open-label, nonrandomized, first in human, phase 1 clinical trial of miridesap followed by dezamizumab in 23 patients with systemic amyloidosis: 12 with AL, 5 with AFib, 3 with transthyretin type (ATTR), 2 with AA, and 1 with AApoAI. Their demographic features, amyloid distribution and load, dezamizumab doses, and rationale thereof, are shown in table S1. Fifteen of the subjects had previously received a single treatment with miridesap followed by dezamizumab in the first part of the trial, designated part A, which has been reported elsewhere (*3*), and eight additional subjects were newly recruited for part B. Among 48 total treatments administered to the 23 trial subjects, each with completed follow-up, 8 subjects received 1 treatment, 5 subjects received 2 treatments, and 10 subjects received 3 treatments.

There were no deaths during the study, no withdrawals during treatment sessions, and no signs of organ toxicity. Injection of miridesap caused mild, transient, non-treatment limiting, local pain and occasional erythema on four occasions, and there were 11 mild adverse events related to intravenous catheter insertion. There were also three serious adverse events. Subject 008 became hypotensive immediately after dezamizumab infusion and recovered but then had tachycardia with blood pressure around 90/60 mmHg about 4 hours later due to insufficient fluid replacement. A temporary increase in serum creatinine concentration thereafter had returned to baseline at day 21. Subject 021 developed an erythema multiform-like rash, starting within 24 hours of dezamizumab

infusion and resolving gradually without sequelae after 60-mg oral prednisolone. Subject 018, with a history of episodic atrial fibrillation, had a spontaneously resolving episode of fast atrial fibrillation 27 days after dezamizumab infusion that was not considered related to study treatment.

Dose-related infusion reactions to dezamizumab consisted of one or more of the following: headache, flushing, feeling hot or cold, chest discomfort, chills, facial, orbital, and peripheral edema, nausea, vomiting, diarrhea, fatigue, tachycardia, presyncope, and hypotension. None were reported at ≤650 mg in part B of the trial, but they occurred in 20% of patients receiving 1000 to 1200 mg and 50% of patients receiving 2000 mg. However, although not formally comprising an infusion reaction, some of these symptoms were reported within 24 hours of dezamizumab administration after 50% of doses at ≤650 mg, 67% of doses at 1000 to 1200 mg, and 75% of doses at 2000 mg. Slowing and interrupting the infusion was helpful and, together with premedication with hydrocortisone and antihistamine, enabled dezamizumab dosing up to 2000 mg in subjects with heavy amyloid loads and 1200 mg in those with small or moderate amyloid loads. In cardiac amyloidosis, dezamizumab administration split over 2 days caused no adverse cardiac events.

Twenty two of 38 recipients of ≥600 mg of dezamizumab developed mild or moderate urticarial or macular rashes, usually within 24 to 36 hours, but there were no associated systemic symptoms, signs, or related test results, or any mucosal involvement. Urticaria responded well to antihistamines. Macular lesions were more persistent but resolved spontaneously without sequelae. Rash incidence generally increased with increasing dezamizumab dose and was most common in subjects with a small or moderate amyloid load given higher doses that produced the highest peak plasma concentrations of dezamizumab. The rash recurred on repeat dezamizumab administration but was not necessarily more severe. Two skin biopsies were obtained.

One showed active leukocytoclastic vasculitis but neither fibrinoid change or necrosis nor detectable immune complexes, immunoglobulin, or complement deposition. The other skin biopsy showed only nonspecific changes. The rash appearance within 48 hours of dezamizumab infusion, rapidly peaking in severity, corresponded with the transient peak circulating concentration of the antibody and, together with the mild vasculitic histology without deposited immunoreactants, suggested that circulating proinflammatory complexes or aggregates derived from dezamizumab might be responsible. Dividing the planned dezamizumab infusion over 2 days enabled the second portion of the dose to be omitted in two subjects who developed a rash soon after the first exposure.

No other adverse effects were attributable to dezamizumab treatment. The acute phase response and complement consumption that always preceded amyloid clearance were not associated with any organ dysfunction. Battery-operated, portable, continuous electrocardiography (EKG) recordings (Holter monitoring) showed no clinically significant abnormalities. No urine sediment abnormalities were seen, and renal function was stable in all subjects, except for subject 008 as noted above.

Pharmacokinetics of miridesap and dezamizumab in patients with systemic amyloidosis

Circulating miridesap concentrations were consistent with previous clinical miridesap studies (*5*, *6*, *8*). The regimen reduced baseline plasma SAP concentrations in all subjects to the target value of <2 mg/liter before dezamizumab was administered. Plasma SAP values had returned to the reference range at day 42.

In subjects with a heavy amyloid load, including hepatic amyloidosis, the circulating dezamizumab concentration typically fell to <50 μg/ml within 24 hours, even after the 2000-mg dose. With small to moderate amyloid loads, without liver involvement, the 24-hour concentration was about 150 μg/ml, falling to <50 μg/ml by 72 hours. After

reduction of hepatic amyloid load by previous dezamizumab treatment, clearance of a subsequent antibody dose was slower, consistent with the rate depending on target-specific binding to amyloid- associated SAP (Fig. 1).

Progressive amyloid removal in patients treated with miridesap followed by dezamizumab

In the first part of the trial (part A), single doses of 246 to 650 mg of dezamizumab substantially cleared hepatic amyloid in five subjects with moderate or heavy liver load, leading to improved liver function tests, but amyloid removal was generally not detected in those with the heaviest liver and whole-body amyloid loads (*3*). In the second part of the trial (part B), which is reported in this study, there was evidence of liver amyloid reduction in some subjects who received 1000 to 1200 mg of dezamizumab but not in other subjects with the heaviest load. However, a 2000-mg dose reduced amyloid load in the liver and/or spleen in five of seven subjects who received it, confirmed by ^{123}I-labeled SAP scintigraphy (Fig. 2, A and B, and Table 1). The proportions of ^{123}I-SAP tracer retained in the liver at 24 hours, corresponding to the Fig. 2A images, were 76.0% pretreatment, 58.5% after the first dose, and 20.0% after the second dose. The exceptions were AL subject 011, whose clone relapsed causing new amyloid accumulation, and subject 019 who only received a single 2000-mg dose (Table 1). Apart from the latter patient, the amyloid load was reduced in the liver and/or other organs after one, two, or three doses of dezamizumab in the other nine participants who had liver amyloid. For example, Fig. 2B shows reduction in amyloid load in the spleen and kidneys of subject 017. The proportions of ^{123}I-SAP tracer retained at 24 hours in the spleen and kidneys were 5.3 and 8.2% before and 3.8 and 5.7% at day 42 after treatment. Amyloid clearance was always preceded by plasma C3 depletion during the first week after dezamizumab

infusion, with the C3 concentration falling to between 23 and 87% of predose values after the 14 treatments in these nine subjects.

Reductions in liver amyloid load detected by SAP scintigraphy were independently corroborated by equilibrium magnetic resonance imaging (MRI) measurements of the liver. The volume of the extra- cellular space, where the amyloid is located, decreased toward normal in all cases. However, liver stiffness, which is markedly increased by amyloid, was the most sensitive marker for hepatic amyloid. Stiffness initially increased in some subjects (Fig. 3A), consistent with the massive early infiltration of macrophages into amyloid deposits seen in the mouse model (*2*). However, liver stiffness then fell substantially (Fig. 3A), consistent with amyloid clearance and the accompanying resolution of the cellular infiltrate reported in that animal model (*2*).

Subjects 011 and 013 with AL amyloidosis, who suffered clonal relapses after receiving their antibody dose in part A, and AL subject 014 who relapsed after a second dose in part B, accumulated additional amyloid between dosing sessions. In subject 109, with hereditary AApoAI amyloidosis and continuous production of amyloidogenic apolipoprotein AI, there was evidence of amyloid removal after each dose, followed by some amyloid reaccumulation. Nevertheless, liver function was closer to normal after the third treatment compared to the original baseline (Table 1).

Reduction in renal amyloid in patients treated with miridesap followed by dezamizumab

Reduction in renal amyloid was observed in 7 of 11 subjects with renal amyloid detected by SAP scintigraphy (five with AFib and one each with AL and AA amyloidosis), generally, those treated with higher doses of dezamizumab. SAP scintigraphy showed renal amyloid reduction in zero of six subjects after <600 mg of dezamizumab, two of six (33%) after 600 to 650 mg, and five of six (83%) after 1200 mg (Fig. 2B and table S1). Renal amyloid

clearance was only seen in the AL case, subject 013, after a first dose of dezamizumab had cleared this patient's hepatic amyloid. The AFib patients had small to moderate whole-body amyloid loads with no detectable liver amyloid. Renal function, serum creatinine and urea concentrations, and urinary protein excretion were unchanged in all subjects up to day 42, the end of the protocol follow-up, similar to what we previously documented for subjects in part A, the initial phase of the trial (*3*).

Preliminary safety data in patients with cardiac amyloidosis

Patients with clinical cardiac amyloidosis were specifically excluded in part A for safety reasons (*3*). After establishing additional safety information in part B, three subjects with AL and three with ATTR cardiac amyloidosis were enrolled for preliminary assessment (Table 2). No actual infusion reactions occurred, but there were some modest systemic symptoms. Crucially, there were no new arrhythmias, no increase in circulating troponin T or creatine kinase concentrations, and no change in existing cardiac abnormalities. Nevertheless, on day 1 after antibody dosing, four of these subjects developed transient, up to fivefold, increases in the circulating concentration of N-terminal pro–B-type natriuretic peptide (NT-proBNP), lasting about 1 week (Fig. 3C), suggesting possible engagement of the target mechanism in the heart. One subject (021) who received three antibody doses showed a reduction of 17% in left ventricular mass by cardiac MRI, greater than the coefficient of variation of the method, suggesting reduction in cardiac amyloid load (Table 2).

DISCUSSION

Systemic amyloidosis is usually diagnosed late after the initial clinical presentation, when organ function is often already severely compromised. There have been major advances in cytotoxic chemotherapy to eliminate the B cell or plasma cell dyscrasias that cause AL,

the most common type of systemic amyloidosis but, unfortunately, not all patients tolerate these toxic regimens or respond to them. About 25% of AL patients still die within the first 6 months after diagnosis and, even when there is a clonal response, regression of amyloid is slow and variable. AA amyloidosis is now rare, and the various underlying inflammatory disorders that cause it can usually be controlled, but amyloid regression is still slow and often limited. Furthermore, there are currently no approved means of reducing production of transthyretin, the amyloidogenic protein in senile and hereditary ATTR amyloidosis, or the amyloidogenic proteins in other types of hereditary amyloidosis, apart from liver transplantation in AFib (*9*). Thus, although reduction of amyloid fibril precursor proteins will always be desirable, there is an urgent need for treatment that removes amyloid from the tissues.

Here, we show that dezamizumab, infused after previous depletion of plasma SAP by miridesap, achieves this objective with acceptable safety. Serial doses, comprising sufficient dezamizumab in relation to each subject's amyloid load, progressively removed amyloid from the liver, spleen, and kidneys in acquired and hereditary systemic amyloidosis. Amyloid clearance from the liver was faster and more extensive than from other organs, as previously observed with spontaneous hepatic AA and AL amyloid regression in effectively treated patients (*10*–*13*). This may reflect the fact that the sinusoidal, fenestrated hepatic capillary endothelium allows unhindered access of antibodies and complement proteins from the blood to the extracellular space where the amyloid deposits are located. Although splenic capillaries also have sinusoidal endothelium, both spontaneous amyloid regression and amyloid clearance by miridesap plus dezamizumab are slower in the spleen, so there may be other factors, such as availability of appropriate macrophage populations. Amyloid clearance from the heart, kidneys, and other organs with tight junction capillary endothelium may also be slower.

Classical complement pathway activation, which is required in the mouse model to engage macrophages and enable amyloid removal (*2*), requires a multimeric assembly of bound antibody molecules (*14*). The effective dezamizumab doses observed in this study were consistent with the requirement to form these assemblies on the amounts of target SAP available in each individual's amyloid, and only dezamizumab doses that triggered plasma C3 depletion produced detectable amyloid clearance. However, regardless of the mechanism, our results indicate that (i) repeated, sufficient doses of dezamizumab should substantially clear amyloid of all types, and (ii) repeated treatments will be required if amyloid accumulation continues when amyloidogenic fibril precursor production cannot be controlled.

Clearance of amyloid from the liver was associated with improved liver function, firmly establishing the relationship between the presence and amount of amyloid and the pathogenesis of organ dysfunction. There was no change in proteinuria or renal function through the 6-week study follow-up; additional dosing and longer follow-up will be required to ascertain preservation or restoration of renal function. Encouraging safety and tolerability data were also obtained in the preliminary study of cardiac AL and ATTR amyloidosis. There was no evidence of myocardial damage, but early transient increases in plasma NT-proBNP concentration after dezamizumab administration suggested that the antibody may be initiating the mechanism for potential amyloid clearance in the heart. A forthcoming larger study of serial anti-SAP dosing at regular and closer intervals will seek to extend safety and establish efficacy in cardiac amyloidosis, which is the major single cause of morbidity and mortality.

No direct adverse effect of dezamizumab on organ function was detected but, as previously reported for part A, systemic infusion reactions to effective doses were universal. They were substantially reduced by antihistamine and hydrocortisone premedication and were further mitigated by divided slow infusion of larger total antibody

doses, enabling use of up to the 2000-mg maximum dose. Nevertheless, total doses of >600 mg caused pleomorphic urticarial and macular skin rashes in most recipients, with the time course suggesting causation by circulating proinflammatory materials derived from dezamizumab. However, the identified and potential risks of the intervention are considered manageable, and thus acceptable, in relation to the demonstrable clinical benefits of removing amyloid from vital organs. There are several limitations to our study. Only 23 subjects have been treated hitherto, so that the scope and scale of potential adverse reactions, especially to larger and repeated doses of dezamizumab, cannot yet be reliably estimated. Despite unequivocal evidence of reduction in renal amyloid load, effects on proteinuria and preservation of renal function will require a longer follow-up than the 6 weeks of the present protocol. Other than preliminary examination of safety in the six cardiac amyloidosis patients reported in this study, the use of miridesap and dezamizumab in subjects with heart involvement will be explored in our forthcoming phase 2 trial.

Clinical trials in AL amyloidosis of two different anti-amyloid antibodies, NEOD001 (Prothena) (*15*) and 11-1F4 (Columbia) (*16*), have reported improvements in some biochemical markers of cardiac function but did not evaluate amyloid removal. NEOD001 does not elicit any systemic reaction and, in contrast to the rapid amyloid load-related clearance of dezamizumab, the 13- to 16-day plasma half-life of NEOD001 approaches that of free immunoglobulin G (*15*). Infusion of 11-1F4 produces systemic reactions and rashes and the antibody demonstrably bound to amyloid in 9 of 18 reported AL cases (*17*). Further observations are required on amyloid clearance and the clinical effects produced by each of these antibodies and by dezamizumab.

MATERIALS AND METHODS

Study design

The two center [Quintiles and GlaxoSmithKline (GSK) Clinical Unit], open-label, nonrandomized, first in human study of the fully humanized monoclonal IgG1 anti-SAP antibody (GSK2398852, dezamizumab) administered after previous infusion of miridesap (CPHPC) was approved by the UK Medicines and Healthcare Products Regulatory Agency and the Berkshire "B" phase 1 accredited Research Ethics Committee. Each dosing session comprised visits for baseline measurements, inpatient treatment, and scheduled outpatient assessments with a follow-up at 6 weeks after dezamizumab dosing for evaluation of amyloid load. Part A, an initial single-dose escalation study reported previously, established safety and proof of mechanism (*3*). Part B, reported in this study, adaptively extended antibody dosing, evaluating up to three treatments at intervals of at least 2 months. Some part A subjects proceeded to part B, for which additional subjects were also recruited. Patients with known cardiac amyloidosis were excluded from part A but, after the acceptable initial safety profile, were included in part B, provided that there was no systolic impairment, New York Heart Association class III/IV decompensated cardiac failure, recent cardiac-related syncope or presyncope, or circulating NT-proBNP >1800 ng/liter in AL amyloidosis.

Participants

Comprehensively characterized, biopsy-proven, systemic amyloidosis patients (n = 23, 11 female), aged 44 to 69 years (table S1), and under the care of the UK National Health Service National Amyloidosis Centre at the Royal Free Campus of University College London were referred for screening. All gave written informed consent, had adequate venous access, and could tolerate the study protocol. Entry to the study required

compliance with stringent requirements for functional status and organ function but did not have constraints regarding previous treatment. Twelve subjects had AL amyloidosis, all of whom had completed chemotherapy with either complete or good partial responses, and all had good functional status, but three of them suffered typical clonal relapses during the study. Two subjects had AA amyloidosis, but their underlying inflammatory conditions were in complete remission and they, together with the remaining nine subjects with hereditary AFib, ATTR, or AApoAI amyloidosis, had received only supportive care.

Anti-SAP antibody intervention

Subjects were admitted for initial plasma SAP depletion, typically by 3 days intravenous infusion of 20-mg/hour miridesap (*8*), to reach the selected target of <2 mg/liter. Dezamizumab was then infused intravenously, designated as study day 1. Miridesap administration was continued by subcutaneous injection, typically for 11 days, to maintain circulating SAP depletion until plasma anti-SAP antibody activity had disappeared. The miridesap dose of 60 mg, three times a day, was adjusted for renal impairment, if necessary, to keep predicted exposure below pre-established protocol-defined safety limits (*8*).

Premedication with 100 mg of parenteral hydrocortisone and an antihistamine substantially mitigated the otherwise dose-limiting reactions caused by infusion of more than 200 mg of dezamizumab in part A, allowing administration of higher doses, and was routinely used in part B. The highest antibody dose was 1200 mg in subjects with small to moderate amyloid load and 2000 mg in those with large whole-body load involving the liver. Repeat treatment depended on toleration of, and response to previous dose(s), and subject availability to comply with the protocol. Each treatment was a discrete event with a minimum interval between doses of 2 months, enabling completion of follow-up and

evaluation of response (interval range, 4 to 19 months for part A subjects in part B; and 2 to 3 months for part B–only participants).

Global dosing strategy and individual subject dosing rationale

Table S1 shows each dezamizumab dose and its rationale. Dose response was initially explored in part A subjects who had shown evidence of hepatic amyloid removal. The decision to administer second or third doses was based on tolerability and response to the previous dose and subject availability, given the substantial time commitment. Each treatment was a discrete event and the interval between doses was variable, ranging from 5 to 19 months between first and second treatments in the part A subjects and 2 to 5 months in the part B–only participants.

Reduction in hepatic amyloid was observed in five subjects in part A (subjects 007, 008, 009, 011, and 014), all with AL amyloidosis and a large liver amyloid load, who were the first to receive a second treatment in part B. This reduced the amyloid load, shown by SAP scintigraphy, in the spleen of subject 008 and liver of subject 014; liver stiffness was reduced in subject 009. There was no SAP scintigraphy change in the liver in subjects 007 and 011, but liver stiffness was reduced in subject 007. Subject 011 suffered a clonal relapse after the initial treatment in part A, which persisted throughout part B. Subjects 009 and 011 had infusion reactions, subject 014 developed a moderate rash, and subject 008 had a serious adverse event: hypotension during dezamizumab infusion leading to a temporary rise in creatinine concentration. After this event, routine premedication with 100-mg hydrocortisone and a nonselective antihistamine was administered to all subjects before each dezamizumab dose.

In part A, reduction of renal amyloid was observed in subject 012 who had no liver involvement. To determine, in part B, whether the treatment could remove renal amyloid, we studied patients with AFib amyloidosis, which always involves the kidneys but typically

has a small to moderate whole-body amyloid load. AL amyloidosis commonly affects the kidneys, but evaluation is complicated by extensive multisystem involvement. Subject 005, who had received only 78 mg of dezamizumab early in part A, was scheduled to receive 600 mg in part B, but the infusion was stopped as a precautionary measure at 330 mg, because subject 008, being treated at the same time, became hypotensive after dezamizumab infusion. Renal amyloid was not reduced in subject 005 after this dose or in subject 004 after 600 mg, but the load was reduced in both cases after a subsequent dose of 1200 mg. Renal amyloid load was also reduced after 1200 mg of dezamizumab in each of the other AFib subjects, 002, 006, and 017.

Dezamizumab doses of 1000 or 1200 mg had little effect on the hepatic amyloid load in subjects 007, 010, 011, 015, and 016 with AL amyloidosis and 009 with AApoAI type, all of whom had a large liver and whole-body amyloid load. However, a subsequent 2000-mg dose reduced the liver and/or spleen amyloid in all except subject 011 who was in clonal relapse. Subject 019, also with a very heavy liver and whole-body AL amyloid load, received 2000-mg dezamizumab as the first dose, but no amyloid reduction was detected and the subject was unable to receive a second dose before the study closed.

Subjects with known cardiac amyloidosis were excluded from part A, but after amyloid clearance from multiple organs with acceptable safety and tolerability during part B, protocol amendment allowed enrolment of six subjects with mild but definite cardiac involvement, three with AL and three with ATTR type, for preliminary safety assessment. Four subjects received one treatment and two subjects received three treatments. Dezamizumab infusion was split over two consecutive days and cardiac safety was closely monitored. The study ended after treatment of the cardiac subjects because the study objectives had been achieved, the supply of dezamizumab was exhausted, and it had become evident that serial repeated treatments, with miridesap followed by doses of

dezamizumab appropriate for the amyloid load in each individual, would be required to optimize amyloid clearance.

Study measures

Comprehensive hematological, biochemical, cardiac, renal, and immunological tests were performed at screening, baseline before dosing, during dezamizumab infusion, the subsequent inpatient days, and, if not still an inpatient, on study days 6, 14, and 21, with final follow-up on day 42, along with blood sampling for pharmacokinetic studies. Amyloid load was monitored as follows. Liver stiffness was measured by transient elastography (*18*, *19*) at baseline and days 14 and 42. Extra- cellular volumes of the heart, liver, and spleen were measured by equilibrium MRI (*20*–*22*) at baseline and day 42. ^{123}I-SAP scintigraphy with computed tomography (CT)–single photon emission CT (CT- SPECT) to quantify organ retention of tracer at 24 hours (*24*) was performed at baseline and day 42, when the soluble and amyloid-bound SAP pools had fully re-equilibrated. ATTR amyloidosis subjects underwent ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) CT-SPECT scintigraphy at baseline and day 42 to quantify cardiac ATTR amyloid (*25*). EKGs were monitored by Holter 24-hour recordings on the first day of miridesap infusion, by telemetry during dezamizumab infusion, and by Holter on study days 1 and 3 thereafter.

Study outcomes

In addition to the primary safety outcome measure, dezamizumab pharmacokinetics, plasma miridesap and SAP concentrations, amyloid load, and organ function were monitored.

Statistical analysis

Safety and pharmacokinetic outcomes were assessed without formal hypothesis testing. Changes in absolute values and proportional changes from baseline in the different measures of amyloid load were evaluated in relation to the reference ranges and variances of the respective tests.

SUPPLEMENTARY MATERIALS

Table S1. Demographic features of participants, amyloid type and load, dezamizumab doses administered, and dosing rationale.

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and WO/2009/000926, US7910106 B2, and US9192668 B2, “Combinations of SAP depleting agents and anti-SAP antibodies”. M.B.P. founded and owns shares in Pentraxin Therapeutics Ltd, the University College London spinout company that owns these patents and EP 0915088B1 A1, “d-proline derivatives”, and has licensed them to GSK for development. GSK owns a further relevant patent WO2011/107480, “Antigen binding proteins specific for serum amyloid P component”. P.N.H. owns shares in Pentraxin Therapeutics Ltd. A.W. and J.D.G. have received consultancy fees from GSK. J.M.R. was an employee of Quintiles. Quintiles was paid by GSK to perform the study on some of the subjects reported. J.C.M. has received funding from GSK for research in amyloidosis. All other authors declare that they have no competing interests.

Table 1. Effect of Serial Dezamizumab Doses in Subjects with Hepatic Amyloidosis

Subject	Amyloid Type	Dezamizumab Dose (mg)[a]	Amyloid Load by SAP Scan	Liver ECV Pre-dose	Liver ECV Day 42	Liver Stiffness (kPa) Pre-dose	Liver Stiffness (kPa) Day 42	GGT (IU/L) Pre-dose	GGT (IU/L) Day 42
007	AL	152 600 2,000	No change No change Liver and spleen reduced	0.45 0.40 0.40	0.50 0.43 0.37	10.4 8.4 6.3	9.8 5.9 4.9	93 74 66	96 79 67
008	AL	246 600	Liver reduced Spleen reduced	0.37 0.30	0.33 0.24	14.4 5.7	8.9 8.9	135 44	98 43
009	ApoAI	650 1,000 2,000	Liver reduced No change Liver and spleen reduced	0.48 0.46 0.40	0.42 0.44 0.40	24.2 17.8 12.5	11.9 8.9 6.6	714 264 283	331 278 211
010	AL	400 1,200 2,000	No change No change Liver reduced	0.58 0.61 0.53	0.61 0.66 0.56	46.5 48.0 27.3	25.7 28.0 16.9	181 166 129	158 125 88
011	AL	650 1,000 2,000	Liver reduced No change No change	0.54 0.58 0.65	0.53 0.63 0.63	27.0 28.0 35.3	15.7 23.9 27.0	466 401 526	411 465 751
013	AL	650 600	Liver reduced Kidney reduced Adrenal reduced	0.36 0.33	0.29 0.35	5.7 3.3	2.8 3.7	20 14	16 18
014	AL	600 1,000 500	Liver reduced Liver reduced Liver increased	0.35 0.34 0.31	0.34 0.32 0.32	8.9 4.3 4.8	4.4 7.5 4.8	148 60 32	96 44 33
015	AL	600 2,000	No change Spleen reduced	0.42 0.43	0.38 0.37	4.9 6.3	5.2 4.2	27 24	19 18

016	AL	600 2,000 2,000	No change No change Liver reduced	0.45 0.43 0.36	0.43 0.40 0.33	27.7 35.3 14.8	27.0 17.3 13.3	274 161 106	240 126 77
019	AL	2,000	No change	0.42	0.43	26.6	32.0	69	70

Median normal ECV, 0.29; liver stiffness, 5.3 kPa (90% < 7.0 kPa); GGT, γ glutamyl transpeptidase, 5-45 IU/L.
These 10 subjects were those who had definite detectable hepatic amyloidosis. Subjects 011 and 013 entered clonal relapse after first dosing session. Subject 014 suffered clonal relapse after second dose and developed rash in session 3, thus receiving only half the planned 1,000 mg dose.
[a] Doses shown are as planned unless administered doses differed greatly.

Table 2. Effect of Dezamizumab on Measures of Cardiac Amyloid

Subject Number Amyloid Type	Dose of Dezamizumab (mg)[a]	LV Mass Pre-dose (g)	LV Mass Day 42 (g)	Cardiac DPD Scan
018 AL	600 1,200 1,200	258 248 254	246 249 243	N/A
020 AL	600	213	211	N/A
021 AL	600 1,200 1,200	264 251 225	244 228 220	N/A
023 ATTR	1,200	248	255	Perugini grade 2 cardiac uptake. No change
024 ATTR	1,000	255	260	Perugini grade 2 cardiac uptake. No change
025 ATTR	600	196	205	Perugini grade 2 cardiac uptake. No change

[a] Dezamizumab was administered in 2 equal infusions, each lasting approximately 6 hours, on days 1 and 2.

Figure legends

Fig. 1. Pharmacokinetics of Dezamizumab. Subject 013 received 650 mg of dezamizumab in Session 1 (Part A) (◆) and 600 mg in Session 2 (Part B) (◇). Subject 016 received an ineffective first antibody dose in Part A but then an effective second dose of 2000 mg in Session 2 (Part B) (▲)followed by a further 2000 mg dose (in Session 3 (Part B) (△).

Fig. 2. Effect on Amyloid Load of Treatment with Miridesap plus Dezamizumab. (**A**) Anterior SAP scintigraphy scans of subject 014 with systemic AL amyloidosis. Before treatment, left; 42 days after first dezamizumab dose, center; 42 days after second dezamizumab dose, right. (**B**) Posterior SAP scintigraphy scans of subject 017 with hereditary systemic AFib amyloidosis. Before treatment, left; 42 days after dezamizumab, right.

Fig. 3 Effect on Liver Stiffness and NT-proBNP of Treatment with Miridesap plus Dezamizumab. (**A**) Serial measurements of liver stiffness by transient elastography after start of dezamizumab infusion on day 1 in subjects with hepatic amyloidosis. PD, pre-dose measurement before each dezamizumab infusion. Median normal liver stiffness, 5.3 kPa (90% < 7.0 kPa). Upper panel: subjects with initial baseline stiffness ≤15kPa. Subject 007 (●) received sequential doses of 152, 600 and 2,000 mg dezamizumab. Subject 008 (■) 246, 600 mg. Subject 013 (○) 650, 600 mg. Subject 014 (□) 600, 1,000, 500 mg. Subject 015 (△) 600, 2,000 mg. Lower panel: subjects with initial baseline stiffness >15kPa. Subject 009 (▲) 637, 1,000, 2,000 mg. Subject 010 (▼) 400, 1,200, 2,000 mg. Subject 011 (◆) 650, 1,000, 2,000 mg). Subject 016 (▽) 600, 2,000, 2,000 mg. Subject 019 (◇) 2,000 mg. The interval between doses was variable: range 3-12 months. (**B**) Serial measurements of circulating NT-proBNP after dezamizumab treatment in subjects with proven cardiac amyloidosis. All available results are shown. S, value at screening

before study; PD, pre-dose value before each dezamizumab infusion; results after first dose shown on an expanded scale. Subject 018 (AL type) (●) received sequential doses of 600, 1,200, 1,200 mg dezamizumab. Subject 020 (AL) (□) 600 mg. Subject 021 (AL) (▲) 600, 1,200, 1,200 mg. Subject 023 (ATTR) (△) 1,200 mg. Subject 024 (ATTR) (◆) 1,000 mg). Subject 025 (ATTR) (◇) 600 mg. The interval between doses was variable: range 2-3 months.

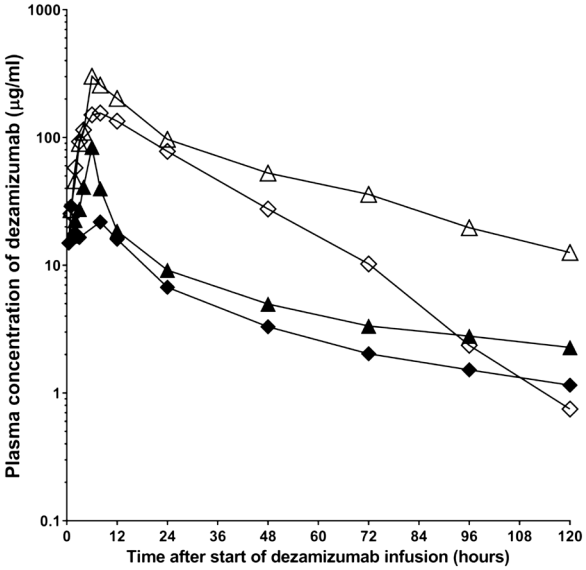
Plasma concentration of dezamizumab (µg/ml)
1000
100
10
1
0.1
0
12
24
36
48
60
72
84
96
108
120
Time after start of dezamizumab infusion (hours)

Fig. 1

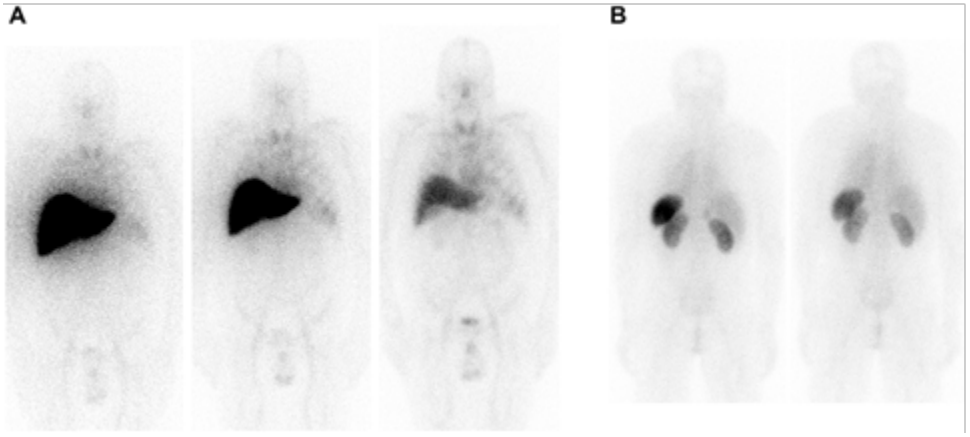
A
B

Fig. 2

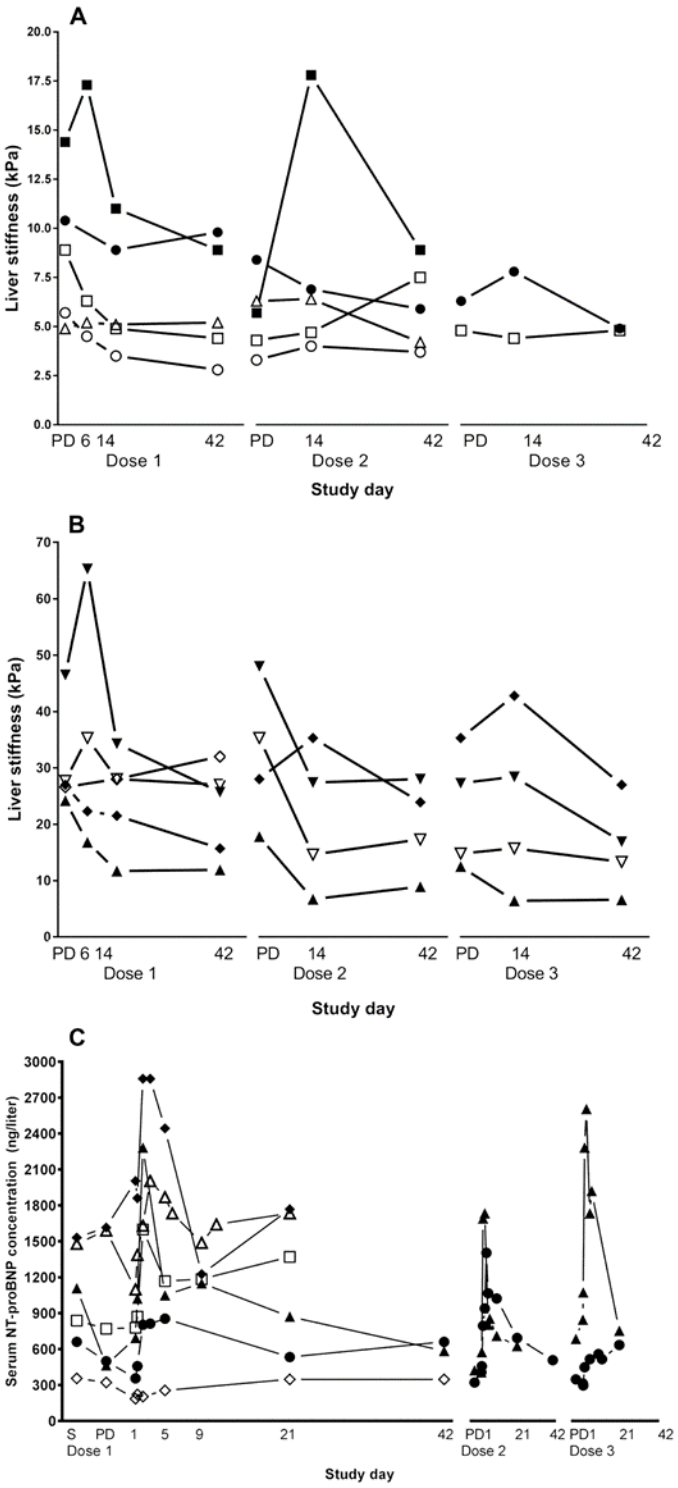
A
Liver stiffness (kPa)
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
PD 6 14 42
Dose 1
PD 14 42
Dose 2
PD 14 42
Dose 3
Study day
B
Liver stiffness (kPa)
70
60
50
40
30
20
10
0
PD 6 14 42
Dose 1
PD 14 42
Dose 2
PD 14 42
Dose 3
Study day
C
Serum NT-proBNP concentration (ng/liter)
3000
2700
2400
2100
1800
1500
1200
900
600
300
0
S PD 1 5 9 21 42
Dose 1
PD1 21 42
Dose 2
PD1 21 42
Dose 3
Study day

Fig. 3

Making amyloid vanish

Fatal systemic amyloidosis is caused by extracellular amyloid deposition that disrupts tissue structure and function. The normal plasma protein, serum amyloid P component (SAP), is always present within amyloid deposits. Richards *et al.* now show that previous depletion of circulating SAP by the drug, miridesap, uniquely enables subsequent administration of the humanized anti-SAP antibody, dezamizumab, to patients with systemic amyloidosis. Dezamizumab bound to residual SAP in the amyloid deposits and triggered their removal. Repeat cycles of miridesap followed by dezamizumab progressively removed amyloid from the liver, spleen, and kidneys of the patients. Evidence of clinical benefit suggests that this new approach has potential to improve management and outcome for patients with systemic amyloidosis.

Supplementary Materials for

Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis

Duncan B. Richards, Louise M. Cookson, Sharon V. Barton, Lia Liefaard, Thirusha Lane, David F. Hutt, James M. Ritter, Marianna Fontana, James C. Moon, Julian D. Gillmore, Ashutosh Wechalekar, Philip N. Hawkins, Mark B. Pepys*

*Corresponding author. Email: m.pepys@ucl.ac.uk

Table S1. Demographic features of participants, amyloid type and load, dezamizumab doses administered, and dosing rationale.

Subject[a]	Amyloid Type[b] and Load	Age	Sex	Dezamizumab Dosing[c]					
				First Dose (mg)	Rationale	Second Dose (mg)	Rationale	Third Dose (mg)	Rationale
001	AA Moderate kidney, spleen; no liver	60	F	5	Fixed dose per escalation plan	No further dose as amyloid load moderate and scope for benefit limited			
002	AFib Small kidney, spleen; no liver	58	M	5	Fixed dose per escalation plan	1,200	Preferred dose for renal amyloid, associated with higher response rate than 600 mg	No third dose as response with dose 2	
004	AFib Small kidney, spleen; no liver	68	M	81	1 mg/kg per escalation plan	600	Evaluation of 600 mg dose in subjects with renal amyloid	1,200	Preferred dose for renal amyloid, associated with higher response rate than 600 mg
005	AFib Small kidney, spleen; no liver	60	M	78	1 mg/kg per escalation plan	330 (600 mg planned)[d]	Evaluation of 600 mg dose in subjects with renal amyloid	1,200	Preferred dose for renal amyloid, associated with higher response rate than 600 mg
006	AFib Small kidney, moderate spleen; no liver	62	F	82	1 mg/kg per escalation plan	1,200	Preferred dose for renal amyloid, associated with higher response rate than 600 mg	No third dose as response with dose 2	
007	AL Large liver, moderate spleen	65	F	152	3 mg/kg per escalation plan	600	Evaluation of 600 mg in subjects with AL with hepatic amyloid	2,000	Dose escalation as no response at previous doses
008	AL Moderate liver, large spleen, small bone marrow and kidney	61	M	246	3 mg/kg per escalation plan	600	Evaluation of 600 mg in AL with hepatic amyloid	No third dose after serious adverse effect with dose 2	
009	ApoAI Large liver, spleen	46	F	637	10 mg/kg per escalation plan	1,000	Evaluation of 1,000-1,200 mg in hepatic amyloid	2,000	Dose escalation as limited response at previous dose
010	AL Large liver, spleen	60	M	400	Dose reduced owing to infusion reaction in subject 009	1,200	Evaluation of 1,000-1,200 mg in hepatic amyloid	2,000	Dose escalation as limited response at previous doses
011	AL Large liver, spleen; moderate bone marrow	63	F	650	Dose increased as no response to 400 mg in subject 010	1,000	Evaluation of 1,000-1,200 mg in hepatic amyloid	2,000	Dose escalation as no response to previous dose

Subject[a]	Amyloid Type[b] and Load	Age	Sex	Dezamizumab Dosing[c]					
				First Dose (mg)	Rationale	Second Dose (mg)	Rationale	Third Dose (mg)	Rationale
012	AA Large spleen, small kidney and adrenals; no liver	62	F	650	Repeat evaluation of 650 mg following response in subject 011	Further dosing awaiting additional information about potential effect of SAA response to antibody infusion on AA amyloid			
013	AL Large liver; moderate spleen; small kidney, bone marrow; amyloid lymph node	49	F	650	Repeat evaluation of 650 mg following responses in subjects 011 and 012	600	Dose repeated as good response to dose 1	Left study due to clonal relapse and referral for high dose chemotherapy and stem cell transplant	
014	AL Large liver; moderate spleen	53	M	600	Responses in subjects 011-013 but also infusion reactions. 300mg + 300 mg split dose to improve tolerability	1,000	Evaluation of 1,000-1,200 mg in hepatic amyloid	500 (1,000 planned)[e]	Good response to dose 2 so repeat intended but dosing interrupted by rash
015	AL Moderate liver, large spleen	67	F	600	Repeat evaluation as for subject 014	2,000	Dose escalation as no response to 600 mg	Unable to return before study end	
016	AL Large liver, spleen	44	F	600	Repeat evaluation as for subject 014	2,000	Dose escalation as no response to 600 mg	2,000	Repeat dose as response with previous dose
017	AFib Small kidney, moderate spleen	69	M	1,200	Preferred dose for renal amyloid, associated with higher response rate than 600 mg	No further dosing after response to dose 1			
018	AL Small spleen. Interventricular septum 15 mm. Ejection fraction 61%. Impaired global strain rate	50	M	600	Initial test dose in cardiac amyloidosis	1,200	Dose escalation as 600 mg well tolerated	1,200	Repeat dose. No escalation due to rash
019	AL Large liver and large spleen	69	F	2,000	High dose as large hepatic amyloid load present	Unable to return before study end			
020	AL Small kidney, moderate spleen, small adrenals. LV[f] non-dilated, normal systolic function, ejection fraction 72%, wall 14 mm	50	M	600	Initial test dose in cardiac amyloidosis	Unable to return before study end			

Subject[a]	Amyloid Type[b] and Load	Age	Sex	Dezamizumab Dosing[c]					
				First Dose (mg)	Rationale	Second Dose (mg)	Rationale	Third Dose (mg)	Rationale
021	AL Small kidney, moderate spleen. Preserved systolic function; impaired longitudinal contraction; grade 2 diastolic dysfunction; wall 17 mm; ejection fraction 60%	47	F	600	Initial test dose in cardiac amyloidosis	1,200	Dose escalation as 600 mg well tolerated	1,200	Repeat dose. No escalation due to rash
023	ATTR DPD scan: Perugini grade 2 cardiac uptake	66	M	1,200	Evaluation of 1,200 mg in cardiac ATTR as 600 mg well tolerated in previous cardiac amyloidosis cases	Unable to return before study end			
024	ATTR DPD scan: Perugini grade 2 cardiac uptake	68	M	1,000	Evaluation of 1,000 mg in cardiac ATTR as 600 mg well tolerated in previous cardiac amyloidosis cases	Unable to return before study end			
025	ATTR DPD scan: Perugini grade 2 cardiac uptake	66	M	600 (1,200 planned)[e]	Evaluation of 1,200 mg in cardiac ATTR as 600 mg well tolerated in previous cardiac amyloidosis cases	Unable to return before study end			

[a] Subjects 001- 016 participated in part A and all except 001 and 012 also participated in part B; subjects 017-025 were in part B only. Subjects 003 and 022 were screened but not enrolled due to poor venous access and scheduling difficulties respectively.

[b] Amyloidosis nomenclature: AA, amyloid A protein type; ApoAI, apolipoprotein AI type, AFib, fibrinogen A α-chain type, AL, monoclonal immunoglobulin light chain type, ATTR, transthyretin type.

[c] Maximum of 3 treatment sessions in Parts A and B. Doses shown are as planned unless administered doses differed greatly.

[d] Dosing stopped because subject 008, being treated at the same time, experienced a serious adverse effect.

[e] Dosing stopped due to onset of rash.

[f] LV, left ventricle.