Genetics

Effect of the Proprotein Convertase Subtilisin/Kexin 9 Monoclonal Antibody, AMG 145, in Homozygous Familial Hypercholesterolemia

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Background—Homozygous familial hypercholesterolemia is a rare, serious disorder with a substantial reduction in low-density lipoprotein (LDL) receptor function, severely elevated LDL cholesterol, cardiovascular disease, and often death in childhood. Response to conventional drug therapies is modest. Monoclonal antibodies to proprotein convertase subtilisin/kexin 9 (PCSK9) reduce LDL cholesterol in heterozygous familial hypercholesterolemia. The effect in homozygous familial hypercholesterolemia is unknown and uncertain. We evaluated the efficacy and safety of AMG 145 in an open-label, single-arm, multicenter, dose-scheduling pilot study in patients with homozygous familial hypercholesterolemia.

Methods and Results—Eight patients with LDL receptor–negative or –defective homozygous familial hypercholesterolemia on stable drug therapy were treated with subcutaneous 420 mg AMG 145 every 4 weeks for ≥12 weeks, followed by 420 mg AMG 145 every 2 weeks for an additional 12 weeks. All patients completed both treatment periods. Mean change from baseline in LDL cholesterol at week 12 was −16.5% (range, 5.2% to −43.6%; *P*=0.0781) and −13.9% (range, 39.9% to −43.3%; *P*=0.1484) with 4- and 2-week dosing, respectively. No reduction was seen in the 2 receptor-negative patients. Over the treatment periods, mean±SD LDL cholesterol reductions in the 6 LDL receptor–defective patients were 19.3±16% and 26.3±20% with 4- and 2-week dosing, respectively (*P*=0.0313 for both values), ranging from 4% to 48% with 2-week dosing. No serious side effects were reported.

Conclusion—This study demonstrates significant and dose-related LDL cholesterol lowering with a PCSK9 monoclonal antibody in homozygous familial hypercholesterolemia patients with defective LDL receptor activity but no reduction in those who were receptor negative.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT01588496 and NCT01624142.
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Key Words: AMG 145 ■ antibodies, monoclonal ■ cholesterol, LDL ■ hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) is a rare but serious clinical disorder caused by a substantial reduction in low-density lipoprotein (LDL) receptor function.[1] As a result, LDL cholesterol levels are severely elevated, leading to cardiovascular disease and often death in childhood.[1] More than 95% of HoFH patients have a mutation in the LDL receptor, <4% in have a mutation in apolipoprotein B, and <0.5% have a mutation in proprotein convertase subtilisin/kexin 9 (PCSK9).[2,3] Although true genetic HoFH is not uncommon, the majority of patients are compound heterozygotes.[4] The residual LDL receptor activity, either negative (<2% function) or defective (2%–25% function), is associated with severity of LDL cholesterol elevation and the propensity for early cardiovascular disease.[1]

Clinical Perspective on p 2120

Conventional therapies such as statins[5,6] and ezetimibe[7] are the most commonly used drugs for HoFH and result in LDL cholesterol reductions of 15% to 25%. Patients usually also require LDL apheresis when available.[8] These improvements in LDL cholesterol, particularly with statins, appear to reduce cardiovascular disease morbidity and mortality.[9] Recently, 2 drugs, lomitapide[10] and mipomersen,[11] both of which reduce hepatic lipoprotein production and are not dependent on LDL receptor function, have been approved by the US Food and Drug Administration solely for the treatment of HoFH. AMG 145, a fully human monoclonal antibody to PCSK9, significantly reduces LDL cholesterol in heterozygous familial

hypercholesterolemia,[12] but because HoFH patients have either no or minimal LDL receptor function, defined as <2% or between 2% and 25% of normal, respectively, it is uncertain whether PCSK9 inhibition would be effective. We evaluated the efficacy and safety of AMG 145 in an open-label, single-arm, multicenter, dose-scheduling pilot study in patients with HoFH.

Methods

Patients

The Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities (TESLA) allowed the inclusion of patients with HoFH by either genetic confirmation or clinical diagnosis (history of an untreated LDL cholesterol concentration >13 mmol/L [500 mg/dL] plus either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents). Regardless of prior LDL receptor and apolipoprotein B DNA genotyping, all patients were regenotyped and on the basis of known defects in LDL receptor function were designated receptor negative or defective.

At screening, male or female patients 12 to 65 years of age and >40 kg were required to be stable on a low-fat diet and existing lipid-lowering therapies (including statins, cholesterol-absorption inhibitors, bile acid sequestrants, nicotinic acid, or combinations thereof) for at least 4 weeks, with a fasting LDL cholesterol concentration ≥3.4 mmol/L (≥130 mg/dL) and triglyceride concentration ≤4.5 mmol/L (≤400 mg/dL). Background lipid-lowering therapy was unchanged during the trial.

Patients receiving LDL apheresis within 8 weeks of the screening visit, those scheduled to receive LDL apheresis during the study, and those treated with mipomersen or lomitapide within 5 months of screening were excluded.

Additional exclusion criteria are given in the online-only Data Supplement.

Study Design and Oversight

This was an investigator-initiated trial designed jointly with Amgen. The institutional review board at each site approved the protocol, and all patients (and legal guardian if a minor) provided written informed consent before entering the trial. Patients were enrolled in an open-label, single-arm, multicenter, dose-scheduling pilot study with subcutaneous AMG 145 at a dose of 420 mg every 4 weeks for 12 weeks (www.clinicaltrials.gov, trial NCT01588496), maintained for an additional 12 weeks of treatment at 4-week intervals, and then administered 420 mg AMG 145 every 2 weeks for an additional 12 weeks (www.clinicaltrials.gov, trial NCT01624142; Figure 1). The 12-week every-4-week dosing maintenance period was necessitated by the protocol amendment process to add every-2-week dosing to the subsequent 12-week phase. Patients

meeting eligibility at screening returned within 5 to 10 days for enrollment in the treatment phase (day 1). Subsequent study visits were conducted at weeks 4, 8, and 12 for each treatment phase (Figure 1), with optional laboratory visits at weeks 2 and 10. At clinic visits, assessments included side effects, dietary compliance, concomitant lipid drugs, other prescription drugs, vital signs, physical examination, and 12-lead ECGs. Blood for laboratory testing was obtained under fasting (>10 hours, water only) conditions, and laboratory tests included lipid and safety measurements, anti–AMG 145 antibodies, biomarker sample collection, serum pregnancy testing (female subjects of childbearing potential), and urinalysis. Study drug was administered on site by trained study staff.

Efficacy and Safety Evaluations

The primary efficacy end point was percentage change from baseline in LDL cholesterol by ultracentrifugation at week 12 of each of the 4- and 2-week treatment periods. Secondary efficacy end points included absolute change and percentage change from baseline in non–high-density lipoprotein cholesterol, apolipoprotein B, apolipoprotein A1, lipoprotein(a), high-density lipoprotein cholesterol, and PCSK9, as well as the proportion of patients with a response (defined as a ≥15% reduction in LDL cholesterol from baseline). The primary safety end point was the incidence of treatment-emergent adverse events; other safety end points included the incidence of anti–AMG 145 antibodies, laboratory abnormalities, and changes in ECG parameters. Adverse events were coded by use of the *Medical Dictionary for Regulatory Activities*, version 15.1. An independent Data Monitoring Committee regularly reviewed data from this and other ongoing AMG 145 studies prepared by an external biostatistical group.

Laboratory Methods

All lipid and apolipoprotein analyses, including measurement of LDL cholesterol by preparative ultracentrifugation, were performed in a Centers for Disease Control and Prevention Part III–standardized central lipid laboratory, and safety testing was conducted in a College of American Pathology–accredited central laboratory as previously described.[12] Free PCSK9 measurements were performed by ELISA.[12] All patients were genotyped by Progenika Inc (Medford, MA) to identify or confirm mutations in LDL receptor or apolipoprotein B genes.

Statistical Analysis

The analyses of baseline demographics, lipid parameters, efficacy, and safety end points included data from all enrolled patients. The baseline for lipid parameters was the average of screening and day 1 values. In addition to the change from baseline at week 12, the mean percentage change and absolute change in millimoles per liter from baseline over each treatment period were assessed using data from weeks 4, 8, and 12. Statistical analyses in this open-label, single-arm study are descriptive
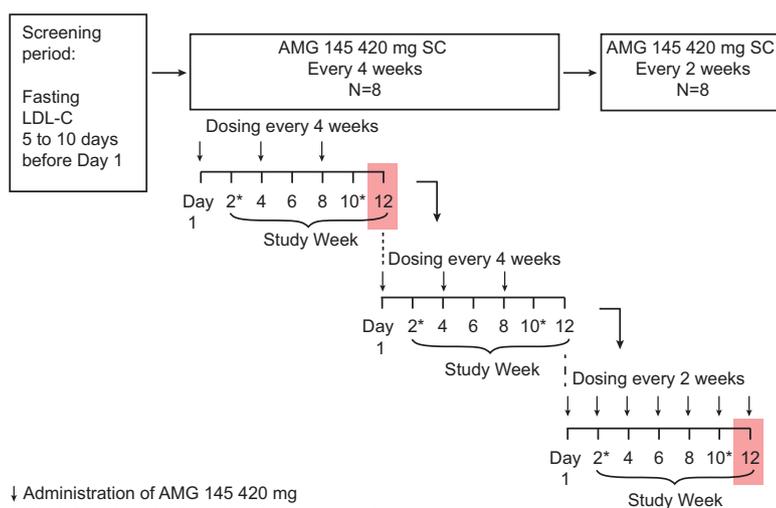

Figure 1. Study design. Eight patients with genetically confirmed homozygous familial hypercholesterolemia on stable drug therapy were enrolled. LDL-C indicates low-density lipoprotein cholesterol.

in nature. No statistical inference or missing value imputation was performed. All efficacy end points for the initial 12-week period of 4-week dosing and the 12 weeks of 2-week dosing were summarized with descriptive statistics. Significance differences were tested with the signed-rank test. Safety end points were reported over the entire duration of the trial as patient incidence. Summary statistics reported for continuous variables include the number of patients, mean, median with interquartile range, standard deviation, and minimum and maximum. For categorical variables, frequency and percentage are reported.

Results

Patient Characteristics

The first patient was screened on March 5, 2012, and the last patient completed the trial on April 9, 2013. The 8 patients were from 2 sites: Johannesburg, South Africa, and Cincinnati, OH, USA. All patients had LDL receptor mutations confirmed in both alleles (Table 1). Demographic and baseline characteristics are shown in Table I in the online-only Data Supplement, and additional details on cardiovascular history and baseline lipid therapy shown for each patient in Table II in the online-only Data Supplement. All patients were white with a mean age 34.3 years (range, 14 to 54 years); 6 patients were male; and 6 had clinical or angiographic evidence of coronary artery disease. All patients were receiving at a minimum both ezetimibe and intensive statin therapy at baseline. The LDL receptor activity of 6 patients was consistent with defective status and of 2 patients with negative status, both of which were consistent with their prior skin fibroblast measurements. The mean LDL cholesterol by ultracentrifugation at baseline was 11.4 mmol/L (range, 5.6 to 14.6 mmol/L [441.7 mg/dL; range, 218 to 563 mg/dL]; Table 2). Individual LDL cholesterol values are shown in Figure I in the online-only Data Supplement.

Efficacy Outcomes

LDL Cholesterol

Changes and percentage changes in lipid-related parameters are shown in Table 2. At week 12 of every-4-week treatment, the mean LDL cholesterol by ultracentrifugation decreased from baseline by 17% (1.8 mmol/L [70.6 mg/dL]), with a range from 5% to −44% (0.6 to −5.9 mmol/L [23 to −228 mg/dL];

$P=0.0781$). Individual responses are shown as percent change from baseline in Figure 2A and Figure IIA in the online-only Data Supplement, with 4 patients experiencing a reduction in LDL cholesterol of ≥15% and 3 patients experiencing a reduction of ≥30%. The 2 patients with negative LDL receptor activity did not demonstrate reductions in LDL cholesterol. Absolute changes in millimoles per liter for each patient are shown in Figure I in the online-only Data Supplement.

After 12 weeks of every-2-week treatment, the mean LDL cholesterol decrease from baseline was 14% (1.6 mmol/L [60.8 mg/dL]; $P=0.1484$). Again, no LDL cholesterol reduction was seen in the 2 LDL receptor–negative patients, but a greater reduction occurred over the 12-week treatment period in the 6 patients with receptor-defective function (Table 3, Figure 2A, and Figure IIC in the online-only Data Supplement). Mean±SD LDL cholesterol reductions averaged over the 12 weeks of treatment in the receptor-defective patients were 19.3±16% ($P=0.0313$) and 26.3±20% ($P=0.0313$) with 4- and 2-week dosing, respectively (Table 3 and Figure IIB and IID in the online-only Data Supplement). In the LDL receptor–defective group, LDL cholesterol changes ranged from 2% to −43% with 4-week dosing and from −4% to −48% with 2-week dosing (Figure IIA and IIC in the online-only Data Supplement).

Additional Efficacy Outcomes

The changes from baseline at week 12 in apolipoprotein B with 4- and 2-week dosing (Table 2) were consistent with those seen in LDL cholesterol. The mean±SD change in lipoprotein(a) was −11.7±11% and −18.6±12% with 4- and 2-week dosing, respectively, and did not appear to be related to LDL receptor activity (Table 3 and Figure 2B). Triglycerides, high-density lipoprotein cholesterol, and apolipoprotein A1 were essentially unchanged with either dosing schedule (Table 2). Mean±SD reductions in free PCSK9 at week 12 after every-4-week and every-2-week treatment with 420 mg AMG 145 were 22.7±37% and 87.6±8%, respectively (Table 2 and Figure 2C).

Safety

During the study, 6 of the 8 patients reported adverse events, all of which were considered not serious and unrelated to

Table 1.   Patient Genotypes

Patient	Mutation Allele 1 (Estimated LDLR Function)	Mutation Allele 2 (Estimated LDLR Function)	Overall LDLR Function
1	Asp266Glu (15%–30%)	Asp266Glu (15%–30%)	Receptor defective
2	1187-10 G>A* (not determined)	Asp266Glu (15%–30%)	Receptor defective
3	Asp224Asn (<2%)	Cys296Tyr (not determined)	Negative†
4	Deletion exons 4–18 (not determined)	Cys197Gly (not determined)	Negative†
5	Asp221Gly (<2%)	Asp227Glu (5%–15%)	Receptor defective
6‡§	Asp227Glu (5%–15%)	Asp227Glu (5%–15%)	Receptor defective
7‡§	Asp227Glu (5%–15%)	Asp227Glu (5%–15%)	Receptor defective
8	Asp175Asn (not determined)	Asp227Glu (5%–15%)	Receptor defective

LDLR indicates low-density lipoprotein receptor.

*Mutation at splice acceptor site 10 nucleotides upstream of the first nucleotide of exon 9, 1187.

†Confirmed by fibroblast culture.

‡True homozygous patient.

§Patients share the same genotype.

Table 2.   Efficacy Outcomes (Overall)

Parameter*	Baseline Value	AMG 145 (n=8)							
		Week 12, Every-4-Week Dosing			Average Week 4, 8, 12, Every-4-Week Dosing	Week 12, Every-2-Week Dosing			Average Week 4, 8, 12, Every-2-Week Dosing
		Value	Change From Baseline	Percentage Change From Baseline, %	Percentage Change From Baseline, %	Value	Change From Baseline	Percentage Change From Baseline, %	Percentage Change From Baseline, %
LDL cholesterol (ultracentrifugation), mmol/L									
Mean (SD)	11.4 (2.9)	9.6 (3.7)	−1.8 (2.4)	−16.5 (19.0) (P=0.0781)*	−13.3 (17.5)	9.9 (4.1)	−1.6 (3.2)	−13.9 (27.2) (P=0.1484)*	−16.9 (25.9)
Range	5.6 to 14.6	4.9 to 14.6	−5.9 to 0.6	−43.6 to 5.2	−38.8 to 11.7	5.1 to 15.9	4.5 to −5.6	39.9 to −43.3	−48.2 to 27.6
Calculated LDL cholesterol, mmol/L	11.6 (3.0)	9.6 (3.7)	−2.0 (2.4)	−17.2 (18.8)	−14.3 (16.7)	10.0 (4.1)	−1.6 (3.1)	−13.8 (25.8)	−17.3 (24.6)
HDL cholesterol, mmol/L	0.9 (0.2)	0.9 (0.3)	0.0 (0.2)	4.7 (22.2)	3.9 (15.9)	0.9 (0.3)	−0.0 (0.2)	−1.4 (20.7)	−0.2 (17.6)
Apolipoprotein B, g/L	2.7 (0.5)	2.3 (0.6)	−0.4 (0.4)	−14.9 (14.2)	−13.1 (14.4)	2.4 (0.7)	−0.3 (0.5)	−12.5 (18.9)	−16.0 (19.6)
Apolipoprotein A1, g/L	1.0 (0.2)	1.0 (0.1)	0.0 (0.1)	1.3 (14.0)	4.0 (9.6)	1.0 (0.2)	0.0 (0.1)	5.2 (11.7)	3.9 (9.4)
Triglycerides, mmol/L	1.3 (0.7)	1.1 (0.6)	−0.1 (0.2)	−5.7 (15.7)	−6.8 (14.2)	1.2 (0.5)	−0.02 (0.5)	5.8 (25.8)	−4.3 (18.1)
Lipoprotein(a), nmol/L†	246. 5 (61.5 to 276.0)	170.6 (116.5)	−24.6 (23.3)	−11.7 (10.6)	−11.7 (10.6)	168.0 (120.1)	−27.3 (21.9)	−18.6 (12.1)	−20.7 (11.2)
Free PCSK9, nmol/L	8.31 (1.68)	6.21 (2.90)	−2.10 (3.21)	−22.7 (37.1)	−17.2 (23.9)	1.02 (0.67)	−7.30 (1.71)	−87.6 (7.8)	−89.6 (3.5)

Conventional unit conversion factors: To convert values for cholesterol to milligrams per deciliter, divide by 0.0259. To convert values for free PCSK9 to nanograms per millilitre, multiply by 72. Values are mean (SD) unless otherwise stated. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and PCSK9, proprotein convertase subtilisin/kexin type 9.

*Signed-rank test.

†Median (interquartile range).

treatment by the investigator (Table III in the online-only Data Supplement). Antibodies to AMG 145 were not detected during treatment. No patients had creatine kinase elevations >5 times the upper limit of normal or liver enzymes (alanine aminotransferase or aspartate aminotransferase) >3 times the upper limit of normal (Table III in the online-only Data Supplement).
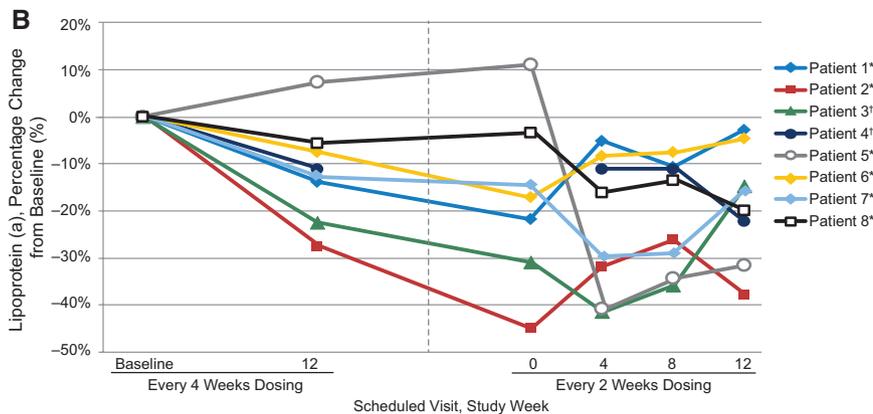
Discussion

This first study of PCSK9 inhibition in HoFH patients demonstrates that additional LDL cholesterol reduction is achievable in LDL receptor–defective patients when AMG 145 is added to high-dose statin and ezetimibe. Although the study included only 2 patients who were receptor negative, neither experienced LDL cholesterol reduction even with dosing every 2 weeks and nearly 90% reduction in plasma PCSK9. However, the mean decrease in all 8 patients of 17% (1.8 mmol/L [70.6 mg/dL]) at week 12 with 420 mg AMG 145 every 4 weeks compares favorably with reductions achieved with statins in this population. This proof-of-concept trial of 8 patients is larger than the initial proof-of-concept trials in HoFH for lomitapide[13] and mipomersen[14,15] and is as large as the statin trials.[6] The study with simvastatin enrolled 12 homozygous patients, with 8 patients randomized to 80 mg/d and 4 patients randomized to 40 mg/d for 9 weeks, and reported LDL cholesterol reductions of 14% and 25%, respectively.[6] The homozygous rosuvastatin

trial (n=21) reported mean LDL cholesterol reductions from baseline after crossover treatment with rosuvastatin 80 mg/d and atorvastatin 80 mg/d of 19% and 18%, respectively.[5] A 12-week trial in 50 homozygous patients comparing ezetimibe 10 mg added to 40 mg/d statin with increasing the statin to 80 mg/d reported a reduction of 20.7% versus 6.7%, respectively.[7] The phase III trial with mipomersen, an apolipoprotein B synthesis inhibitor, randomized 51 homozygous patients on stable maximal drug therapy but not on LDL apheresis to subcutaneous mipomersen 200 mg/wk or placebo for 26 weeks.[15] The mean percentage reduction in LDL cholesterol from baseline was 24.7% (placebo reduction, 3.3%) from a baseline of 11.4 mmol/L (440 mg/dL).[15] The most effective reductions in LDL cholesterol with drug therapy in HoFH, a mean of 50% decrease after 26 weeks, have been reported in a phase III trial with the microsomal triglyceride transfer protein inhibitor lomitapide.[16] The open-label trial enrolled patients on background drug therapy, including 18 also on LDL apheresis, and reported results on the 23 of 29 patients who completed up to 78 weeks of therapy.
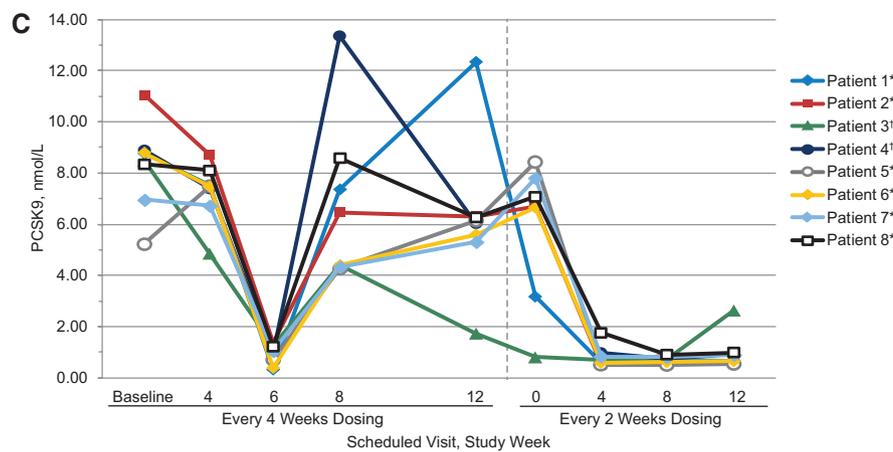
Assessment of response based on LDL receptor function has not been systematically performed in prior HoFH trials, although with statins and mipomersen, it has been suggested that patients with receptor-defective status responded better than those with receptor-negative status.[6,15] In the present
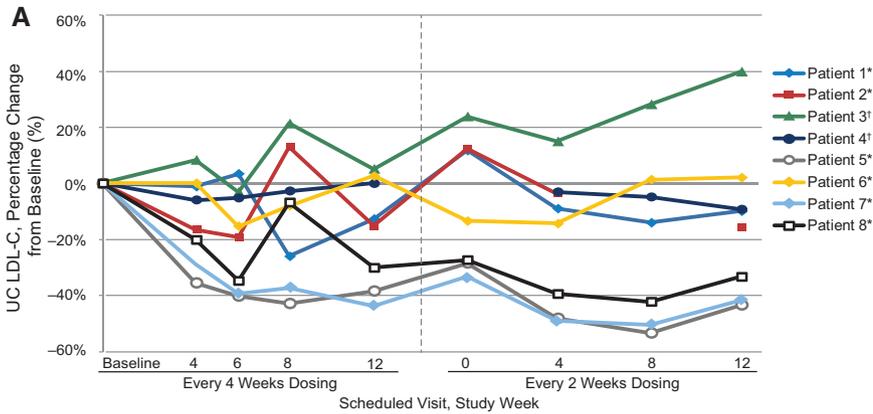
An unconnected line indicates a missing value between two timepoints.
The dashed line indicates time between the two dosing periods of the study.
*Defective LDLR function; †Negative LDLR function

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Figure 2. Efficacy of AMG 145 in the treatment of patients with homozygous familial hypercholesterolemia. **A**, Percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) by ultracentrifugation at weeks 4, 6, 8, and 12 of the 4-week dosing period and weeks 4, 8, and 12 of the 2-week dosing period (n=8). As shown, data for patient 2 were missing at week 8 of the 2-week dosing period, and data for patient 4 were missing at week 0 of the 2-week dosing period. **B**, Percentage change in lipoprotein(a) from baseline and week 12 of the 4-week dosing period and weeks 4, 8, and 12 of the 2-week dosing period. As shown, data for patient 4 were missing at week 0 of the 2-week dosing period. **C**, Proprotein convertase subtilisin/kexin (PCSK9) levels by patient at baseline and weeks 4, 6, 8, and 12 of the 4-week dosing period and weeks 4, 8, and 12 of the 2-week dosing period. As shown, data for patient 4 were missing at week 0 of the 2-week dosing period. LDLR indicates low-density lipoprotein receptor; and UC, ultracentrifugation.

trial, there was no LDL cholesterol response seen in the 2 LDL receptor–negative patients. Although this may have been anticipated, LDL cholesterol reductions have been reported in LDL receptor–negative patients with statins. However, a significant ($P<0.05$) reduction in LDL cholesterol was seen over the 12 weeks of treatment in the 6 receptor-defective patients that averaged 19% (2.1 mmol/L [81.5 mg/dL]) and 26%

(3 mmol/L [115 mg/dL]) with 4- and 2-week dosing, respectively. The additional LDL cholesterol reduction of 7% (average of weeks 4, 8, and 12) with more frequent dosing in these patients is similar to that reported with a doubling of statin dose.[17] Interestingly, 2 LDL receptor–defective patients with identical mutations (patients 6 and 7, Table 1) and very similar baseline LDL cholesterol levels had markedly different

Table 3. Efficacy Outcomes Based on Mutation Status

| | Percentage Change From Baseline, Mean (SD), % | | | | | |
| | Week 12, Every-4-Week Dosing | | | Week 12, Every-2-Week Dosing | | |
Mutation Status	UC LDL-C	Apolipoprotein B	Lipoprotein(a)*	UC LDL-C	Apolipoprotein B	Lipoprotein(a)
Defective LDL receptor (n=6)	−22.9 (17.5)	−18.3 (14.9)	−10.0 (11.5)	−23.6 (18.5)	−17.9 (18.0)	−18.7 (14.1)
Negative LDL receptor (n=2)	2.6 (3.7)	−4.5 (3.5)	−16.8 (8.0)	15.3 (34.7)	3.4 (14.0)	−18.5 (5.3)
	Average of Week 4, 8, and 12, Every-4-Week Dosing			Average of Week 4, 8, and 12, Every-2-Week Dosing		
Defective LDL receptor (n=6)	−19.3 (15.5) P=0.0313†	−18.0 (13.1)	−10.0 (11.5)	−26.3 (20.4) (P=0.0313)†	−22.1 (18.7)	−20.0 (12.1)
Negative LDL receptor (n=2)	4.4 (10.3)	1.4 (5.6)	−16.8 (8.0)	11.0 (23.6)	2.1 (7.9)	−22.7 (11.2)

LDL indicates low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and UC, ultracentrifugation.

*Lipoprotein(a) was collected only at week 12 for every-4-week dosing.

†Signed-rank test.

responses (Figure I in the online-only Data Supplement), with patient 7 showing the largest response and patient 6 showing the smallest response in this receptor subgroup. The heterogeneity in response in HoFH patients with the identical mutations (FH Afrikaner-1) has also been reported with mipomersen, which showed LDL cholesterol reductions ranging from −0.8% to −47.3%.[14] Our hope is that trials with AMG 145 in larger numbers of patients with the same mutations will yield additional information on the response differences.

Although the percentage reductions in HoFH LDL receptor–defective patients with AMG 145 are lower than in non HoFH patient populations in prior trials, the mean absolute reduction in LDL cholesterol with 4-week dosing of 2.1 mmol/L (81.5 mg/dL) is similar to the reductions seen in non-FH patients, whereas the reduction of 3 mmol/L (115 mg/dL) with 2-week dosing exceeds that seen in heterozygous FH and all other PCSK9 monoclonal antibody trials.[12,18–20]

The reduction in LDL cholesterol achieved with 420 mg AMG 145 every-2-week dosing in the LDL receptor–defective patients is very similar to the reduction seen with mipomersen (26% versus 24.7%) from an almost identical mean baseline LDL cholesterol of 11.4 mmol/L (440 mg/dL).

Comparison with lomitapide is somewhat more complicated because the baseline mean LDL cholesterol in the lomitapide trial was significantly lower than in all prior HoFH trials at 8.7 mmol/L (335 mg/dL) and because the trial reported results only in those completing 26, 52, and 78 weeks of treatment with mean LDL cholesterol reductions of 50%, 44%, and 38% respectively. Thus, the mean absolute reductions in LDL cholesterol at 26, 52, and 78 weeks were 4.4, 3.8, and 3.3 mmol/L, respectively. Although the percentage reductions reported with lomitapide were superior to those seen with 420 mg AMG 145 given every 2 weeks, the absolute reductions in the LDL receptor–defective patients of 3.0 mmol/L approached those seen with longer-term lomitapide therapy.

In terms of relevancy for all HoFH patients, it is important to note that in 2 large studies[9,21] of >200 HoFH patients, 70% to 75% had mutations consistent with defective LDL receptor function, with ≈15% receptor negative and the remainder unknown. If the response seen in this trial is confirmed, AMG 145 may offer an additional therapeutic option for a large number of these patients. In addition, the lack of LDL

cholesterol response in LDL receptor–negative patients should be confirmed in a larger cohort because there were only 2 such patients in this trial.

Of additional interest were the high baseline levels of PCSK9, well above those recently reported in a larger cohort of HoFH and heterozygous familial hypercholesterolemia patients,[21] who required higher doses and more frequent dosing with AMG 145 to reduce PCSK9 levels to those achieved in prior trials with AMG 145.[12] Despite the greater, almost 90%, decrease in free PCSK9 levels, no LDL cholesterol reduction was seen in LDL receptor–negative patients, whereas the additional reductions seen in receptor-defective patients suggest that 2-week dosing may be more optimal for these patients.

The importance of the elevated lipoprotein(a) observed in HoFH patients is uncertain, but elevated lipoprotein(a) has been reported to contribute to accelerated cardiovascular disease in heterozygous familial hypercholesterolemia.[22] The elevated lipoprotein(a) levels at baseline in the present study were reduced by 11.7% and 18.6% with every-4-week and every-2-week dosing of AMG 145, respectively. Interestingly, patients with LDL receptor–negative function appeared to experience a reduction in lipoprotein(a); however, because it was based on only 2 patients, this finding needs to be validated. Reductions in lipoprotein(a) in homozygotes were reported with mipomersen, but no significant reductions were seen with statins, ezetimibe, or longer-term treatment with lomitapide.[5–7,16] This effect with AMG 145 on lipoprotein(a), although not well understood, is consistent with that seen in nonhomozygote patients.[12,23] The effects on high-density lipoprotein cholesterol and apolipoprotein A1 are also consistent with prior trials of AMG 145 and contrast with lomitapide, which significantly reduced high-density lipoprotein cholesterol and its associated apolipoprotein A1 by 12% and 14%, respectively.[16]

The mechanism for LDL cholesterol reduction appears to be consistent with further upregulation of residual LDL receptor function, as exemplified by the lack of response in those patients with minimal or no LDL receptor activity. The large variation in response in the 2 genetically homozygous patients with receptor-defective function and identical mutations is puzzling. It is possible that other minor modifying genes contribute

to the variability; we hope that larger trials will assist in elucidating these differences. It is also possible that contributions to cholesterol excretion via an alternative pathway in the gut may be involved. Recently, Le May and colleagues[24] demonstrated transintestinal cholesterol excretion in human intestine, confirming the findings previously described in mice in which this mechanism accounts for ≈30% of total intestinal cholesterol excretion. They also showed that the delivery of cholesterol for excretion depended on the LDL receptor but that an independent pathway for excretion also existed. Using LDL receptor knockout mice, Le May and colleagues[24] showed a 40% increase in transintestinal cholesterol excretion, suggesting that such a mechanism could play a role in HoFH.

This trial, although small, assessed the safety and tolerability over a period of 36 weeks (Figure 1), including 12 weeks of every-2-week administration of 420 mg AMG 145, a dose administered only every 4 weeks in prior trials.[12,23,25,26] All enrolled patients completed the trial without any significant adverse clinical or laboratory experiences. Injection site reactions were minimal and no different in frequency from those reported in the large phase II trials in nonhomozygote patients.[12,23,25,26] The low incidence of injection site reactions with AMG 145 contrasts with the other subcutaneously administered drug for HoFH, mipomersen; 76% of patients receiving mipomersen reported injection site reactions and 18% (6 of 34) discontinued therapy in the first 26 weeks.[15] In the homozygote lomitapide trial, 21% of patients (6 of 29) discontinued therapy within 26 weeks, and ≈80% of patients reported diarrhea, 65% reported nausea, 35% experienced vomiting, and 28% had abdominal pain.[16] Administration of AMG 145, including 420 mg every 2 weeks, was not associated with elevated hepatic transaminases, a frequent finding with both mipomersen and lomitapide therapy.[15,16] In the 26-week trials, hepatic transaminase elevations >3 times the upper limit of normal were reported in 12% (4 of 34) of those on mipomersen[15] and 34% (10 of 29) of those on lomitapide.[16] These increases were associated with significant hepatic fat accumulation[21,27] and are consistent with similar findings seen in nonhomozygote patients treated with these drugs.[28,29] The long-term impact of these side effects is not known, and it is unlikely that large trials of adequate duration in any patient population with either drug will ever effectively answer this issue. Because of the risk of hepatotoxicity, both mipomersen and lomitapide are available only through a restricted program under a Risk Evaluation and Mitigation Strategy.[10,11] AMG 145 administration has already been reported in >900 patients in the phase 2 program[12,23,25,26] with no increase in hepatic transaminases. The safety will be further assessed in a large phase 3 program, including a large cardiovascular outcome trial involving >22 500 high-risk patients.[30] This extensive safety program will presumably also provide reassurance for homozygote patients.

The present trial was a proof-of-concept, open-label study of 8 patients and thus has a number of limitations. However, based on these results, a larger, double-blind, randomized, placebo-controlled trial of AMG 145 in HoFH has begun.[31]

This study demonstrates for the first time that LDL cholesterol lowering is achievable with a PCSK9 monoclonal antibody in HoFH patients, specifically those with receptor-defective status. An ongoing larger, placebo-controlled study will be able to better assess PCSK9 targeting therapy in HoFH patients and could provide more insight for efficacy in LDL receptor–negative patients.

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CLINICAL PERSPECTIVE

Homozygous familial hypercholesterolemia, a rare, serious clinical disorder caused by severe impairment in low-density lipoprotein (LDL) receptor function, results in very high LDL cholesterol and very early coronary artery disease. Current therapies fail to achieve optimal LDL cholesterol. Proprotein convertase subtilisin/kexin (PCSK9) monoclonal antibodies effectively reduce LDL cholesterol in heterozygous familial hypercholesterolemia. The effect in homozygous familial hypercholesterolemia is unknown and uncertain. We evaluated AMG 145, a fully human PCSK9 monoclonal antibody, in a pilot study in patients with homozygous familial hypercholesterolemia already on maximally tolerated lipid-lowering therapy. The open-label trial enrolled 8 patients with a mean baseline LDL cholesterol of 11.4 mmol/L (441 mg/dL) who received 420 mg AMG 145 every 4 weeks and then every 2 weeks. The mean LDL cholesterol reduction after 12 weeks was 17% and 14% with 4- and 2-week dosing, respectively. Two patients with negative LDL receptor activity had no reduction in LDL cholesterol. Significant (P=0.03) reductions occurred in the 6 receptor-defective patients; mean LDL cholesterol, averaged over the monthly visits during the 12-week treatment periods, decreased 19.3% and 26.3% with 4- and 2-week dosing, respectively. Although the percentage reductions were substantially lower than in prior patient populations in AMG 145 trials, the mean absolute LDL cholesterol reduction with 4-week dosing of 2.1 mmol/L (81.5 mg/dL) is similar to that seen in patients without familial hypercholesterolemia, and the reduction with 2-week dosing of 3 mmol/L (115 mg/dL) exceeds that in heterozygous familial hypercholesterolemia trials. No serious side effects were seen. This study demonstrates LDL cholesterol lowering with a PCSK9 monoclonal antibody in patients with homozygous familial hypercholesterolemia with defective LDL receptor activity.

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Supplemental Material

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Supplemental Methods

Exclusion Criteria

Exclusions included New York Heart Association (NYHA) class III or IV or most recent measured left ventricular ejection fraction <30%; cardiac arrhythmia within past 3 months not controlled by medication; myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months of enrollment; planned cardiac surgery or revascularization within 20 weeks of screening; systolic blood pressure (SBP) >180 mmHg or diastolic BP (DBP) >110 mmHg; estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2; persistent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x the upper limit of normal (ULN), creatine kinase (CK) >5x ULN without a known cause; known major active infection, or major hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction; or deep vein thrombosis or pulmonary embolism within 3 months prior to enrollment.

Female patients were excluded if pregnant or breast feeding and premenopausal females were required to use at least 1 highly effective method of birth control during treatment and for an additional 15 weeks after the end of treatment.

Supplemental Table S1. Patient Baseline Characteristics

Characteristic, no. (%)	AMG 145 420 mg (N = 8)
Age, years, mean (range)	34.3 (14 - 54)
Male sex, no. (%)	6 (75.0)
Clinical cardiovascular disease, no. (%)	6 (75.0)
Lipid-regulating medications, no. (%)	
Ezetimibe	8 (100.0)
Statins	8 (100.0)
Atorvastatin 40 mg	1 (12.5)
Atorvastatin 80 mg	5 (62.5)
Rosuvastatin 40 mg	2 (25.0)

Supplemental Table S2. Baseline Demographics, Cardiovascular Disease and Lipid Therapy of Individual Patients

Patient number	Date of birth	Gender	CVD	Baseline Daily Lipid Rx	Baseline LDL-C
6001	22/02/1958	Male	Age 27: PTCA for 90% mid-right coronary artery occlusion Age 39: repeat PTCA right coronary artery	atorva 80 mg ezetimibe 10 mg ER-Niacin 2 gram	5.5 mmol/L
6002	23/10/1965	Male	Age 24: 3 vessel CABG all saphenous vein grafts Age 26: repeat CABG with left internal mammary artery Age 24: aortic valve stenosis noted; vale replacement age 43	rosuva 40 mg ezetimibe 10 mg colestipol 12 gram	10.7 mmol/L
6003	12/11/1983	Female	Age 14: minimal luminal irregularities on angiogram Age 28: 20-30% narrowing left anterior descending and diffuse mild coronary atherosclerosis throughout	rosuva 40 mg ezetimibe 10 mg	11.9 mmol/L
6004	07/05/1997	Male	Age 15: CT angiogram: right coronary ostial < 25%, proximal right coronary artery lesion < 25% Age 7: 60% ostial stenosis unchanged on angiogram Age 4: 60% right coronary ostial stenosis	atorva 40 mg ezetimibe 10 mg colesevelam 3.75 gm IR Niacin 1500 mg	14.5 mmol/L
1001	02/11/1985	Male	Age 14: 46-55% occlusion right coronary artery: moderate supravalvular aortic stenosis	atorva 80 mg ezetimibe 10 mg	9.8 mmol/L
1002	22/02/1977	Female	Age 33: Angina, 40% narrowing left main and right coronary ostium: severe supravalvular aortic stenosis	atorva 80 mg ezetimibe 10 mg	14.3 mmol/L
1004	04/07/1980	Male	Moderate supravalvular aortic stenosis	atorva 80 mg ezetimibe 10 mg	13.7 mmol/L
1005	11/05/1973	Male	Age 31: 3 vessel CABG; Age 36: Stent, severe aortic stenosis with valve replacement	atorva 80 mg ezetimibe 10 mg	12.7 mmol/L

ER = extended release   IR = immediate release   atorva = atorvastatin   rosuva = rosuvastatin

CABG = coronary artery bypass graft   PTCA = Percutaneous transluminal coronary angioplasty

Supplemental Table S3. Adverse Events Reported During 36 Weeks of Treatment

Adverse events, no. of patients (%)	AMG 145 (N = 8)
Treatment emergent adverse events	
Serious	0 (0)
Leading to discontinuation of investigational product	0 (0)
Treatment-related adverse events	0 (0)
Serious treatment-related adverse events[†]	0 (0)
Deaths	0 (0)
Muscle-related adverse events	0 (0)
Adverse events reported in 2 or more patients	0 (0)
Grade 1 adverse events (reported in 1 patient each)	Contusion, pain, angina pectoris, hypertension, aortic valve incompetence, nasopharyngitis, syncope, injection site hematoma
Grade 2 adverse events (reported in 1 patient each)	Allergic rhinitis, sinusitis, dyspepsia, bronchitis, upper respiratory tract infection, hematuria
Laboratory Test Data	
Alanine aminotransferase or aspartate aminotransferase >3 times upper limit of normal at any post-baseline visit	0 (0)
Creatine kinase >5 times upper limit of normal at any post-baseline visit	0 (0)

[†] A treatment-related adverse event was defined as one considered possibly related to the investigational product by the investigator.

SE: standard error

Supplemental Figure S1. Change in from baseline in calculated LDL cholesterol (mmol/L), weeks 4, 8, and 12 of the 4-week and 2-week dosing periods.
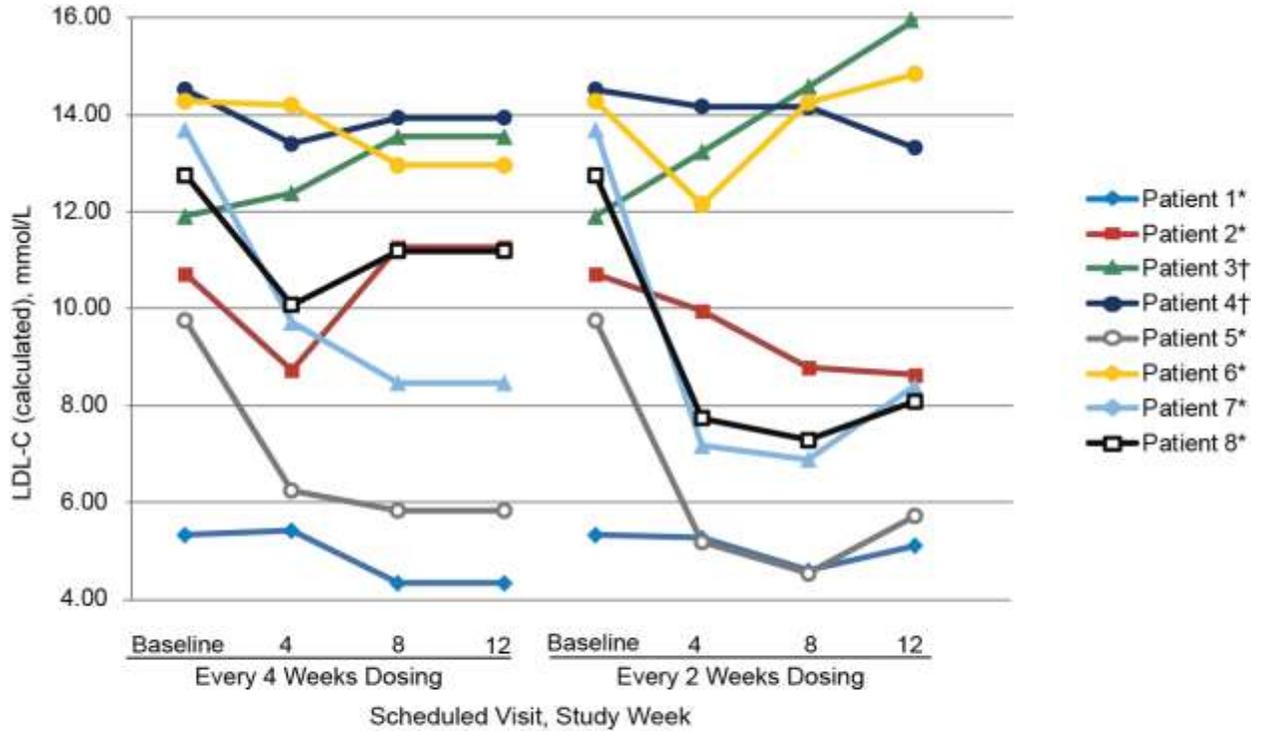
Unconnected lines indicate time between the two dosing periods of the study.
The baseline value for every-2-week dosing is the original study baseline.

*Defective LDL-r function; †Negative LDL-r function
LDL-C = low-density lipoprotein cholesterol; LDL-r = low-density lipoprotein receptor

Supplemental Figure S2. Individual changes in LDL cholesterol by ultracentrifugation at week 12 and over the 12 week treatment period (mean of weeks 4, 8 and 12) for 4-week (Panels A and B) and 2-week (Panels C and D) dosing with AMG 145 420 mg.