agreement on the consensus interpretation, independent of prior interpretations. Only the consensus reads were utilized in the analyses. All echocardiograms were independently and centrally interpreted by two board certified cardiologists with Level III training and experience in echocardiography (Echocardiography Laboratory Directors). Measurements were taken according to the Guidelines of the American Society of Echocardiography (Guidelines for Quantification of the Left Ventricle by Two-Dimensional Echocardiography; Schiller et al, JASE Vol. 2, No.5, pp.358-367, October 1989).

The sponsor was asked to provide an assessment of concordance between the primary and secondary readers for all echoes with respect to valvular insufficiency for each valve. The concordance assessments are provided below as well as an overall assessment of the consensus reads.

Table 10.1.1.45. Study 717 Aortic Valve Insufficiency Data

	READER TWO Degree of aortic-valve insufficiency					
	None	Trace	Mild	Moderate	Severe	Not Evaluable
	N	N	N	N	N	N
READER ONE Degree of aortic-valve insufficiency						
None	164	4	1	0	0	3
Trace	7	23	10	0	0	0
Mild	0	4	26	13	0	1
Moderate	0	0	1	2	2	0
Severe	0	0	0	0	3	0
Not Evaluable	30	0	1	0	0	6

Table 10.1.1.46 Study 717 Pulmonary Valve Insufficiency Data

	READER TWO Degree of pulmonic-valve insufficiency					
	None	Physiologic	Mild	Moderate	Severe	Not Evaluable
	N	N	N	N	N	N
READER ONE Degree of pulmonic-valve insufficiency						
None	60	14	0	0	0	3
Physiologic	5	17	16	0	0	1
Mild	1	1	13	13	0	1
Moderate	0	0	1	2	0	0
Severe	1	0	0	0	0	0
Not Evaluable	61	9	6	0	1	75

Table 10.1.1.47 Study 717 Mitral Valve Insufficiency Data

	READER TWO Degree of mitral-valve insufficiency					
	None	Physiologic	Mild	Moderate	Severe	Not Evaluable
	N	N	N	N	N	N
READER ONE Degree of mitral-valve insufficiency						
None	77	25	3	0	0	2
Physiologic	29	67	12	0	0	2
Mild	0	12	28	2	0	1
Moderate	0	0	3	6	0	0
Severe	0	0	0	0	0	0
Not Evaluable	20	2	0	0	1	9

Table 10.1.1.48 Study 717 Tricuspid Valve Insufficiency

	READER TWO Degree of tricuspid-valve insufficiency					
	None	Physiologic	Mild	Moderate	Severe	Not Evaluable
	N	N	N	N	N	N
READER ONE Degree of tricuspid-valve insufficiency						
None	30	14	0	1	0	3
Physiologic	27	102	19	0	0	6
Mild	0	3	18	14	0	0
Moderate	0	0	0	3	1	0
Severe	0	0	0	0	0	0
Not Evaluable	23	6	1	0	2	28

Table 10.1.1.49 Study 717 Consensus

	Valve Type			
	Aortic	Pulmonic	Mitral	Tricuspid
	N	N	N	N
Degree of valve insufficiency				
None	169	69	101	44
Trace	37	0	0	0
Physiologic	0	33	109	140
Mild	43	33	44	36
Moderate	7	9	9	11
Severe	5	0	0	1
Not Evaluable	40	157	38	69

Analyses focused on measures of central tendency

Centralized Echocardiography Results

Quantitative Cardiac Chamber Results

The table below presents descriptive statistics for echocardiography quantitative chamber measurements at baseline and end of study (Week 52/LVA) and for change from baseline to this time point across all 107 lanreotide-treated patients. Changes from baseline to end of study were small and not statistically significant for left atrial area, aortic root measurement, left ventricular internal diameter at diastole and left ventricular end-systole diameter. Statistically significant mean decreases from baseline to end of study were noted for left ventricular wall thickness of the septum (-0.04 ± 0.16 cm), left ventricular post wall thickness (-0.05 ± 0.18 cm) and left ventricular mass (-14.8 ± 49.6 g). These changes are small and moved in parallel with the change in body size so that the left ventricular mass corrected (indexed) for body size was not significantly changed. Across all patients with data available, mean weight decreased -1.7 ± 5.3 kg from baseline to end of study. Mean (± SD) left ventricular end-diastolic volume decreased -9.9 ± 20.3 mL from baseline to the end of the study and mean left ventricular end-systolic volume decreased -5.4 ± 16.1 mL; these changes from baseline were statistically significant and concordant with the changes in left ventricular mass and body size. Because both end diastolic and end systolic volumes changed, change from baseline to end of study was not significant for ejection fraction with a mean increase of 0.7 ± 9.5% noted.

Table 10.1.1.50. Descriptive Statistics for Echocardiography Parameters (Quantitative Chamber Measurements) at Baseline and End of Study and for Change from Baseline to End of Study (Safety Population, N=107)

	Lanreotide Autogel, N=107		
Echo Parameter	Baseline	End of Study (Week 52/LVA)	Change from Baseline to End of Study
Left Atrium (cm)			
N	88	95	83
Median	3.59	3.60	-0.04
Mean ± SD	3.63 ± 0.62	3.67 ± 0.63	-0.00 ± 0.49
Minimum, Maximum	2.36, 5.03	2.33, 5.38	-0.98, 2.24
Aorta (cm)			
N	89	95	84
Median	3.18	3.16	-0.03
Mean ± SD	3.18 ± 0.43	3.18 ± 0.47	-0.01 ± 0.29
Minimum, Maximum	2.33, 4.28	2.15, 4.83	-0.70, 0.92
$LVID_d$ (cm)			
N	81	80	63
Median	4.72	4.75	0.04
Mean ± SD	4.78 ± 0.77	4.83 ± 0.76	-0.01 ± 0.56
Minimum, Maximum	3.09, 9.04	3.36, 9.08	-1.46, 1.47
$LVID_s$ (cm)			
N	75	77	60
Median	3.39	3.51	0.11
Mean ± SD	3.44 ± 0.72	3.57 ± 0.76	0.02 ± 0.67
Minimum, Maximum	1.97, 6.54	2.34, 7.30	-2.08, 1.35
IVS (cm)			
N	83	84	68
Median	0.97	0.93	-0.03
Mean ± SD	0.99 ± 0.22	0.96 ± 0.23	-0.04 ± 0.16
Minimum, Maximum	0.57, 2.09	0.53, 2.02	-0.64, 0.38
LVPW (cm)			
N	82	82	65
Median	0.97	0.89	-0.05
Mean ± SD	0.98 ± 0.20	0.94 ± 0.17	-0.05 ± 0.18
Minimum, Maximum	0.58, 1.81	0.67, 1.36	-0.52, 0.36
LV Mass (g)			
N	81	80	63
Median	182.30	177.8	-14.6
Mean ± SD	201.7 ± 100.4	193.4 ± 93.9	-14.8 ± 49.6
Minimum, Maximum	68.6, 866.7	87.3, 777.2	-166.0, 69.8
LV Mass Index (g/m^2)			
N	78	77	60
Median	91.5	87.9	-6.4
Mean ± SD	103.9 ± 49.8	100.4 ± 46.6	-6.9 ± 26.8
Minimum, Maximum	40.6, 429.7	46.5, 385.3	-72.4, 49.9
End Diastolic Volume (mL)			
N	61	72	53
Median	95.0	83.5	-8.0
Mean ± SD	98.3 ± 43.4	87.1 ± 26.4	-9.9 ± 20.3
Minimum, Maximum	38, 343	38, 146	-93, 30

Echo Parameter	Lanreotide Autogel, N=107		
	Baseline	End of Study (Week 52/LVA)	Change from Baseline to End of Study
End Systolic Volume (mL)			
N	61	72	53
Median	41.0	38.0	-2.0
Mean ± SD	46.2 ± 27.5	40.3 ± 17.1	-5.4 ± 16.1
Minimum, Maximum	19, 197	16, 102	-73, 22
Ejection Fraction (%)			
N	61	72	53
Median	54.0	55.0	0.0
Mean ± SD	53.5 ± 8.0	54.1 ± 8.3	0.7 ± 9.5
Minimum, Maximum	24, 70	23, 76	-18, 29

Sponsor's Table 73, Module 5, Vol 53, pg. 180

Analyses focused on outliers or shifts from normal to abnormal

Valvular Regurgitation

The sponsor's table below presents shifts from baseline to week 52/LVA for valvular regurgitation across all 107 lanreotide-treated patients.

Table 74. Valvular Regurgitation - Shifts from Baseline (Safety Population)

Valve	Baseline Status	End of Study Status				
		None	Physiologic	Mild	Moderate	Severe
Mitral Valve						
None	34/89 (38%)	25/89 (28%)	8/89 (9%)	1/89 (1%)	0	0
Physiologic	37/89 (42%)	11/89 (12%)	21/89 (24%)	5/89 (6%)	0	0
Mild	15/89 (17%)	1/89 (1%)	5/89 (6%)	7/89 (8%)	2/89 (2%)	0
Moderate	3/89 (3%)	1/89 (1%)	1/89 (1%)	1/89 (1%)	0	0
Severe	0	0	0	0	0	0
Total	89/89 (100%)	38/89 (43%)	35/89 (39%)	14/89 (16%)	2/89 (2%)	0
Aortic Valve						
None	60/88 (68%)	54/88 (61%)	3/88 (3%)	3/88 (3%)	0	0
Physiologic	12/88 (14%)	4/88 (5%)	6/88 (6%)	3/88 (3%)	0	0
Mild	12/88 (14%)	0	3/88 (3%)	8/88 (9%)	1/88 (1%)	0
Moderate	2/88 (2%)	0	0	0	2/88 (2%)	0
Severe	2/88 (2%)	0	0	1/88 (1%)	0	1/88 (1%)
Total	88/88 (100%)	58/88 (66%)	11/88 (13%)	15/88 (17%)	3/88 (3%)	1/88 (1%)
Tricuspid Valve						
None	20/78 (26%)	7/78 (9%)	13/78 (17%)	0	0	0
Physiologic	39/78 (50%)	4/78 (5%)	32/78 (41%)	3/78 (4%)	0	0
Mild	14/78 (18%)	1/78 (1%)	10/78 (13%)	3/78 (4%)	0	0
Moderate	4/78 (5%)	0	0	3/78 (4%)	1/78 (1%)	0
Severe	1/78 (1%)	0	0	1/78 (1%)	0	0
Total	78/78 (100%)	12/78 (15%)	55/78 (71%)	10/78 (13%)	1/78 (1%)	0
Pulmonic Valve						
None	17/42 (40%)	14/42 (33%)	1/42 (2%)	1/42 (2%)	1/42 (2%)	0
Physiologic	12/42 (29%)	5/42 (12%)	5/42 (12%)	2/42 (5%)	1/42 (2%)	0
Mild	12/42 (29%)	1/42 (2%)	4/42 (10%)	5/42 (12%)	2/42 (5%)	0
Moderate	1/42 (2%)	0	0	1/42 (2%)	0	0
Severe	0	0	0	0	0	0
Total	42/42 (100%)	20/42 (48%)	9/42 (21%)	9/42 (21%)	4/42 (10%)	0

Data source: Appendix 16.1.10 (Tables 8.7.4.1.1B through 8.7.4.1.4B).

Note: Shaded values represent no changes from Baseline to End of Study.

Sponsor's evaluation:

The mitral regurgitation evaluation was performed using color Doppler jet area compared to left atrial area. This assessment was adequate and available at both baseline and end of study in 89 of the 107 patients. According to the sponsor, a total of 53 (60%) of the 89 patients did not have a shift in valvular regurgitation from baseline to end of study. Twenty patients (22%) showed 1, 2 or 3 grade improvement from baseline and 16 patients (18%) showed a 1 or 2 grade worsening. No patient had severe mitral regurgitation at either time point.

Aortic regurgitation was assessed by color Doppler jet width as compared to the left ventricular outflow tract diameter. A total of 88 of 107 patients had adequate color Doppler assessment of aortic regurgitation at both visits to assess for a change over time. Seventy (80%) of the 88 patients showed no change in regurgitation from baseline to end of study; 8 patients (9%) showed a 1 or 2 grade improvement and 10 (11%), a 1 or 2 grade worsening. One patient had severe aortic regurgitation at both the beginning and at the end of the study but no patient had a shift to severe aortic valve regurgitation at the end of the study.

Tricuspid regurgitation was assessed in a total of 78 of the 107 patients at both baseline and end of study. Forty-three (55%) of the 78 patients showed no shifts in tricuspid regurgitation between baseline and week 52/LVA. A total of 19 patients (24%) showed a 1 or 2 grade improvement and 16 (21%), a 1 grade worsening. The sponsor states that this most likely represents physiologic and measurement variability of tricuspid regurgitation. No patient had severe tricuspid regurgitation at the end of the study.

Lastly, pulmonary regurgitation was adequately assessed on the echocardiograms at baseline and at end of study in 42 of the 107 patients. Most patients (23 of 42, 55%) did not have a shift from baseline to end of study for pulmonary regurgitation. Eleven patients (26%) showed a 1 or 2 grade improvement and 8 patients (19%) showed a worsening (5 patients with a 1 grade worsening, 2 patients with a 2 grade worsening and 1 patient with a worsening of 3 grades). No patient had severe pulmonary regurgitation at either time point.

Clinical Reviewer's evaluation:
Of 107 patients with echo results, 35 (33 %) had only a baseline study, 27 (25%) had baseline and only ~Week 16 studies, and 45 (42%) had echo results at baseline and end-of-study (~Week 52).

In evaluating the echoes, the grades of 'none' and 'physiologic' were not considered clinically meaningful and therefore shifts between these categories were summarized as no change by this reviewer. For mitral, tricuspid and pulmonic valves, shifts between mild to none were considered significant but not between physiologic to mild as this seemed to occur frequently in both directions and was felt to represent measurement variability.

For mitral regurgitation, five patients showed a worsening from baseline to ~Week 52: Pt No. 724.0005 had mild MR at baseline which worsened by one grade to moderate at Week 16 and 52; Pt No. 701.0030 had mild MR at baseline which worsened by one grade to moderate at Week 16 and 53; Pt No. 707.0005 had mild MR at baseline which worsened by one grade to moderate at Week 36; Pt No. 702.0005 had no MR at baseline which worsened by two grades to mild at

Week 54; and Pt No. 717.0002 had no MR at baseline which worsened by two grades to mild at Week 52.

For mitral regurgitation, three patients showed an improvement from baseline to ~Week 52: Pt No. 701.0017 had severe MR at baseline which improved by one grade to moderate at Week 50; Pt No. 701.0032 had moderate MR at baseline which improved by one grade to mild at Week 16 and 52; and Pt No. 703.0010 had mild MR at baseline which improved by two grades to none at Week 17 and 56.

For aortic regurgitation, two patients showed a worsening from baseline to ~Week 52: Pt No. 725.0006 had mild AR at baseline which worsened by one grade to moderate at Week 52; and Pt No. 734.0010 had physiologic MR at baseline which worsened by one grade to mild at Week 51. No patients had an improvement.

For tricuspid regurgitation, four patients showed a worsening from baseline to ~Week 52: Pt No. 701.0030 had moderate TR at baseline which worsened by one grade to severe at Week 16 and was not assessable at Week 53; Pt No. 712.0001 had no TR at baseline and Week 16 which worsened by two grades to mild at Week 48; Pt No. 702.0005 had no TR at baseline which worsened by two grades to mild at Week 54; and Pt No. 724.0006 had no TR at baseline which worsened by two grades to mild at Week 15.

For tricuspid regurgitation, five patients showed an improvement from baseline to ~Week 52: Pt No. 707.0005 had moderate TR at baseline which improved by one grade to mild at Week 18 and 36; Pt No. 701.0016 had severe TR at baseline which improved by one grade to moderate at Week 20; Pt No. 725.0007 had moderate TR at baseline which improved by one grade to mild at Week 16; Pt 703.0002 had mild TR at baseline and Week 16 which improved by two grades to none at Week 52; and Pt. 731.0007 had mild TR at baseline which improved by two grades to none by Week 51.

For pulmonic regurgitation, three patients showed a worsening from baseline to ~Week 52: Pt Nos. 707.0005, 712.0001, and 733.0008 had mild PR at baseline which worsened by one grade to moderate by end of study (Week 36, 48 and 51, respectively).

For pulmonic regurgitation, one patient showed an improvement (No. 727.0002) from mild at Week 0 and 17 to none at Week 52.

In conclusion, this reviewer believes the minor changes in valvular regurgitation during the course of Study 717 most likely represent both the variability in the degree of valvular regurgitation over time and measurement variability.

Marked outliers and dropouts for echocardiography abnormalities
Four patients had a treatment-emergent clinically significant abnormality reported by the investigator on echocardiography.

In Patient 701.0002, an 84-year-old female Caucasian patient with a history of acromegaly since 1960

enrolled into Study 717 on 03 May 2000, baseline mild aortic stenosis had increased to severe stenosis at week 20; this was reported as an adverse event (moderate aortic stenosis possibly related to study treatment) that occurred during treatment with 60 mg lanreotide. This patient experienced five other cardiac adverse events: swelling in feet (travel related) of mild intensity; worsening of hypertension of moderate intensity, two episodes of sinus bradycardia, one of which was pre-injection (lanreotide 90 mg), and a case of swelling in feet (dependent edema) of moderate intensity. This patient presented with four abnormal ECGs, of which one was considered clinically significant: sinus bradycardia (55 bpm), left axis deviation, LVH with QRS widening. The patient completed the study and the study drug was not discontinued at any stage.

Patient 701.0030 is a 59-year old Caucasian female with a history of acromegaly since 1994 who enrolled in the study on 09 Jan 2001. She had worsening tricuspid regurgitation (a change from moderate to severe) noted on the echocardiogram that was reported as an adverse event of severe intensity possibly related to study treatment; dose at onset of the event was 90 mg lanreotide. Worsening of mitral regurgitation was diagnosed by the local investigator following a change from mild mitral valve regurgitation on 20 February 2001, to moderate mitral valve regurgitation on 13 June 2001. However, the consensus reading reported no changes in tricuspid or mitral valve regurgitation at these timepoints. This patient presented with four abnormal ECGs, of which two were considered clinically significant. On 20 Feb 01 she experienced AF with RVR (107 bpm), anterolateral infarct age undetermined and on 21 Mar 01 she experienced AF (bpm 71) and anterolateral infarct age undetermined. She also developed metastatic adenocarcinoma of the right lung during the study. Of note, at baseline this patient had a history of AF with RVR (1993), hypokinesis of LV (2000), marked LAE and RAE(2000), LV and RV Enlargement(2000), borderline concentric LV hypertrophy (1993), calcified mitral annulus (2000), mild MR (2000), increased mitral leaflet echoes consistent with leaflet thickening and/or calcification (2000), multiple echoes in aortic root suggestive of calcification (2000), moderate TR (200), trace aortic regurgitation (2000), pulmonic valve regurgitation (2000), and anterolateral infarct, age undetermined (2000).

Patient 724.0005, a 51-year-old female Caucasian patient with a history of acromegaly since 1980 enrolled into Study 717 on 19 April 2001, with mild mitral valve regurgitation at baseline had moderate regurgitation noted at weeks 16 and 52; moderate left ventricular hypertrophy (mild LVH at baseline) was reported as an adverse event at week 52 (dose at onset of 120 mg). All ECGs were reported as normal and the patient experienced no other cardiac adverse events.

Patient 724.0006, a 60-year-old female Caucasian patient with a history of acromegaly since January 2001 enrolled into Study 717 on 09 July 2001, had no tricuspid valve regurgitation and normal aortic valve evaluation at baseline and had both mild aortic stenosis and mild tricuspid regurgitation reported on echocardiogram read out by the local investigator and reported as adverse events at week 15 during treatment with 120 mg lanreotide. The consensus reading reported a change from mild tricuspid valve regurgitation on 09 July 2001 (baseline) to physiologic tricuspid valve regurgitation on 12 November 2001 (Visit 10) and 18 July 2002 (Visit 19). ECGs were normal and no other cardiac adverse events were reported for this patient.

Cardiac dimensions were unchanged other than a decrease in left ventricular septal and posterior wall thickness and left ventricular cavity which corresponded to a decrease in left ventricular mass. This reduction was concordant with a change in body size. This reviewer concludes that the valvular regurgitations seen in this population in Study 717 did not appear to show any clinically worrisome changes over time.

Treatment-emergent adverse events related to echocardiography assessment and reported in the Myo-, Endo- and Pericardial & Valve Disorders body system during the entire study included heart valve disorders (3%), aortic stenosis (2%), aortic valve incompetence (2%), atrial septal defect (<1%) and mitral insufficiency (<1%).

Gallbladder Ultrasound Findings

Gallbladder ultrasounds were done at Visit 35 (Week 0/Injection #1), Visit 10 (Week 16/Injection #5) and Visit 19 (Week 52, but procedure done only in case of withdrawal or discontinuation).

A total of 30 (30%) of the 100 lanreotide-treated patients who had a baseline ultrasound performed had gallstones and/or sludge present in the gallbladder at baseline including 19 patients (19%) with gallstones and 14 patients (14%) with sludge. Across the lanreotide treatment groups, 27%, 29% and 33% of patients in the 60, 90 and 120 mg groups had gallstones and/or sludge present at baseline.

Patients whose last dose administered was 120 mg were more likely to develop gallstones and sludge during the study than patients whose last dose was 60 or 90 mg. Among those patients who did not have gallstones present at baseline and who had post-baseline ultrasound performed (LVA, N = 81), 13 (16%) had new (and persistent) formation of gallstones including 1 (6%) of 16 patients whose last dose administered was 60 mg, 0 of 10 patients who last dose was 90 mg and 12 (22%) of 55 patients who last dose was 120 mg. Three patients developed a new gallstone which disappeared during the course of the study.

Similarly, among those patients who did not have sludge present at baseline and who had postbaseline ultrasound performed (LVA, N = 84), 13 (15%) had new (and persistent) formation of sludge including 1 (6%) of 18 patients whose last dose administered was 60 mg, 1 (9%) of 11 patients who last dose was 90 mg and 11 (20%) of 55 patients who last dose was 120 mg. Three patients had disappearance of baseline sludge and occurrence of new sludge and 6 patients had occurrence and disappearance of new sludge. Four patients, all in the 120-mg group, had new formation of gallstones and sludge.

In total, 22 out of 70 patients (31%) who did not have baseline abnormalities on ultrasound (gallstones or sludge) had new formation of gallstones or sludge at LVA. A total of 32 patients had cholelithiasis reported as a treatment-emergent adverse event at some point during the study; review of the adverse event terms for these patients reveals that new onset of gallstones and / or sludge both were coded to the adverse event term of cholelithiasis. All 22 patients who did not have baseline abnormalities on ultrasound and had new formation of gallstones or sludge at LVA had cholelithiasis reported as an adverse event. Review of the ultrasound data for the 10 additional patients with adverse event reports of cholelithiasis revealed that for 8 of these 10 patients, the ultrasound was negative at baseline, positive at some point during the study and then negative at the last assessment. For the 2 remaining patients, sludge was reported as present at baseline with a negative ultrasound noted during the study and return of the sludge at the last assessment. Thus, the adverse event incidence of 32 (30%) of 107 patients concurs with the ultrasound data.

5 These procedures did not need to be performed if there was documentation that the procedure was performed within the previous 3 months and the results did not give the investigator cause to repeat it (i.e., all data were collected according to protocol and CRF requirements).

Gallbladder ultrasound revealed that the incidence of new onset of lithiasis or sludge by study end was ~31% [22 of patients with no baseline gallstones or sludge (70)] with data available at baseline and post-baseline. 98 subjects had data available at baseline and post-baseline, of which 17 had baseline gallstones and 14 had baseline sludge. As per the sponsor's analysis, where patients with baseline gallstones or sludge are included in the denominator, then there is an incidence of ~22% (22/98). However, this reviewer believes that the incidence of new stones and/or sludge should be based on the number of patients with paired gallbladder ultrasound data (on baseline and at least once on study drug, n=98), excluding patients who have undergone cholecystectomy and those with stones/sludge at baseline (n=28). An additional 9% (9/98) of patients had transient (present during the study and absent at end of study) reports of gallstone and/or sludge. Patients whose last dose administered was 120 mg appeared more likely to have new onset of lithiasis and sludge (~20%) compared to patients who received the lower doses of lanreotide acetate(≤ 10%).

Thus, according to this reviewer, of the 98 subjects who had data available at baseline and post-baseline, 17 (17%) had baseline gallstones which persisted throughout the study; 65 (66%) had no gallstones at baseline and end-of-study; 13 (13%) developed new gallstones which persisted; and 3 (3%) developed the occurrence and disappearance of a gallstone during the course of the trial. If the 17 subjects with baseline gallstones are removed from the denominator, there are 13/81 (16%) who developed new gallstones that persisted throughout the course of the study and 16/81 (20%) who developed new gallstones at any time during the study.

The sponsor was asked to confirm these numbers and was specifically asked to provide the incidence of gallstones and sludge based on the number of patients with paired gallbladder ultrasound data (on baseline and at least once on study drug), excluding patients who have undergone cholecystectomy and those with stones at baseline. Patients should be counted only once and for the more severe abnormality (stones>sludge). The table below describes the sponsor's re-analysis of the incidence of gallstones and sludge occurring during lanreotide therapy over the course of the study. For gallstones, this excludes patients with prior cholecystectomy, patients missing either a baseline or postbaseline result and patients with gallstones at baseline. For sludge, this excludes patients with prior cholecystectomy, patients missing either a baseline or postbaseline result, patients with gallstones or sludge at baseline and patients who develop gallstones over the course of the study. By excluding patients who developed gallstones during the study, patients who developed both gallstones and sludge were counted only once for gallstones, the more severe abnormality.

Table 10.1.1.51. Number (%) of Patients in Acromegaly Studies with New Gallstones or new Gallbladder Sludge during Lanreotide Therapy over the Course of Study

	Total	Number (%) of patients with findings
Gallstone	79 (100.0) [a]	16 (20.3)
Sludge	54 (100.0) [b]	10 (18.5)

(a) Number of assessed patients at risk of developing new gallstones over the course of the study. This excludes patients with prior cholecystectomy, patients missing either a baseline or post-baseline result and patients with gallstones at baseline.
(b) Number of assessed patients at risk of developing new sludge over the course of the study. This excludes patients with prior cholecystectomy, patients missing either a baseline or post-baseline result, patients with gallstones or sludge at baseline and patients who develop gallstones over the course of the study. By excluding patients who developed gallstones during the study, patients who developed both gallstones and sludge were counted only once for gallstones, the more severe abnormality.

Other

Pituitary MRI/CT Findings
Pituitary MRI or CT scan was performed at Weeks 0, 16 and 52 (end of study) corresponding to visits 3, 10 and 19 to assess tumor status. A total of 91 (85%) of the 107 patients had pituitary tumor present on baseline MRI/CT scan, including 91%, 83% and 81% of patients randomized to received 60, 90 and 120 mg lanreotide acetate, respectively. At the end of the double/single-blind phase (Week 16) clinically significant changes from baseline were reported for 5 (5%) of the 104 patients with data available including 2, 2 and 1 patients in the 60, 90 and 120 mg groups, respectively. The sponsor was asked to provide details on these 5 cases. Of the five patients with clinically significant changes at Visit 10, four had CRF AE reports associated with the event, namely 'tumor shrinkage; decrease in the adenoma size; slight reduction in anterior pituitary volume on MRI scan; and 0.55 mm decrease to focal area or poor enhancement in left side of the pituitary.' The remaining patient did not have an AE form associated with the event, but a psychiatric report done later on describes a 50% reduction the volume of her adenoma.

At the end of the study clinically significant changes from the previous evaluation were reported for 2 (2%) of the 105 patients with data available. Of the two patients experiencing clinically significant changes at Visit 19, one was detailed as 'question increased fullness right cavernous sinus on MRI of brain' and one as 'tumor shrinkage.' Only the event 'question increased fullness right cavernous sinus on MRI of brain' was translated into an AE. In this study, changes in patients' MRI scans were not classified as an AE, unless these changes represented a deviation from normal physiology, or a worsening of an existing abnormality.

Anti-lanreotide Antibody
Blood samples for determination of anti-lanreotide antibody levels were obtained at Weeks 0, 4, 16, 36 and 52 (end of study) corresponding to visits 3, 4, 10, 15 and 19 and submitted to the central laboratory for analysis.

The presence of putative antibodies to lanreotide acetate was observed in one of the 107 lanreotide-treated patients. Putative antibodies were determined in two samples for Patient 704.0005, at Week 0 (visit 3, prior to the first lanreotide administration) and at Week 4 (visit 4, four weeks after the first administration). No assessment of putative antibodies was performed on later samples. The sponsor postulates that the presence of antibodies before the first administration of acetate could be due to the previous long-term treatment of this patient with lanreotide 30 mg every 12 to 16 days. No allergic type reactions were reported in this patient during the study; the only drug-related adverse event was diarrhea reported at week 15. This patient showed response to treatment with IGF-1 normalized by Week 16.

Deep subcutaneous administration of lanreotide acetate appeared to be minimally immunogenic. Putative antibodies against lanreotide were observed in only one of the 107 lanreotide-treated patients.

Sponsor's Conclusions:
Lanreotide acetate at doses of 60, 90 and 120 mg was significantly more effective than placebo in reducing mean GH and IGF-1 levels 4 weeks after a single injection. Repeated administration of lanreotide acetate every 4 weeks at a constant dose for 16 weeks followed by a dose titration period to maximum effect continued to be effective in reducing GH and IGF-1 levels and in reducing the symptoms of acromegaly. The three dose levels were safe and well tolerated over a duration of treatment of up to 52 weeks.

Lanreotide acetate exhibited linear pharmacokinetics in acromegalic patients over the range of 60 to 120mg after four consecutive dose administrations every 28 days. The population mean of EMAX (maximum GH reduction) was estimated to be around 82%, demonstrating the effectiveness of lanreotide.

Sponsor's Safety Conclusions
• A total of 108 patients received at least one injection of study medication including 27, 27, 29 and 25 patients who received 60, 90 and 120 mg of lanreotide and placebo, respectively, during the double-blind phase. A total of 107 patients received at least one dose of lanreotide acetate during the study including 34 patients who received 60 mg, 36 who received 90 mg, and 37 who received 120 mg during the single-blind phase.
• Median total lanreotide acetate dose administered during the study was 1140 mg with a range of 270 to 1560 mg; the average monthly dose was 98.6 mg. Median duration of active treatment in this 52-week study was 364 days indicating that most patients were able to complete the study; the range of treatment duration was 86 to 400 days.
• A higher proportion of patients in the active treatment groups (60%) experienced at least one adverse event during the double-blind study phase compared to patients in the placebo group (36%). Across lanreotide dose groups, the incidence of reported events was 41%, 70% and 69% for the 60, 90 and 120 mg treatment groups, respectively, during the double-blind phase.
• Among the most commonly reported events, those reported more frequently during the double-blind phase in patients receiving active treatment as compared to patients receiving placebo included diarrhea, bradycardia, weight decrease, anemia and flatulence. Only 2 of these most commonly reported events, diarrhea and flatulence, exhibited an increased incidence across lanreotide dose. Abdominal pain, also one of the most commonly reported adverse events, occurred with similar frequency in lanreotide-treated and placebo-treated patients.
• Across all 3 study phases, a total of 98 (92%) of the 107 patients who received lanreotide experienced at least one adverse event during lanreotide treatment. The incidence of any adverse event across lanreotide dose at onset of the event was highest in the 120 mg dose group (91%) compared to rates observed in the 60 mg (72%) and 90 mg (71%) dose groups. The majority of patients [74 (69%) of 107] received at least one dose of 120 mg lanreotide acetate during the study.
• The most commonly reported adverse events during lanreotide treatment across all 3 study phases were diarrhea (48%), cholelithiasis (30%), abdominal pain (21%), bradycardia (14%),

arthralgia (13%), anemia (12%), alopecia (12%), injection site mass (10%), flatulence (10%) and nausea (10%).

- The incidence of diarrhea (22%, 29% and 47% for the 60, 90 and 120 mg groups respectively), abdominal pain (11%, 14% and 15%, respectively) and flatulence (4%, 5%, 9%, respectively) increased with lanreotide dose. In addition, the incidence rates of cholelithiasis (17%, 14% and 24%, respectively) and injection site mass (4%, 3% and 11%, respectively) were highest during treatment with 120 mg lanreotide acetate.
- No deaths were reported during the study. Eighteen (17%) of the 107 lanreotide-treated patients experienced serious adverse events during the 3 study phases including 9%, 12% and 11% of patients during treatment with 60, 90 and 120 mg, respectively One serious event, pancreatitis associated with gallbladder lithiasis migration, was judged by the investigator to be related to study treatment.
- Four patients withdrew from the study due to treatment-emergent adverse events, including 3 patients during treatment with 90 mg and one during treatment with 120 mg. None of the events reported as the reason for withdrawal were assessed as drug-related by the investigator.
- There were no clinically significant changes in hematology, chemistry or vital signs parameters associated with lanreotide acetate following repeated injections through 52 weeks of treatment.
- ECG and echocardiographic analysis was unremarkable. For the majority of assessments, mean quantitative cardiac electrophysiologic and chamber dimensions were within normal limits for this population and did not appear to show any major changes over time. Lanreotide-treated patients had a decrease in heart rate and concomitant changes in the ECG intervals that follow heart rate. There were no increases in clinically significant ECG abnormalities. Cardiac dimensions were unchanged other than a decrease in left ventricular septal and posterior wall thickness and left ventricular cavity which corresponded to a decrease in left ventricular mass. This reduction was concordant with a change in body size. The valvular regurgitations seen in this population are typical of a population of patients with acromegaly and did not appear to show any clinically meaningful changes over time.
- Gallbladder ultrasound revealed that the incidence of new onset of lithiasis and sludge by study end was ~21% of patients with data available at baseline and post-baseline; an additional 9% of patients had transient (present during the study and absent at end of study) reports of gallstone and/or sludge. Patients whose last dose administered was 120 mg appeared more likely to have new onset of lithiasis and sludge (~20%) compared to patients who received the lower doses of lanreotide acetate (≤ 10%).

Medical Officer's Conclusions:

Efficacy:

A significantly higher proportion of lanreotide-treated patients (13 of 83, 16%) had mean GH ≤ 2.5 ng/mL and normalized IGF-1 at Week 4 as compared to placebo (0 of 25) ($p = 0.033$). Thus, lanreotide acetate at doses of 60, 90 and 120 mg was significantly more effective than placebo in reducing mean GH and IGF-1 levels 4 weeks after a single injection.

A total of 13 out of 83, (16%) of lanreotide-treated patients had a mean GH ≤ 2.5 ng/mL and normalized IGF-1 at Week 4. A total of 41 (38%) of the 107 lanreotide-treated patients had mean

GH ≤ 2.5 ng/mL and normalized IGF-1 at Week 16 including 38%, 42% and 35% of patients in the 60, 90 and 120 mg treatment groups, respectively. The proportion of patients with this level of response was increased to 45% (46 of 103 patients) at Week 32 and decreased to 43% (42 of 98 patients) at Week 52. Symptoms of acromegaly improved between baseline and Week 16 including 45%, 43%, 37%, 36% and 27% of patients with improvement in perspiration, swelling of extremities, joint pain, fatigue and headaches, respectively. Fewer patients showed improvements in impotence or oligomenorrhea. No apparent trend was noted for improvement in acromegaly symptoms with increasing lanreotide dose. By the end of the study (LVA), the acromegaly symptoms of headache, perspiration, fatigue, swelling of extremities, and joint pain had improved from baseline or were stable in 88% to 94% of patients.
Thus, repeated administration of lanreotide acetate every 4 weeks at a constant dose for 16 weeks followed by a dose titration period to maximum effect continued to be effective in reducing GH and IGF-1 levels and in reducing the symptoms of acromegaly.

In the majority of eligible patients, the last dose of lanreotide administered during the dose titration phase was titrated to a higher level, including 42 (62%) of 68 patients who had received 60 or 90 mg during the double/single-blind phase. Very few patients were titrated to a lower dose by the end of the study [12 (17%) of 71 patients who had received 90 or 120 mg during the double/single-blind phase].

For the primary endpoint in study 717, the proportion of patients with a greater than 50% decrease in mean GH from baseline, the results were similar in all patient subpopulations (Naïve, Not treated within 3 month, Previously treated). Similar results were seen for a median reduction in mean GH. For all other efficacy parameters, there was a general trend towards a higher response rate within the previously treated population compared to the naive patient group.

Safety:
No deaths were reported during the study. Eighteen (17%) of the 107 lanreotide-treated patients experienced serious adverse events during the 3 study phases including 9%, 12% and 11% of patients during treatment with 60, 90 and 120 mg, respectively One serious event, pancreatitis associated with gallbladder lithiasis migration, was likely to be related to study treatment.

Four patients withdrew from the study due to treatment-emergent adverse events. This reviewer believes it is unlikely that lanreotide caused the event that led to the withdrawals. Of note, 4 additional patients withdrew due to a lack of efficacy.

During the double-blind placebo-controlled phase (weeks 0 to 4) the most commonly reported events (by preferred term) were diarrhea (31% vs. 0% of lanreotide-treated and placebo-treated patients, respectively), abdominal pain (7% vs. 4%), bradycardia (8% vs. 0%), weight decrease (8% vs. 0%), anemia (7% vs. 0%) and flatulence (6% vs. 0%). Among these commonly reported events, diarrhea and flatulence exhibited an increased incidence across lanreotide dose.

The most commonly reported adverse events during lanreotide treatment across all 3 study phases were diarrhea (48%), cholelithiasis (30%), abdominal pain (21%), application site

disorders (injection site mass/pain/reaction) (21%), hyperglycemia (includes hyperglycemia, elevated HbA1C, new onset + aggravated DM) (15%), bradycardia (14%), arthralgia (13%), anemia (12%), alopecia (12%), flatulence (10%), nausea (10%), and hypertension (includes HTN + aggravated HTN) (8%).

The incidence of diarrhea (22%, 29% and 47% for the 60, 90 and 120 mg groups respectively), abdominal pain (11%, 14% and 15%, respectively) and flatulence (4%, 5%, 9%, respectively) increased with lanreotide dose. In addition, the incidence rates of cholelithiasis (17%, 14% and 24%, respectively) and injection site mass (4%, 3% and 11%, respectively) were highest during treatment with 120 mg lanreotide acetate.

The clinically significant changes in hematology or chemistry parameters associated with lanreotide acetate following repeated injections were anemia (12% patients), hyperglycemia (9%), hypoglycemia (4%), increased alkaline phosphatase (3%), hypercholesterolemia (3%) and bilirubinemia (3%). Thyroid function was not monitored during this study.

Lanreotide-treated patients had a decrease in heart rate and concomitant changes in the ECG intervals that follow heart rate. Treatment-emergent adverse events related to ECG assessment and reported in the Heart Rate and Rhythm Disorders body system during the entire study included bradycardia (14%), atrial arrhythmia (2%), atrial fibrillation (2%), heart block (2%), ventricular arrhythmia (<1%) and bundle branch block (<1%).

The cardiac valvular regurgitations seen in this population did not appear to show any clinically meaningful changes over time.

Gallbladder ultrasound revealed that the incidence of new onset of lithiasis and sludge by study end was ~31% of patients with data available at baseline and post-baseline and excluding those who had abnormalities at baseline. Patients whose last dose administered was 120 mg appeared more likely to have new onset of lithiasis and sludge (~20%) compared to patients who received the lower doses of lanreotide acetate (≤ 10%).

Of the 98 subjects who had data available at baseline and post-baseline, 17 (17%) had baseline gallstones which persisted throughout the study; 65 (66%) had no gallstones at baseline and end-of-study; 13 (13%) developed new gallstones which persisted; and 3 (3%) developed the occurrence and disappearance of a gallstone during the course of the trial. If the 17 subjects with baseline gallstones are removed from the denominator, there are 13/81 (16%) who developed new gallstones that persisted throughout the course of the study and 16/81 (20%) who developed new gallstones at any time during the study.

Putative antibodies against lanreotide were observed in only one of the 107 lanreotide-treated patients.

The most common adverse events in study 717 by somatostatin analog history (Naïve, Not treated within 3 month, Previously treated) show that the System Organ Class (SOC) 'Gastrointestinal disorders' has the highest percentage of adverse events across all treatment

groups, and a numerically higher percentage among the Naïve (73.3%) and Not treated for 3 months (69.2%) groups than the Previously treated group (62.7%). Within the SOC Gastrointestinal disorders, the Preferred Terms (PT) diarrhea and abdominal discomfort have numerically higher percentages among the Naïve (diarrhea 40.0%, abdominal discomfort 6.7%), and Not treated for 3 months (diarrhea 59.0%, abdominal discomfort 7.7%) groups than the Previously treated group (diarrhea 29.4%, abdominal discomfort 3.9%). Similarly, the PTs cholelithiasis and headache were notably more frequent in the Naïve (46.7% and 20.0% respectively) and Not treated within 3 months groups (46.2% and 5.1% respectively) than the Previously treated group (15.7% and 3.9% respectively).

10.1.2 Study Title: Phase III, multicenter, open study to assess the efficacy and safety of lanreotide Acetate (60, 90 or 120 mg) in acromegalic patients previously treated or not by somatostatin analogues.

Study Number: E-54-52030-081

Investigators:
A total of 17 investigators, 16 in France and one in Switzerland, participated in this study that was supervised by the Co-ordinating Investigator, Dr. Chanson, Hôpital de Bicêtre, 78, avenue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France.

Study center(s): 17 centers (16 located in France and 1 in Switzerland)

Study period: 13 October 2000 to 15 July 2002

Phase of Development: III

Publications Based on the Study: None

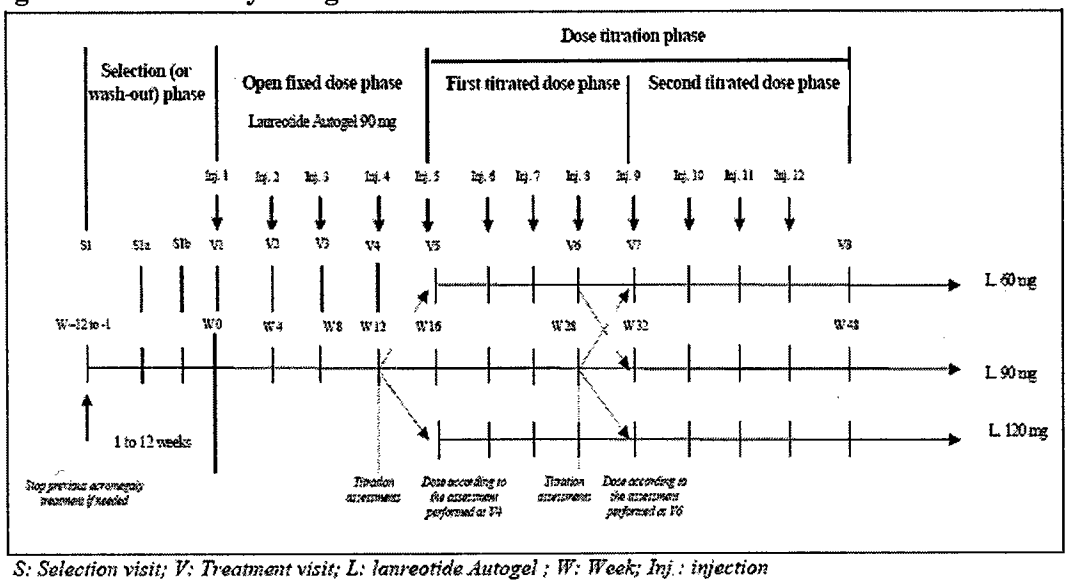
Primary Objectives:
Primary objective:
To evaluate the long-term efficacy of repeated injections of lanreotide acetate administered at titrated doses in terms of percentage of patients having a normal (age-adjusted) serum IGF-1 level at end point.

Secondary Objectives:
1) To document the long-term efficacy of repeated injections of lanreotide acetate in terms of:
• Variation from baseline of the IGF-1 levels expressed as a percentage of the upper limit of the age-adjusted normal range,
• Mean GH levels,
• Number of patients having a serum GH level ≤2.5 ng/ml,
• Number of patients having a serum GH level ≤ below 1 ng/ml,
• Number of patients with no or reduced clinical signs of acromegaly,
• Lanreotide serum levels
2) To document the long-term safety of repeated injections of lanretide acetate in terms

of:
• Local and systemic tolerance,
• Standard hematology and biochemistry tests,
• Ultrasound examination of the gallbladder,

Design:
This is an unblinded, open-label study with no control group. Baseline controlled study evaluating the effect of lanreotide acetate on GH/IGF-1 levels compared to pre-treatment values, in 63 acromegalic patients.

Figure 10.1.2.1 Study Design



S: Selection visit; V: Treatment visit; L: lanreotide Autogel ; W: Week; Inj.: injection

Sponsor's Figure 1, Module 5, Vol 97, pg 20

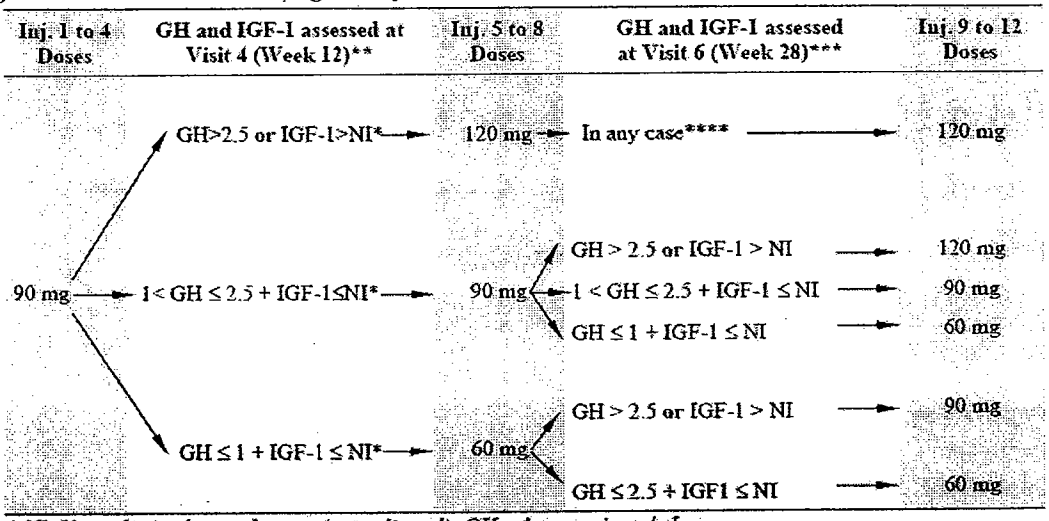
Patient Population:
Inclusion criteria:
• Informed consent; ≥18 years of age,
• Patient having documentation supporting diagnosis of active acromegaly in one of the following definitions:
- Patient having received neither somatostatin analogue nor dopaminergic agonist within the previous 12 weeks and having an IGF-1 level at least 1.3 times the upper limit of the age-adjusted normal range,
- Patient being treated with a somatostatin analogue (other than lanreotide acetate) or a dopaminergic agonist when attending the first visit and having at the end of the washout period an IGF-1 level at least 1.3 times the upper limit of the age-adjusted normal range.
Exclusion criteria:
• Patient having had pituitary surgery within the previous 3 months,
• Patient having received radiotherapy for acromegaly disease within the previous 36 months (Amendment dated 24 July 2000),

• Patient being predicted to require pituitary surgery (adenomectomy) or receive radiotherapy during the study period,
• Patient having received lanreotide acetate at any time before the study,
• Patient having an active malignant disease, clinically significant renal or hepatic abnormalities, pregnant or lactating,

Treatment Groups:
There was only one patient group. All patients received a fixed dose of 90 mg for four injections, and then the dose could be titrated (60, 90 or 120 mg lanreotide acetate) depending on the patient's GH and IGF-1 levels.

Dose and Mode of Administration
Twelve deep subcutaneous injections of lanreotide acetate every 4 weeks
• Fixed dose phase (Injections 1 to 4): four injections of lanreotide acetate 90 mg.
• First titrated dose phase (Injections 5 to 8): lanreotide acetate to be administered at titrated doses (60, 90 or 120 mg), according to the clinical response of the patient as follows:

Figure 10.1.2.2 Dose During Study



** NI; Upper limit of normal range (age-adjusted); GH values are in ng/mL.*
*** Before the fourth injection.*
**** Before the eighth injection.*
***** In case of dose increase at Visit 5, no re-adjustment was allowed at Visit 7.*

Sponsor's Figure 2, Module 5, Vol 97, pg 26

Duration of Treatment:
The study design included three distinct study phases:
• A 1 to 12-week selection/washout period for patients previously treated with a somatostatin analogue or a dopaminergic agonist (1-week screening period for all other patients). The duration of the washout period was designed to provide sufficient time for washout of prior treatment and to obtain baseline GH and IGF-1 levels off treatment.

• A 16-week open-label fixed-dose phase in which patients received four injections of 90 mg lanreotide acetate; steady state for lanreotide acetate is reached after four injections.
• A 32-week open-label dose titration phase in which patients received eight injections. During the latter phase, two dose adjustments based on biochemical efficacy (i.e., GH and IGF-1 levels) could be instituted, and allowed all patients to receive their optimal dose for control of acromegaly.

Of the 63 eligible patients who entered the treatment phase of the trial, 57 completed the 48-week treatment period. Six patients withdrew prematurely; two due to AE (#0302, #1502), one due to lack of efficacy (#0403), one withdrew consent (#0608), and two for other reasons (missing injections from Week 10 to 12 for patient #0104 and important time difference between injections for patient #0201). Visit 7=Week 32

Table 10.1.2.1 Extent of Exposure by Dose Group

Visit	Dose	Number of Patients (N=63)
Visit 1	60 mg 90 mg 120 mg	0 (0%) 63 (100%) 0 (0%)
Visit 5	60 mg 90 mg 120 mg	11 (17%) 4 (6%) 44 (70%)
Visit 7	60 mg 90 mg 120 mg	9 (14%) 4 (6%) 46 (73%)

Sponsor's Table 15, Module 5, Vol 97, pg 50

Endpoints:
Efficacy:
Primary criterion:
- Proportion of patients with normal IGF-1 levels at the end of the study.

Secondary criteria:
• Proportion of patients with a decrease in mean GH level >50%,
• Proportion of patients with mean GH ≤2.5 ng/mL,
• Proportion of patients with mean GH ≤1 ng/mL,
• Clinical signs of acromegaly, including headache, excessive perspiration, asthenia, swelling of extremities.

Safety:
- Clinical AEs reporting
- Standard hematology and biochemistry
- Physical examination (blood pressure, heart rate, and body weight)
- Gallbladder ultrasonography: assessed at Visit 1, Visit 6 (Week 28) and Visit 8 (Week 48).

Patients' hematology, biochemistry, GH and IGF-1 levels were measured at Weeks 12, 28 and at the end of the study (Week 48). Gallbladder ultrasonography was performed at Weeks 28 and 48, while clinical examination and evaluation of acromegaly symptoms were documented at each visit.

Statistical Analyses:
For continuous data: sample size, mean, median, Q1, Q3, minimum, maximum values, standard deviation were given. Sample size was reported in integers. Statistics were rounded to the first decimal.

For qualitative data (safety and efficacy): frequencies and percentages were given for categorical data. Frequency and percentages were reported in integers. Percentages were calculated using the denominator of all patients in a specified population.

No interim analysis was planned.

The primary population for the assessment of efficacy was the intent-to-treat (ITT) population. All recruited patients who received at least one injection of lanreotide acetate and had data for at least one key efficacy variables (i.e. GH or IGF-1 data at any visit after Visit 1) were included in the ITT population.

All patients who received at least one injection of lanreotide acetate were included in the safety population.

Protocol Amendments:
The original study protocol, dated 16 June 2000 was amended once in order to change the disease-related exclusion criterion No 2 from "patient having received radiotherapy for acromegaly disease within the previous 24 months" to "patient having received radiotherapy for acromegaly disease within the previous 36 months".

It was specified in the protocol that lanreotide serum levels would be used to document drug concentration measurements. The coordinating investigator and Beaufour Ipsen decided in March 2002 not to perform these analyses.

Results:

Patient Demographics
There were 38 males (60%) and 25 females (40%) aged from 30 to 77 years. At Visit 1, the weight ranged from 53 to 141 kg while the systolic blood pressure ranged from 100 to 175 mmHg (mean 133.7 ± 14.6 mmHg), the diastolic blood pressure from 60 to 110 mmHg (mean 80.8 ± 9.7 mmHg) and the heart rate from 52 to 125 beats/min (mean 73.5±10.3 beats/min).

The time since diagnosis ranged from 0.2 to 33.3 months. At the time of inclusion, 46 patients (73%) had macro-adenomas, and 11 (17%) had micro-adenomas.

With regard to previous treatment for acromegaly, 37 patients (59%) had undergone pituitary surgery, 12 (19%) had received pituitary radiotherapy and 49 (78%) had been medically treated.

As displayed in the table below, baseline GH levels ranged from 0.7 to 49.7 ng/mL (mean 6.2 ± 8.4 ng/mL). At inclusion, 22 out of 63 patients (35%) had GH ≤2.5 ng/mL, while 7 patients (11%) had GH ≤1ng/mL. Basal IGF-1 levels were 1.3 to 5.8 times the upper limit of normal, ranging from 377.0 to 1,524.0 ng/mL (mean 743.7 ± 291.2 ng/mL).

Table 10.1.2.2 Baseline Characteristics

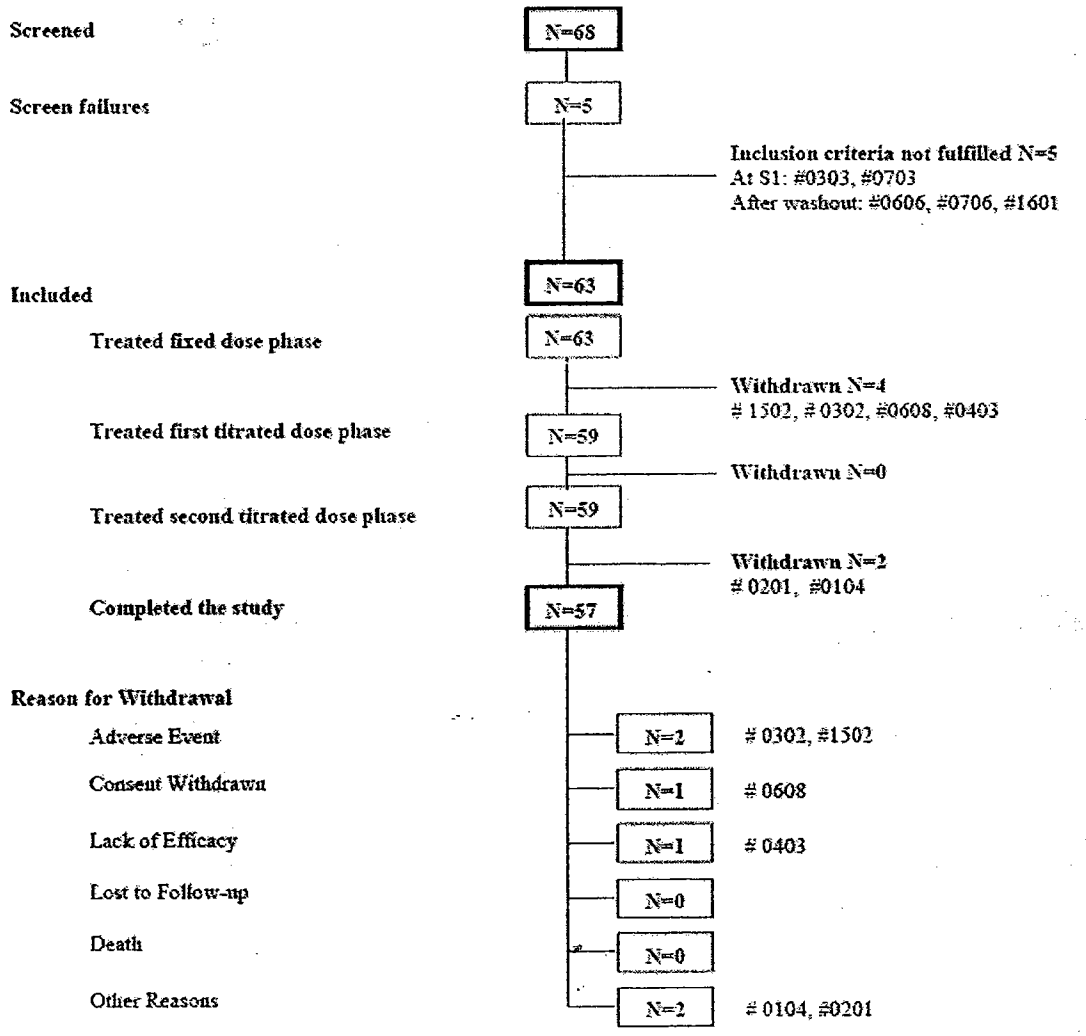
Parameter		**N=63**
Age (years)	Mean	55.3
	Median	54.8
	Range	30 to 77
Sex	Male	38 (60%)
	Female	25 (40%)
Weight (kg)	Mean	133.7
	Median	132,5
	Range	100 to 175
Time since diagnosis (years)	Mean	7.8
	Median	6.7
	Range	0.2 to 33
GH level (ng/mL)	Mean	6.2
	Median	3.6
	Range	0.7 to 49.7
Micro-adenoma	yes	11 (17%)
Macro-adenoma	yes	46 (73%)
Pituitary surgery	yes	37 (59%)
Pituitary radiotherapy	yes	12 (19%)
Medical treatment	yes	49 (78%)
Essential Hypertension		19 (30%)
Cholelithiasis		12 (19%)
Cholecystectomy		6 (10%)
Other disorder of the gallbladder		5 (8%)
Calculus of the gallbladder and bile duct without cholecystitis		3 (5%)
Diabetes Mellitus		12 (19%)
Hypothyroidism		10 (16%)
CHF		4 (6%)
Aortic valve disorder		3 (5%)
Mitral stenosis with insufficiency		2 (3%)
Atrial fibrillation		3 (5%)
Cardiomyopathy		2 (3%)

Patient Disposition

Of the 63 eligible patients who entered the treatment phase of the trial, 57 completed the 48-week treatment period. Six patients withdrew prematurely; three due to AE (#0302, #1502, #0608), one due to lack of efficacy (#0403), and two for other reasons (missing injections from Week 10 to 12 for patient #0104 and important time difference between injections for patient #0201). Pt #0608 was counted by the sponsor as withdrew secondary to withdrawal of consent but review of the narrative shows that the patient withdrew secondary to injection site pain.

All 63 treated patients were included in the safety population and all provided at least one key efficacy data, hence they were all included in the ITT population. All patients entered the study after the first amendment dated 24 July 2000 was approved: the first patient was selected on 26 September 2000 and the last patient completed the study on 15 July 2002.

Figure 10.1.2.3 Patient Disposition



Sponsor's Figure 3, Module 5, Vol 97, pg 39

Patient Exposure to Study Drug

All 63 patients included in the safety population received four injections of lanreotide acetate at the assigned dose of 90 mg, except two patients (# 0403 and 0608) who received only three injections at 90 mg.

According to the GH and IGF-levels assessed at Visit 4 (Week 12) and Visit 7 (Week 32), the subsequent doses of lanreotide were adjusted as shown in the table below.

Table 10.1.2.3: Extent of Exposure (Doses received at Visits 1, 5 and 7) by Dose Group

Visit	Dose	Number of Patients (N=63)
Visit 1	60 mg	0 (0%)
	90 mg	63 (100%)
	120 mg	0 (0%)
Visit 5	60 mg	11 (17%)
	90 mg	4 (6%)
	120 mg	44 (70%)
Visit 7	60 mg	9 (14%)
	90 mg	4 (6%)
	120 mg	46 (73%)

Sponsor's Table 15, Module 5, Vol 97, pg 50

Treatment Adherence

Sixty-three patients were enrolled in the study, all of whom completed the fixed-dose phase, 59 completed the first titrated phase and 57 completed the treatment up to Week 48 (second titrated dose phase; Visit 8).

Concomitant Medication Use

Prior therapy: Patients previously treated with lanreotide acetate or who had radiotherapy for acromegaly within the past 36 months were ineligible. Patients previously treated with a somatostatin analogue (other than lanreotide acetate) or a dopaminergic agonist were allowed to enter the study, provided that, at the end of the washout period, their IGF-1 level was 1.3 times the upper limit of the age-adjusted normal range.

Concomitant therapy: Somatostatin analogues (other than the study drug) and dopaminergic agonists were not permitted during the study; administration of cyclosporin also was not allowed. The investigator was permitted to prescribe other concomitant medications during the study as required.

Primary Efficacy Outcomes

As described in the table below, treatment with lanreotide acetate resulted in normalized IGF-1 levels in 27 of the 63 patients (43%) by the end of study (ITT population; last value available).

Table 10.1.2.4. Normal Age-Adjusted IGF-1 Levels at the End of the Study (ITT Population)

Normal Age-Adjusted IGF-1 Level *	End of Study ** (N=63)
Yes	27 (43%) (95% CI: 30.64, 55.08)
No	36 (57%)

* Only patients with a value higher than the upper normal range were considered as abnormal.
** Last value available.
Sponsor's Table 6, Module 5, Vol 97, pg 43

The IGF-1 age adjusted normal values used by the central lab for study E-54-52030-081 are listed in the table below.

Table 10.1.2.5 Age Adjusted IGF-I Values for E-54-52030-081 used for Screening after December 26, 2000. Baseline and Visit Assessments

Age	Low * (ng/ml)	High* (ng/ml)
18-30	219	644
31-40	183	405
41-50	54	336
51-65	71	284
66-85	45	259

*Male and Female

For those patients screened prior to December 26, 2000 screening was performed using normal values different from those above (see table below). All baseline and in study evaluations of IGF-1 in study 081 utilized the normal values from the table above.

Table 10.1.2.6 Age Adjusted IGF-I Values for E-54-52030-081 used for Screening prior to December 26, 2000

Age	Low * (ng/ml)	High * (ng/ml)
20-65	92	308
66-85	45	259

*Male and Female

Secondary Efficacy Outcomes

IGF-1 Levels

As shown in the table below, mean serum IGF-1 levels decreased throughout the study period. After four injections of 90 mg lanreotide acetate, mean circulating IGF-1 levels declined from 743.7 ± 291.2 ng/mL (range: 377.0 to 1,524.0 ng/mL) to 432.3 ± 217.8 ng/mL (range: 109.0 to 981.0.ng/mL). Then, it slightly decreased during the dose titration phase to reach 387.5 ± 203.9

ng/mL at Visit 6 (Week 28) and 376.9 ± 211.4 ng/mL by the end of the study. Mean IGF-1 concentration after treatment completion was 1.3 ± 0.7 times the upper normal limit (range: 0.3, 4.0), compared to 2.5 ± 1.1 times the upper normal limit at baseline (range: 1.3, 5.8)

Table 10.1.2.7: Mean Serum IGF-1 levels by Visit (ITT Population)

Parameters (IGF-1, ng/mL)	Baseline * (N=63)	Visit 4 (N=61)	Visit 6 (N=59)	Visit 8 (N=57)	End-of-Study (N=63)
Mean (±SD)	743.7 (291.2)	432.3 (217.8)	387.5 (203.9)	374.8 (200.1)	376.9 (211.4)
Median (range)	689.0 (377.0, 1524.0)	382.0 (109.0, 981.0)	334.0 (112.0, 971.0)	317.0 (119.0, 1047.0)	317.0 (119.0, 1047.0)

* Baseline was defined as last value available between Visit S1, S1a or S1b.
Sponsor's Table 10, Module 5, Vol 97, pg 44

Mean GH Levels
As shown in the table below, mean GH levels decreased throughout the study period.

Table 10.1.2.8: Mean Serum GH Levels by Visit (ITT Population)

Parameters (GH, ng/mL)	Baseline * (N=63)	Visit 4 ** (N=61)	Visit 6 ** (N=59)	Visit 8 *** (N=57)	End-of-Study** (N=62)
Mean (±SD)	6.2 (8.4)	2.1 (2.0)	1.6 (1.2)	1.3 (1.0)	1.5 (2.1)
Median (range)	3.6 (0.7, 49.7)	1.6 (0.1, 10.7)	1.5 (0.1, 5.4)	1.1 (0.1, 4.0)	1.1 (0.1, 15.5)

* Baseline was defined as last value available between Visit S1, S1a or S1b.
** All available GH values at this visit were used to calculate the mean GH level.
*** Patients still on study.
Sponsor's Table 11, Module 5, Vol 97, pg 45

The proportion of patients with mean GH levels below 2.5 ng/mL increased during the fixed-dose phase from 35% to 77% after the first four injections and reached 85% at the study end. The proportion of patients with mean GH levels less than 1 ng/mL increased throughout the treatment period from 11% at baseline to 31% at Week 12. The proportion of patients with mean GH levels less than 1 ng/mL remained stable over four titrated doses but had increased to 45% by the end of the study.

After the fixed-dose phase (Visit 4), three of the 16 patients who had normalized IGF-1 levels also had a GH level of between 2.5 and 1 ng/mL, while 11 also had a GH of less than 1 ng/mL (Table 10.1.2.7).

Table 10.1.2.9: IGF-1 and GH Levels at Visit 4* by Lanreotide Dose Group (ITT Population)

Parameter	60 mg (N=0)	90 mg (N=61) *	120 mg (N=0)
Normal IGF-1	N=0	N=16 (26%)	N=0
GH <1 ng/mL	0	11 (69%)	0
GH ≥1 ng/mL and ≤2.5 ng/mL	0	3 (19%)	0
GH >2.5 ng/mL	0	2 (13%)	
Abnormal IGF-1 **	N=0	N=45 (74%)	N=0
GH <1 ng/mL	0	8 (18%)	0
GH ≥1 ng/mL and ≤2.5 ng/mL	0	25 (56%)	0
GH >2.5 ng/mL	0	12 (27%)	0

* 61 patients were being treated at Visit 4.
** Only patients with an IGF-1 value higher than the upper range of normal were considered as abnormal.
Sponsor's Table 12, Module 5, Vol 97, pg 45

Fifty-nine of the 63 treated patients had data available after one dose titration at Visit 7 (Week 32). Of these, 16 (27%) had both normal IGF-1 levels and a GH level of less than 1 ng/mL (Table 10.1.2.8).

Table 10.1.2.10: IGF-1 and GH Levels at Visit 7* by Lanreotide Dose Group (ITT Population)

Parameter	60 mg (N=9)	90 mg (N=4)	120 mg (N=46)
Normal IGF-1	N=9 (100%)	N=3 (75%)	N=12 (26%)
GH <1 ng/mL	8 (89%)	2 (67%)	6 (50%)
GH ≥1 ng/mL and ≤2.5 ng/mL	1 (11%)	1 (33%)	5 (42%)
GH >2.5 ng/mL	0 (0%)	0 (0%)	1 (8%)
Abnormal IGF-1 *	N=0 (0%)	N=1 (25%)	N=34 (74%)
GH <1 ng/mL	0	1 (100%)	10 (29%)
GH ≥1 ng/mL and ≤2.5 ng/mL	0	0 (0%)	18 (53%)
GH >2.5 ng/mL	0	0 (0%)	6 (18%)

* 59 patients were being treated at Visit 7.
** Only patients with an IGF-1 value higher than the upper range of normal were considered as abnormal.
Sponsor's Table 13, Module 5, Vol 97, pg 46

At the end of treatment, 24/63 (38%) patients had both normal IGF-1 levels and a GH level of less than or equal to 2.5 ng/mL and 17/63 patients (27%) had both normal IGF-1 levels and a GH level of less than 1 ng/mL (using last available data; Table 10.1.2.9).

Table 10.1.2.11: IGF-1 and GH Levels at the End of the Study* by Lanreotide Dose Group (Last Available Data, ITT Population)

Parameter	60 mg (N=9)	90 mg (N=8)	120 mg (N=46)
Normal IGF-1	N=9 (100%)	N=5 (63%)	N=12 (26%)
GH <1 ng/mL	8 (89%)	3 (60%)	6 (50%)
GH ≥1 ng/mL and ≤2.5 ng/mL	1 (11%)	1 (20%)	5 (42%)
GH >2.5 ng/mL	0 (0%)	1 (20%)	1 (8%)
Abnormal IGF-1 **	N=0 (0%)	N=3 (38%)	N=34 (74%)
GH <1 ng/mL	0	1 (33%)	10 (29%)
GH ≥1 ng/mL and ≤2.5 ng/mL	0	1 (33%)	18 (53%)
GH >2.5 ng/mL	0	1 (33%)	6 (18%)

* All 63 treated patients had an End-of-Study Visit.
** Only patients with an IGF-1 value higher than the upper range of normal were considered as abnormal.
Sponsor's Table 14, Module 5, Vol 97, pg 46

The prevalence of patients with normalized IGF-1 and GH ≤1 ng/mL was higher in the 60 mg group than in the 120 mg group. This likely reflects that patients who were not at goal were titrated to a higher dose rather than implying that the 60-mg dose is more efficacious. Thus, more patients at goal would be in the 60 mg group.

Most patients reported acromegaly symptoms that were of mild or moderate intensity. The most common symptom observed at Visit 1 (Week 0) was asthenia (43 of the 62 patients in whom it was recorded [69%]). Other symptoms observed at Visit 1 were joint pain (35/62 patients [56%]) swelling of extremities (29/62 patients [47%]), excessive perspiration (26/62 patients [42%]), and headache (22/62 patients [35%]).

Overall, at the end of the study, asthenia had improved with treatment in 27 (63%) of the 43 patients who recorded this symptom at Visit 1 and was absent at the end of the study in 36/63 (57%) patients versus 19/62 (31%) patients at Visit 1.

Other symptoms of active acromegaly were significantly improved by the end of the study in the majority of patients:
• Joint pain was improved in 27 (77%) of the 35 patients who recorded this symptom at Visit 1, and at the end of the study was absent in 42/63 (67%) patients versus 27/62 (44%) patients at Visit 1.
• Swelling of extremities was improved in 23 (79%) of the 29 patients who recorded this symptom at Visit 1, and at the end of the study was absent in 49/63 (78%) patients versus 33/62 (53%) patients at Visit 1.
• Excessive perspiration was improved in 21 (81%) of the 26 patients who recorded this symptom at Visit 1, and at the end of the study was absent in 51/63 (81%) patients versus 26/62 (42%) patients at Visit 1.
• Headache was improved in 15 (68%) of the 22 patients who recorded this symptom at Visit 1, and at the end of the study was absent in 47/63 (75%) patients versus 40/62 (65%) patients at Visit 1.

Efficacy Conclusions
At the end of treatment, 24/63 (38%) patients had both normal IGF-1 levels and a GH level of less than or equal to 2.5 ng/mL and 17/63 patients (27%) had both normal IGF-1 levels and a GH level of less than 1 ng/mL. This hormonal control correlated with an improvement of acromegaly symptoms throughout the study.

Safety Data:

Deaths
No deaths occurred during the trial.

Serious Adverse Events
Thirteen patients experienced at least one SAE during the treatment period. All SAEs were unrelated to study drug with the exception of one that was assessed by the investigator as

possibly related. Thus, patient #0302 had a severe event of thrombophlebitis that led to drug discontinuation and the patient's premature withdrawal; however, this reviewer does not believe the event was related to study drug (see below).

1) Center 01-Patient 03: Surgery for inguinal hernia
2) Center 01-Patient 04: Cardiac insufficiency, 64-year-old male with history of non-ischemic, non-obstructive cardiomyopathy since 1990 through a first episode of cardiac failure. On —— the patient was hospitalized for a second episode of severe cardiac failure. He was treated medically and digitoxin therapy was reintroduced (was stopped July 2001). On —— he was considered as recovered without sequelae and was subsequently discharged from hospital. The patient was maintained in the study. This reviewer assessed the event as not related to the study drug, but due to the patient's pre-existing condition.
3) Center 02-Patient 01: increase urinary retention, pelvectomy secondary to urethral adenoca of uncertain origin, melena. This reviewer assessed these events as not related to the study drug, but due to the patient's pre-existing condition.
4) Center 02-Patient 03: superficial left phlebitis, vertigo increased. 44-year-old male patient with history of diabetes and vertigo who experienced superficial thrombophlebitis 2 weeks after the first injection of study drug which resolved with treatment, drug was continued. Patient also experienced an exacerbation of his pre-existing vertigo. This reviewer assessed this event as not related to the study drug, but due to the patient's pre-existing condition
5) Center 03-Patient 02: thrombophlebitis; 77-year-old female patient with a history of post-surgery left lower limb thrombophlebitis requiring a caval umbrella filter and multiple medical problems who developed severe left lower limb thrombophlebitis 14 days after her 4th injection of lanreotide acetate. The investigator reported the event as "possibly" related to study drug but thus reviewer thinks that it is unlikely that it is related due to the patient's pre-existing medical problems.
6) Center 06-Patient 01: Atrial flutter. This reviewer assessed this event as not related to the study drug, but due to the patient's pre-existing condition.
7) Center 06-Patient 02: Entropion
8) Center 06-Patient 13: Right shoulder luxation. This reviewer assessed this event as not related to the study drug
9) Center 07-Patient 01: Chemonucleolysis for cervicobrachialgia. This reviewer assessed this event as not related to the study drug, but due to the patient's pre-existing condition [cervicobrachial pain syndrome (since 1999), chronic cervical pain (since 1996), and lumbar canal syndrome (since 1999)].
10) Center 07-Patient 07: Surgery for eventration. This reviewer assessed this event as not related to the study drug
11) Center 08-Patient 01: Surgery for inguinal hernia. This reviewer assessed this event as not related to the study drug
12) Center 12-Patient 01: Cholecystectomy. At inclusion in the study, a macro-cholelithiasis was diagnosed (March 2001) by a protocol-related abdominal ultrasonography. The patient underwent an elective cholecystectomy. The patient was maintained in the study

and lanreotide acetate therapy was continued. This reviewer assessed this event as not related to the study drug

13) Center 14-Patient 01: multiple myeloma, medullar compression post myeloma. This reviewer assessed these events as not related to the study drug.

Adverse Events that Led to study Withdrawal

Adverse events that led to study drug discontinuation were recorded in four patients. Of these, three patients experienced severe events (thrombophlebitis [#0302]; respiratory insufficiency [#0403]; abdominal pain and diarrhea [#1502]) and one [#0608] experienced an event of injection site pain that was of moderate intensity. In addition, patient #0302 also experienced a mild event of rectal bleeding that was also recorded as resulting in study drug discontinuation. Of these four patients, two were recorded by the sponsor as withdrawn from the study due to AE (#0302 and #1502). Patient #0403, was recorded as withdrawn due to lack of efficacy and patient #0608 withdrew their consent to participate in the study.

After review of the CRFs, this reviewer believes that Pt # 0608 and Pt #1502 experienced treatment-related AEs that led to study withdrawal.

1) Center 04-Patient 03: respiratory insufficiency increased
This reviewer assessed the event as not related to the study drug, but due to the patient's pre-existing condition. The primary reason for the patient's withdrawal from the study was recorded as lack of efficacy.

2) Center 06-Patient 08: Pain at injection site
During her third injection of lanreotide acetate (on 23 May 2001), the patient was recorded to have experienced an adverse event of injection site pain that was of moderate intensity (not serious), and which the investigator assessed as possibly related to study drug. The patient did not receive any treatment for the event and she was reported to have recovered with sequelae. This patient had also experienced injection site pain (of moderate intensity, possibly related, not serious) during her first injection of lanreotide acetate on 29 March 2001. The patient subsequently withdrew consent to her participation in the study and she did not receive any further study medication. This reviewer assessed the event as an AE that led to study withdrawal and related to the study drug.

3) Center 15-Patient 02: abdominal pain, diarrhea
The patient received the first injection of study drug (lanreotide acetate 90 mg) on19 February 2001 and he received his last (fourth) injection of lanreotide acetate 90 mg on 15 May 2001. The patient had experienced abdominal pain ranging from mild to severe in intensity and mild to moderate diarrhea between 20 February and 15 May 2001. On 06 June 2001 the patient was recorded to have experienced severe adverse events of abdominal pain and diarrhea (both not serious), which the investigator assessed as probably related to study drug. The patient was treated with spasfon(molecule: Phloroglucinol Trimethylphloroglucinol, therapeutical class: musculotropic antispasmodic) for the abdominal pain and received smectite (dioctahedral smectite is a natural adsorbent clay used in treating acute diarrhea) for his diarrhea. Study drug was permanently discontinued and the

patient was withdrawn from the study due to the adverse events. The patient was recorded as recovered without sequelae 6 days later. This reviewer assessed the event as an AE that led to study withdrawal and related to the study drug.

4) Center 03-Patient 02: thrombophlebitis; 77-year-old female patient with a history of post-surgery left lower limb thrombophlebitis requiring a caval umbrella filter and multiple medical problems who developed severe left lower limb thrombophlebitis 14 days after her 4th injection of lanreotide acetate. The investigator reported the event as "possibly" related to study drug but thus reviewer thinks that it is unlikely that it is related due to the patient's pre-existing medical problems.

Adverse Events

Table 10.1.2.12: Display of AEs

Body System/Preferred Term	**Total (N=63)**
Gastrointestinal System Disorders	**48 (76%)**
Diarrhea	36 (57%)
Abdominal pain	17 (27%)
Nausea	4 (6%)
Constipation	3 (5%)
Gastroesophageal reflux	3 (5%)
Vomiting	1 (2%)
Liver and Biliary System Disorders	**16 (25%)**
Cholelithiasis	10 (16%)
Gallbladder disorder	6 (10%)
Musculoskeletal Disorders	**15 (24%)**
Cramps	4 (6%)
Body as a Whole – General Disorders	**14 (22%)**
Lumbar pain	3 (5%)
Respiratory System Disorders	**12 (19%)**
Bronchitis	3 (5%)
Rhinitis	3 (5%)
Urinary System Disorders	**8 (13%)**
Urinary tract infection	3 (5%)
Metabolic Disorders	**7 (11%)**
Hypoglycemia	2 (3%)
Weight decrease	2 (3%)
Diabetes Mellitus	1 (2%)
DM aggravated	1 (2%)
Application Site Disorders	**6 (10%)**
Injection site pain	4 (6%)
Injection site mass	2 (3%)

The most common side effects of lanreotide acetate were gastrointestinal (48 [76%] patients), including diarrhea in 36 (57%) of patients, which was mainly of mild (N=16, 25%) or moderate intensity (N=14, 22%), but six (10%) episodes were severe with one leading to patient withdrawal. Abdominal pain occurred in 17 (27%), nausea in 4 (6%), constipation in 3 (5%), GE reflux in 3 (5%), and vomiting in 1 (2%).

Liver and biliary system disorders occurred in 16 (25%) of patients and included cholelithiasis [N=10, 16%], this included the 8 patients with a new gallstone at end of study and the 2 patients with a gallstone at Visit 6 which was not present at Visit 8, and gallbladder disorders [N=6, 10%]). Cholelithiasis was accompanied by abdominal pain in three of the 10 cases (patients #0401, #1201 and #1502) and in no cases was it accompanied by events of fever. In all six cases, events of coded to gallbladder disorder were events of sludge. All events of cholelithiasis or sludge identified on gallbladder ultrasonography were recorded as adverse events, irrespective of whether or not the patient had had a baseline ultrasonography reading performed (See Special Studies section for details).

Forty-seven patients had gallbladder ultrasonography performed at both Visit 1 and at the end of the study. One of the six patients with cholecystectomies at baseline, patient 007 at site 007, had gallbladder ultrasonography during the study. Patient 007 had had gallbladder ultrasonography at baseline (Visit 1) as well as Visits 6 and 8. Ten patients (21%) had gallstones at both Visit 1 and at the end of the study. Of the patients who did not have gallstones or a cholecystectomy at baseline, eight out of 36 **(22%)** had a new gallstone at the last evaluation. Twenty-eight out of 36 (78%) did not have gallstones at either Visit 1 or at the end of the study.

Other common AEs were musculoskeletal system disorders (N=15, 24%), including cramps in 4 (6%); general disorders (N=14, 22%), including lumbar pain in 3 (5%); respiratory system disorders (N=12, 19%), including bronchitis in 3 (5%) and rhinitis in 3 (5%); urinary system disorders (N=8, 13%), including UTI in 3 (5%); metabolic disorders (N=7, 11%), including hypoglycemia in 2 (3%), weight decrease in 2 (3%), DM in 1 (2%) and aggravated DM in 1 (2%); and application site disorders (N=6, 10%), including injection site pain in 4 (6%) and injection site mass in 2 (3%).

Adverse events that coded to "Cardiovascular Disorders, General", "Heart Rate & Rhythm Disorders" or "Myo Endo Pericardial Valve Disorders" were recorded in two (3%) patients for high blood pressure (patients #0103 and #1504; moderate and mild, respectively, both not serious) or as single cases. There was also one event each of cardiac failure (#0104; severe, not related, serious), hypotension (#0608; mild, not related, not serious), atrial flutter (#0608; mild; not related, serious), extrasystoles (#0103; moderate, not related, not serious) and aortic incompetence (#0605; mild, not related, not serious). Echocardiogram and electrocardiogram (ECG) were not routinely performed in this study; no cardiac enzymes or markers of cardiac damage were measured.

Adverse events relating to glucose regulation were reported for four patients. One patient (#0501) who had a medical history of diabetes and a fasting blood glucose value of 6.9 mmol/L at baseline experienced an AE of diabetes aggravated at Visit 6 (glucose reading, 11.3 mmol/L). This patient had a history of diabetes but was not being treated with antidiabetic therapy at the time of the event; treatment of the event commenced one month later. Another patient (#1401), who had a fasting blood glucose level within the normal range at baseline (6.5 mmol/L), experienced an event of diabetes mellitus (glucose reading, 7.1 mmol/L at the end-of-study visit). This patient started treatment for DM one month later. An additional two patients (#0608 and #1603) experienced AEs of hypoglycemia. Both patients had fasting blood glucose levels within

the normal range at baseline (5.2 mmol/L) and neither was being treated with antidiabetic therapy at the time of the events.

Most treatment-emergent AEs were mild (96 AEs in 16 patients, 25%) or moderate (86 AEs in 22 patients), while 23 AEs affecting 16 patients (25%) were severe leading to early withdrawal of patients #0301 and #1502.

Laboratory Parameters
In the majority of patients, laboratory abnormalities recorded post-treatment were also present at baseline. Clinically significant abnormal values of glucose were observed in 21 patients (33%) at baseline and increased to 25 (40%) at study end. Adverse events relating to glycoregulation were reported for four patients; one patient had diabetes aggravated, one had diabetes mellitus and two had hypoglycemia.

Hematology
The majority of patients had normal hematological values.

Hemoglobin: One patient (#0608) had a low hemoglobin value at baseline that was considered clinically significant (<20% below the lower limit of normal [LLN]).

Erythrocytes: Low values of erythrocytes (<20% below the LLN) were observed in one patient at Visit 6 (Week 28) and at the end of the study (#1401: this patient experienced the SAE of multiple myeloma and medullar compression post myeloma.).

Leucocytes: Leucocytes <20% below the LLN were observed in two patients at baseline (#0304 and #0406), two at Visit 4 (Week 12) (#0302 and #0704), two at Visit 6 (Week 28) (#0901 and #1401), and one at Visit 8 (#1401). Leucocytes >30% above the upper limit of normal (ULN) fluctuated during study, but were absent at study end;

Platelets: Platelets <20% below the LLN at baseline occurred in one patient (#0304) and remained at <20% below the LLN at Visits 4 and 6. Patient #1401 had a platelet value <20% below the LLN at the end of the study.

Biochemistry
Glucose: The number of patients with fasting blood glucose values above 6.5 mmol/L increased during treatment, from 21 (33%) at inclusion to 25 (40%) at the end of the study. Patients with the highest glucose abnormalities included Patient #1101 with a baseline glucose of 9.90 mmol/L (upper range of normal is 6.6 mmol/L) that increased to 11.30 by end of study; Patient 1002 with a baseline glucose of 8.50 mmol/L that increased to 10.60 by end of study; and Patient #0603 with a baseline glucose of 6.80 mmol/L that increased to 9.10 by end of study.

ALT: The number of patients with ALT twice the upper limit fluctuated during the study: there were four patients with such an abnormal value at baseline (#0104, #1001, #1101 and #1301), decreasing to one patient at Visit 4 (#0701), increasing to three patients at Visit 6 (#0304, #0701

and #1101), and dropping to one patient (#0302) at the end of the study. The highest ALT value on drug was Patient #0701 with ALT of 77 IU/L (upper range of normal=37) at Visit 4.

Total bilirubin: The number of patients with total bilirubin 50% above the upper normal limit increased slightly from two (3%) (#0901 and #1501) at baseline to three (5%) (#0101, #0610 and #1003) at the end of the study. Highest value was Pt # 0610 with a value of 35 µmol/L at Visit 6 (17 µmol/L is upper range of normal).

Creatinine: One patient (#0104) had a clinically significant raised creatinine level (>150 µmol/L) at Visit 6 only.

Vital Signs
Measurement of weight, systolic and diastolic blood pressures at study visits did not reveal any post-treatment change compared to baseline. Other variations were minimal and not clinically significant: mean heart rate decreased from 73.5 ± 10.3 beats per minute [bpm] (range: 52 to 125 bpm) to 68.2 ± 10.5 bpm (range: 44 to 96 bpm) at the end of the study.

Physical Examination
By the end of the study, most frequent disorders affected cardiovascular (N=8 patients), dermatological (N=7 patients) and musculoskeletal (N=7 patients) systems, but the majority of abnormal physical findings were present at baseline. A change in central nervous system (CNS) function was noted for patient # 0203; abnormal CNS function was recorded at Visits 4, 5, 6 and 8 but was normal at baseline. At the time of these visits this patient also had AEs recorded of severe vertigo (at Visits 4, 5 and 6) and severe hallucination (at Visit 8). Neither of the AEs were considered drug- related or SAEs. The number of patients with abnormal genitourinary function increased from one patient (#0201) at baseline (Visit 1) to four patients at Visit 8 (#0201, #0302, #0702, #0904).

Special Safety Studies

Gallbladder Ultrasonography
The prevalence of lithiasis, sludge and other biliary disorders was assessed by performing a gallbladder ultrasonography at baseline (Visit 1), Visits 6 and 8. Forty-seven patients had gallbladder ultrasonography performed at both Visit 1 and at the end of the study. One of the six patients with cholecystectomies at baseline, patient 007 at site 007, had gallbladder ultrasonography during the study. Patient 007 had had gallbladder ultrasonography at baseline (Visit 1) as well as Visits 6 and 8. Ten patients (21%) had gallstones at both Visit 1 and at the end of the study. Of the patients who did not have gallstones or a cholecystectomy at baseline, **eight out of 36 (22%) had a new gallstone at the last evaluation** (Pt #s 0104, 0202, 0304, 0614, 0801, 0903, 1302 and 1502) and 10/36 (28%) developed new gallstones at any time during the study. Twenty-eight out of 36 (78%) did not have gallstones at either Visit 1 or at the end of the study. Two patients (#0401 and #0611) had cholelithiasis at Visit 6 but it was not present by Visit 8. Pt #0401 is a 56-year-old female who received sandostatin 20 mg i.m. from Dec 1997 to 04 Dec 2000 and started lanreotide acetate on 05 Dec 2000. Gallbladder ultrasound done on 11 Sept 2001 detected cholelithiasis. She was treated with Delursan (ursodeoxycholic acid) 750 mg OL from 06 Oct

2001 to 29 Jan 2002. Ultrasound on 29 Jan 2002 showed no presence of gallbladder lithiasis. Pt #0611 is a 68-year-old male who enrolled in the study on 05 Mar 2001. Microlithiasis and sludge were detected by an unspecified method on 07 June 2001 and by gallbladder ultrasound on 28 Set 2001. Following a further gallbladder ultrasound on 15 Feb 2002, the presence of microlithiasis was no longer detected, however sludge was still present and remained at the end of the study.

Of the 47 patients who had gallbladder ultrasonography performed at both Visit 1 and at the end of the study, four (9%) had developed sludge at the last evaluation. None had sludge at both Visit 1 and at the end of the study (one patient, #0611, had sludge at Visit 6 and 8 but no ultrasound was performed at Visit 1). 41 (87%) did not have sludge at either Visit 1 or at the end of the study.

The majority of patients who had gallbladder ultrasonography performed at both Visit 1 and at the end of the study did not have other biliary disorders detected at either Visit 1 or at the end of the study (46/47 [98%]). In one patient (2%), a biliary disorder detected in at Visit 1 was not detected at the end of the study (Pt #1301).

Table 10.1.2.13: Gallbladder Ultrasonography - Descriptive statistics at each visit; Safety Population

		Lithiasis	Sludge	Other
V1	Yes	12 (23%)	3 (6%)	1 (2%)
	No	41 (77%)	50 (94%)	52 (98%)
V6	Yes	16 (30%)	6 (11%)	0 (0%)
	No	38 (70%)	48 (89%)	54 (100%)
End of study	Yes	18 (37%)	5 (10%)	0 (0%)
	No	31 (63%)	44 (90%)	49 (100%)

Sponsor's Table 4.4.1, Module 5, Vol 97, pg 240

Sponsor's Conclusions:
Using Lanreotide acetate with 4-weeks interval, GH hypersecretion was controlled in 85% of patients, while 41% achieved age-adjusted IGF-1 normalization. This hormonal control was correlated with significant improvement of acromegaly symptoms throughout the study.

Normalization of IGF-1 levels was correlated with a strong decrease of basal GH levels from 6.2 ± 8.4 ng/mL to 1.5 ± 2.1 ng/mL after 48 weeks of treatment. At the end of the study, GH levels were below 2.5 ng/mL in 85% of patients and below 1 ng/mL in 45% of patients.

At the end of treatment, 24/63 (38%) patients had both normal IGF-1 levels and a GH level of less than or equal to 2.5 ng/mL and 17/63 patients (27%) had both normal IGF-1 levels and a GH level of less than 1 ng/mL.

In the case of three patients, one or more severe AE led to study drug discontinuation and of these three, two were withdrawn from the study (due to severe AEs of thrombophlebitis in one, and severe abdominal pain and diarrhea in the other). The most common side effects of lanreotide acetate were gastrointestinal, including diarrhea in 57% of patients.

Other common AEs were liver and biliary system disorders (25%), musculoskeletal system disorders (24%), or general disorders (24%). Adverse events recorded in the liver and biliary system disorders body system included cholelithiasis [N=10, 16%] and gallbladder disorders [N=6, 10%].

Gallbladder ultrasonography revealed that eight out of 47 (17%) patients developed gallstones during treatment and four (9%) developed biliary sludge. (The sponsor has included the ten patients who had gallstones at baseline and end-of-study into the denominator.)

In the majority of patients, laboratory abnormalities recorded post-treatment were also present at baseline. Clinically significant abnormal values of glucose were observed in 21 patients (33%) at baseline and increased to 25 (40%) at study end. Adverse events relating to glycoregulation were reported for four patients; one patient had diabetes aggravated, one had diabetes mellitus and two had hypoglycemia.

In conclusion, this clinical study (E-54-52030-081) showed that long term treatment with Lanreotide Acetate is effective in controlling GH and IGF-1 levels and acromegaly symptoms and is well tolerated in acromegalic patients treated every 4 weeks.

Medical Officer's Conclusions:

There were 38 males (60%) and 25 females (40%) aged from 30 to 77 years. The time since diagnosis ranged from 0.2 to 33.3 months. At inclusion, 22 out of 63 patients (35%) had GH $\leq$2.5 ng/mL, while 7 patients (11%) had GH $\leq$1ng/mL.

Of the 63 eligible patients who entered the treatment phase of the trial, 57 completed the 48-week treatment period. Six patients withdrew prematurely; three due to AE (#0302, #1502, #0608), one due to lack of efficacy (#0403), and two for other reasons (missing injections from Week 10 to 12 for patient #0104 and important time difference between injections for patient #0201). Pt #0608 was counted by the sponsor as withdrew secondary to withdrawal of consent but review of the narrative shows that the patient withdrew secondary to injection site pain.

At the end of treatment, 24/63 (38%) patients had both normal IGF-1 levels and a GH level of less than or equal to 2.5 ng/mL and 17/63 patients (27%) had both normal IGF-1 levels and a GH level of less than 1 ng/mL (using last available data). This hormonal control correlated with an improvement of acromegaly symptoms throughout the study.

The most common side effects of lanreotide acetate were gastrointestinal (48 [76%] patients), including diarrhea in 36 (57%) of patients. Abdominal pain occurred in 17 (27%), nausea in 4 (6%), constipation in 3 (5%), GE reflux in 3 (5%), and vomiting in 1 (2%).

Liver and biliary system disorders occurred in 16 (25%) of patients and included cholelithiasis [N=10, 16%], this included the 8 patients with a new gallstone at end of study and the 2 patients with a gallstone at Visit 6 which was not present at Visit 8, and gallbladder disorders (sludge) [N=6, 10%]). Of the 47 patients who had gallbladder ultrasonography performed at both Visit 1 and at the end of the study, four (9%) had developed sludge at the last evaluation. Of the patients who did not have gallstones at baseline, eight out of 37 (22%) had a new gallstone at the last evaluation and 10/37 (27%) developed new gallstones at any time during the study.

Other common AEs were musculoskeletal system disorders (N=15, 24%), including cramps in 4 (6%); general disorders (N=14, 22%), including lumbar pain in 3 (5%); respiratory system disorders (N=12, 19%), including bronchitis in 3 (5%) and rhinitis in 3 (5%); urinary system disorders (N=8, 13%), including UTI in 3 (5%); metabolic disorders (N=7, 11%), including hypoglycemia in 2 (3%), weight decrease in 2 (3%), DM in 1 (2%) and aggravated DM in 1 (2%); and application site disorders (N=6, 10%), including injection site pain in 4 (6%) and injection site mass in 2 (3%).

Clinically significant abnormal values of glucose were observed in 21 patients (33%) at baseline and increased to 25 (40%) at study end. Adverse events relating to glycoregulation were reported for four patients; one patient had diabetes aggravated, one had diabetes mellitus and two had hypoglycemia.

10.1.3 Study Title: A multicenter prospective controlled observer blinded cohort study in patients with acromegaly to evaluate the risk of cardiac valvular regurgitation in patients treated with lanreotide relative to patients treated with octreotide

Study Number: 2-47-52030-721

Investigators: 33 investigators enrolled patients in this study: AM Colao (Principal Investigator),

Study center(s): 33 study centers enrolled patients in this study: three in Belgium, two in the Czech Republic, one in Denmark, seven in France, two in Hungary, six in Italy, three in Spain, three in Sweden, one in Poland and five in the United Kingdom.

Study period: 05 May 2003 to 18 February 2005

Phase of Development: IV (drug is marketed in Europe)

Publications Based on the Study: none

Primary Objectives:
The primary study objective was to determine the risk of new or worsening valvular regurgitation in any valve (mitral, aortic, tricuspid or pulmonic) in patients with acromegaly treated with lanreotide, relative to patients treated with octreotide. The presence of new or worsening valvular regurgitation was assessed by comparing echocardiographic evaluations at 12 months with those performed at baseline.

This study was performed to investigate valvular regurgitation in patients treated with lanreotide, in response to clinical studies with lanreotide microparticle formulation 30 mg, in which several abnormalities of heart valves were reported as adverse events.

Secondary Objectives:
1. To investigate the association of the following potential risk factors with the existence of new or worsening valvular regurgitation:
   - severity and control of disease (as assessed by insulin-like growth factor [IGF-1] and growth hormone [GH])
   - duration of treatment
   - smoking
   - use of dopamine agonists
   - surgery/radiotherapy
   - history of hypertension
   - cardiovascular disease history
   - use of anorexigens

2. To determine the risk of significant valvular regurgitation of the mitral valve in patients with acromegaly treated with lanreotide, relative to patients treated with octreotide.
3. To determine the risk of significant valvular regurgitation of the aortic valve in patients with acromegaly treated with lanreotide relative to patients treated with octreotide.
4. To investigate the incidence of new or worsening valvular regurgitation in individual valves (mitral, aortic, tricuspid, pulmonic).
5. To determine the risk of new or worsening valvular regurgitation in any valve at 6 months compared to baseline.
6. To determine the prevalence of valvular regurgitation at baseline in patients with acromegaly in the overall population and in the subgroups of pre-treated patients (overall, and for lanreotide and octreotide) and *de novo* patients.

Design:
This study was a multicenter, prospective controlled, observer blinded, cohort study.
The index cohort consisted of patients who were receiving treatment with lanreotide and *de novo* patients who were commencing treatment with lanreotide. The matched reference cohort consisted of patients who were already receiving treatment with octreotide and *de novo* patients who were commencing treatment with octreotide. In the absence of a placebo control no inferences are possible regarding a causal role of somatostatin analogues as a class in any of the observed valvular changes.

Patients continued, or commenced treatment with either lanreotide or octreotide as prescribed as part of their normal care by their physician; therefore, the study was not randomized. Patients and Investigators were not blinded.

All eligible patients were invited to participate in the study. After recruitment (at Visit 1) an attempt was made to match each patient with a member of the opposite cohort. If no matching patient was available, the patient became a member of the unmatched index or reference cohort patient pool. Patients in the unmatched patient pool were eligible to be matched to subsequent patients in the opposite cohort. If a match was found both patients were asked to return for baseline Echocardiography (Visit 2). *De novo* patients completed all visits according to the protocol, even if no match was found.

Patients were matched on gender, age (±5 years) and center. For patients who had been in the unmatched pools for at least 24 hours, the calliper approach to matching was used and the criteria were widened from the centre to the country level. If, after a further 24 hours, a match still had not been found the criteria were widened from the country to the study level. If more than one potential match was available, the closest match in age to the new patient was selected. In the case of age ties, the patient recruited first was selected.

Patient Population:
The study population comprised patients aged 18 or over, who were diagnosed with acromegaly and were being treated with either lanreotide or octreotide in any dose form at the selection visit, or were *de novo* patients (patients who had never received treatment with somatostatin analogues) who were due to commence treatment within 2 weeks of the baseline visit.

Inclusion criteria summary:
a) Had a diagnosis of acromegaly in the opinion of the Investigator.
b) Were being treated with either lanreotide or octreotide in any dose form at the selection visit or were *de novo* patients (patients who had never received treatment with somatostatin analogues) who were due to commence treatment within 2 weeks of the baseline visit.
c) Could not change treatment from lanreotide to octreotide or from octreotide to lanreotide for the duration of the study.
d) Started treatment with either lanreotide or octreotide while both products were available on the market within their country.

Exclusion criteria summary:
a) Patients with known significant valve abnormalities prior to treatment with either lanreotide or octreotide.
b) Patients in the lanreotide cohort who had previously received treatment with octreotide for more than 3 months.
c) Patients in the octreotide cohort who had previously received treatment with lanreotide for more than 3 months.
d) Patients who had received treatment with a somatostatin analogue other than lanreotide or octreotide for more than 3 months.
e) Patients who had received treatment with a GH antagonist for more than 3 months.

f) Patients could not be initiated on treatment with dopamine agonists during the study.
g) Patients who had undergone heart valve replacement surgery.

Treatment Groups:
Treatment group:
This group comprises both patients who were receiving treatment with lanreotide at the time of recruitment and *de novo* patients who were commencing treatment with lanreotide. Lanreotide Microparticle Formulation [redacted]) or Somatuline Acetate®, was administered per prescription by primary physician.

Active Control Group:
The control group, comprising both patients who were receiving treatment with octreotide at the time of recruitment and *de novo* patients who were commencing treatment with octreotide, was chosen to provide information on the development of heart valve regurgitation in acromegalic patients receiving a treatment with similar pharmacology to lanreotide. Sandostatin® or Sandostatin LAR® or Longastatina® or Longastatina LAR® was administered per prescription by a primary physician.

Duration of Treatment: 12 months

Endpoints:
Primary endpoint
The primary endpoint was the odds ratio approximation for the relative risk of new or worsening valvular regurgitation in any valve (mitral, aortic, tricuspid, and pulmonic) of lanreotide in comparison to octreotide at 12 months (Visit 4).

Secondary endpoints
The secondary endpoints were:
• The odds ratio approximation for the relative risk of new or worsening valvular regurgitation in any valve (mitral, aortic, tricuspid, pulmonic) of lanreotide in comparison to octreotide at 6 months (Visit 3).
• The odds ratio approximation for the relative risk of new or worsening valvular regurgitation in each of the four valves of lanreotide in comparison to octreotide at both 6 months (Visit 3) and 12 months (Visit 4).
• The odds ratio approximation for the relative risk of significant valvular regurgitation in each of the four valves of lanreotide in comparison to octreotide at both 6 months (Visit 3) and 12 months (Visit 4).
• The prevalence of valvular regurgitation at baseline in patients with acromegaly in the overall population and in the sub-groups of pre-treated patients (overall, and for lanreotide and octreotide) and *de novo* patients.
• GH levels at baseline (Visit 2), 6 months (Visit 3) and 12 months (Visit 4).
• IGF-1 levels at baseline (Visit 2), 6 months (Visit 3) and 12 months (Visit 4).

Exploratory endpoints

Growth hormone and IGF-1 values at 6 months and 12 months were summarized by new or worsening valvular regurgitation and significant valvular regurgitation.

Statistical Analyses:
The primary analysis was designed to detect a relative risk of 2 with greater than 90% power at the 5% significance level assuming an incidence of new or worsening valvular regurgitation of 25% in the octreotide cohort after 12 months. Accordingly, 100 patients per cohort were planned to be recruited, to allow for the completion of 77 patients in each cohort. The primary population for analysis included the pairs of matched patients who were assessed for valvular regurgitation by echocardiography.

An odds ratio approximation for the relative risk of new or worsening valvular regurgitation in any valve (identified by comparing the Month 12 echocardiogram with the echocardiogram at the start of the prospective phase) was estimated using unconditional logistic regression. The risk was adjusted for potential confounders by including terms for factors that are associated with the primary outcome.

There were six analysis populations: the Intention-to-treat (ITT), the ITT matched, the Per protocol (PP), the PP matched, the PP complete cases and the Safety population. The primary analysis was performed on the ITT matched population, which comprised all patients in the ITT population (i.e. recruited patients with either an evaluable assessment of valvular regurgitation at two or more time points on the same valve or an assessment of 'None' or 'Severe' valvular regurgitation at one post-baseline time point) who had a 'match' where both the patient and their match were included in the ITT population.

Table 10.1.3.1 Analysis Populations

Population	Lanreotide			Octreotide		
	De Novo N=13	Pre-treated N=94	Total N=107	*De Novo* N=17	Pre-treated N=101	Total N=118
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Safety	13 (100%)	94 (100%)	107 (100%)	17 (100%)	101 (100%)	118 (100%)
ITT	12 (92%)	84 (89%)	96 (90%)	13 (76%)	87 (86%)	100 (85%)
ITT matched	10 (77%)	72 (77%)	82 (77%)	10 (59%)	72 (71%)	82 (69%)
PP	8 (62%)	72 (77%)	80 (75%)	11 (65%)	71 (70%)	82 (69%)
PP matched	7 (54%)	54 (57%)	61 (57%)	7 (41%)	54 (53%)	61 (52%)
PP complete cases	5 (38%)	40 (43%)	45 (42%)	8 (47%)	34 (34%)	42 (36%)

ITT=intention-to-treat; PP=per protocol
Source: Sponsor Table 14.1.1.2

Protocol Amendments:
There were two protocol amendments implemented during this study.

Amendment 1, 01 May 2003
Changes were implemented to modify visit schedule for '*de novo*' patients so that their baseline assessments (including echocardiography) were performed before they commenced treatment with somatostatin analogue, to modify the matching procedure so that '*de novo*' patients were matched separately to 'pretreated' patients, to allow matching at the study level, and to add a

new secondary endpoint. A secondary analysis was planned to determine the prevalence of valvular regurgitation at baseline in patients with acromegaly in the overall population and in the subgroups of pre-treated patients (overall and for lanreotide and octreotide) and *de novo* patients.

Amendment 2, 07 November 2003
The following change was implemented in order to avoid unmatched patients waiting 6 weeks before they could be matched at the study level:

> The matching process timeline was shortened so that for patients who had been in the unmatched pools for at least 24 hours, rather than for at least 4 weeks, the calliper approach to matching was to be used and the criteria were widened from the center to the country level. If after a further 24 hours, rather than a further 2 weeks, a match still had not been found the criteria were widened from the country to the study level.

This change was made in recognition of the fact that approximately 60% of the first 106 matched patients were matched at the study level.

Changes in the Planned Analyses
• The definition of the ITT population was amended. It was originally planned to include all patients who were assessed by echocardiography, however, the definition was amended to include all patients evaluable for echocardiography at baseline.
• Missing post-baseline valvular regurgitation data was planned to be defaulted to 'new/worsening regurgitation', however this was amended during the study (before database lock and prior to sign-off of the RAP). The sponsor states that the handling of non-evaluable data had a large impact on the study results and could bias the interpretation of the study.

Post Hoc Changes:
The following changes to the planned analyses were made in an addendum to the RAP, dated 28 September 2005, which was after the database lock (26 June 2005). This addendum was made because following review of the planned analyses, the sponsor thought that further analysis of significant regurgitation data and additional analyses of IGF-1 data were warranted.
• The sensitivity analysis defined in the RAP for significant regurgitation was revisited. Any subject who had a significant regurgitation at baseline was excluded from this analysis to assess the impact of valves that were already significant at baseline. For example, a subject who had mild aortic valve regurgitation at baseline and mild aortic valve regurgitation at Month 12 was not counted as having a significant regurgitation and was removed from this sensitivity analysis. This analysis was performed on a per-valve basis. This sensitivity analysis was also performed for 'any valve'. For the 'any valve' analyses, patients with significant regurgitation in all valves at baseline were excluded. If a patient became unmatched due to the exclusion of its pair, they remained in the sensitivity analysis.
• The sponsor thought that IGF-1 data could be skewed. There were large outliers at the top end of the scale for both treatment groups and differences were noted between the means and the medians for each visit within treatment group. Initially a test for normality was performed. This indicated that the IGF-1 data were not normal, therefore, the IGF-1 data were log-transformed to normalize the data.

The following *post-hoc* analyses were performed on IGF-1 data:

• Log-transformed IGF-1 levels were summarized by visit and a one sample t-test used to test for the within-treatment differences for 6 and 12 months.
• A new table was produced to show a simple analysis of covariance (ANCOVA) for the 6 and 12 month IGF-1 results of 'Change from Baseline = Baseline + Treatment'. The adjusted means, 95% CI and p-values were presented. The log-transformed IGF-1 levels were used and the back-transformed least square means presented along with the back-transformed treatment group difference (expressed as a ratio) + 95% CI.
• The IGF-1 data were classified into three categories (as defined in the RAP): 'low', 'normal' and 'high' and a shift table was created for the baseline versus Month 6 and 12 IGF-1 results.
• A table was produced to look at the proportion of patients who were in the 'low' or 'normal' group versus those in the 'high' group. A Fisher's Exact test was used to analyze differences between the lanreotide and octreotide cohorts. The difference in the proportions was presented with the corresponding 95% CI. This analysis was performed at baseline, Month 6 and Month 12. This table was also produced excluding patients who had a low or normal IGF-1 level at baseline. This analysis was performed at Month 6 and Month 12.

Results:

Patient Demographics

Review of demographic data for the overall study population indicated that slightly more patients were female (53%) than male (47%) and most patients (98%) were Caucasian. Patients ranged in age from 24 to 79 years and had a mean (SD) age of 50.3 (12.5) years. Mean (SD) height was 170.4 (11.1) cm and mean (SD) weight was 83.1 (17.3) kg.

The mean (SD) time since diagnosis of acromegaly was 5.7 (6.2) years for lanreotide-treated patients and 5.6 (6.7) years for octreotide-treated patients. A slightly lower proportion of lanreotide-treated patients (64%) had previous pituitary surgery than octreotide-treated patients (71%), although the mean (SD) time since surgery was similar (5.9 [6.3] years in the lanreotide cohort and 5.6 [6.4] years in the octreotide cohort). A similar proportion of patients in each cohort had previous radiation therapy for acromegaly (33% in the lanreotide cohort and 31% in the octreotide cohort). The mean (SD) time since radiation therapy was 3.9 (5.6) years in the lanreotide cohort and 3.9 (6.8) years in the octreotide cohort. For *de novo* patients, three of 12 patients in the lanreotide cohort and three of 13 patients in the octreotide cohort had severe acromegaly. The remaining patients had mild or moderate acromegaly. For pre-treated patients, acromegaly was considered to be controlled for 45% and 39% of patients, respectively, in the lanreotide and octreotide cohorts.

Overall, 59% of patients recruited were matched at the gender, age and study level, 16% were matched at the gender, age and country level and a further 16% were matched at the gender, age and center level. Only 21 patients (9%) were not matched.

In total, 48 lanreotide-treated patients (50%) and 40 octreotide-treated patients (40%) had a medical history (past or active) of cardiovascular disease. The number of patients with a history of regurgitation in each heart valve (tricuspid, pulmonic, mitral and aortic) was greater in the

lanreotide cohort (five, one, 12 and one patient, respectively) than in the octreotide cohort (two, none, three and one patient, respectively). None of the patients had severe regurgitation at baseline. Mild or moderate mitral valve regurgitation was present for more patients in the lanreotide cohort (21%) than the octreotide cohort (12%).

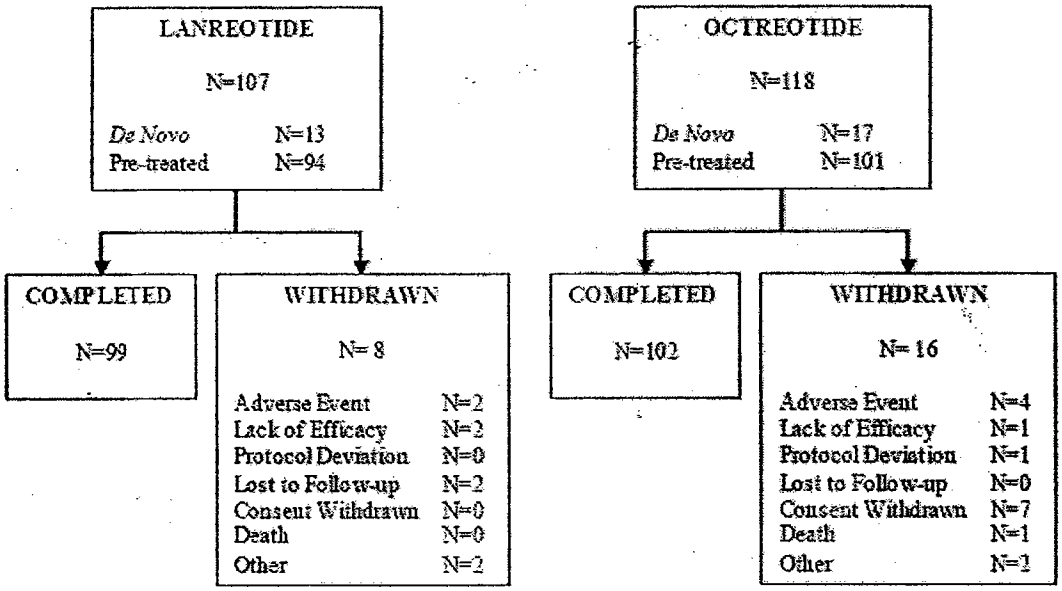
The incidence of other cardiac diseases was generally comparable between cohorts. Co-existing hypertension was present in 33% of patients in the lanreotide cohort and in 25% of the octreotide cohort. Six (6%) lanreotide-treated patients had a history of bradycardia compared with no octreotide-treated patients.

Patient Disposition

A total of 267 patients were identified to participate to the study. Forty-two patients were screen failures. Among these 42 patients, 25 patients did not enter the study because no matches were found for them. Of the 225 patients recruited into the study, 196 patients met the criteria for inclusion in the ITT population, i.e. had an echocardiography assessment that was evaluable for determining the presence or absence of valvular regurgitation at two or more time points on the same valve, or an assessment of 'None' or 'Severe' for valvular regurgitation at one post-baseline time point. Of these 196 patients, 96 were in the lanreotide cohort and 100 were in the octreotide cohort. A total of 25 *de novo* patients were included in the ITT population: 12 in the lanreotide group and 13 in the octreotide group. All 196 patients in the ITT population remained in the study after 6 months; however, nine patients had dropped out by 12 months (5 in the lanreotide cohort and four in the octreotide cohort).

Of the 196 patients included in the ITT population, Italy contributed the highest proportion of patients in the study (26%), followed by France (19%), the Czech Republic (15%) and the United Kingdom (12%).

Figure 10.1.3.1 Patient Disposition (All Patients Recruited)



Source: Sponsor Tables 14.1.1.2 and 14.1.5

Treatment Compliance
No formal assessment of treatment compliance was performed as part of this study.

Concomitant Medication Use
Review of medications received by Anatomic Therapeutic Class indicated that a higher proportion of lanreotide-treated patients (37%) were receiving cardiovascular medications prior to and during the study than octreotide-treated patients (27%). There was a slightly higher incidence of cardiovascular disease in the lanreotide cohort at baseline. A slightly higher proportion of lanreotide-treated patients (23%) than octreotide-treated patients (14%) were receiving nervous system medications prior to the study that were continued during the study. Review of the proportion of patients in each cohort that started medications during the study did not reveal any notable differences within each drug class, with the exception of systemic hormonal preparations (excluding sex hormones) which were started by 10% of octreotide-treated patients but only 2% of lanreotide-treated patients.

Efficacy Outcomes (Secondary and Exploratory Endpoints)
No formal efficacy analyses were performed.

Exploratory analyses of GH and IGF-1 levels were assessed at baseline, Month 6 and Month 12. In the lanreotide cohort, median GH levels at baseline were 2.1 ng/mL, with median reductions from baseline of 0.2 ng/mL at both Months 6 and 12. Median GH levels were similar in the octreotide cohort, with a baseline level of 2.0 ng/mL and median reductions of 0.1 and 0.2 ng/mL at Months 6 and 12, respectively. Mean GH levels were higher in the octreotide cohort than in the lanreotide cohort at each time point, but showed a larger degree of inter-patient variation and much higher maximum values, indicating outlying values.

Table 10.1.3.2. Growth Hormone Levels (ng/mL) by Visit (ITT Matched Population)

Visit		Lanreotide N=81		Octreotide N=82	
		Actual Value (ng/mL)	Change from Baseline (ng/mL)	Actual Value (ng/mL)	Change from Baseline (ng/mL)
Baseline	N	74	–	72	–
	Mean (SD)	4.1 (5.6)	–	5.1 (11.2)	–
	Median	2.1	–	2.0	–
	Range	0.2 – 25.6	–	0.3 – 90.1	–
Month 6	N	75	73	68	68
	Mean (SD)	2.7 (4.0)	-1.4 (4.0)	6.1 (16.7)	0.8 (16.1)
	Median	1.6	-0.2	2.0	-0.1
	Range	0.2 – 29.4	-22.5 – 3.8	0.2 – 133.3	-69.3 –107.9
Month 12	N	64	62	61	61
	Mean (SD)	3.3 (5.1)	-0.8 (4.4)	6.1 (23.6)	1.0 (22.0)
	Median	1.8	-0.2	1.3	-0.2
	Range	0.1 – 33.6	-21.0 – 8.6	0.0 – 183.0	-62.5 –157.6

Source: Sponsor's Table 14.2.1.1
SD=standard deviation

In the sponsor's exploratory analyses, GH and IGF-1 levels were summarized for patients with or without 'new or worsening' or 'significant' valvular regurgitation. The 95% CI for the difference did not suggest any statistically significant difference in mean GH or IGF-1 levels at Months 6 or 12 for patients with or without regurgitation, for lanreotide- or for octreotide-treated patients.

Mean and median IGF-1 levels were generally similar for patients in both cohorts at baseline and at Months 6 and 12. In the lanreotide cohort median IGF-1 levels at baseline were 260 ng/mL, with median reductions of 28 ng/mL and 45 ng/mL at Months 6 and 12, respectively. In the octreotide cohort, a median baseline IGF-1 level of 249 ng/mL was noted with median reductions of 14 ng/mL and 25 ng/mL at Months 6 and 12, respectively.

Table 10.1.3.3 IGF-1 Levels (ng/mL) by Visit (ITT Matched Population)

Visit		Lanreotide N=82		Octreotide N=82	
		Actual Value (ng/mL)	Change from Baseline (ng/mL)	Actual Value (ng/mL)	Change from Baseline (ng/mL)
Baseline	N	82	–	82	–
	Mean (SD)	331 (229)	–	318 (196)	–
	Median	260	–	249	–
	Range	78 – 1026	–	65 – 1027	–
Month 6	N	82	82	82	82
	Mean (SD)	272 (150)	-59 (131)	288 (165)	-30 (193)
	Median	242	-38	235	-14
	Range	64 – 823	-696 – 134	91 – 800	-321 – 208
Month 12	N	79	79	80	80
	Mean (SD)	244 (146)	-91 (136)	262 (155)	-52 (128)
	Median	193	-45	234	-25
	Range	52 – 676	-649 – 247	73 – 967	-516 – 245

Source: Sponsor's Table 14.2.3.1
SD=standard deviation

Following review of the IGF-1 data *post-hoc* analyses were performed. Log-transformation was performed as the data were thought to be skewed. Geometric mean IGF-1 levels at 6 and 12 months were lower than at baseline for both cohorts, however, analyses indicated that results were statistically significantly different from baseline at Months 6 and 12 for the lanreotide cohort and at Month 12 only for the octreotide cohort (ITT matched population).

The proportion of patients with low or normal IGF-1 results at baseline, 6 months or 12 months was 61%, 63% and 71%, respectively, in the lanreotide cohort and 55%, 65% and 67%, respectively, in the octreotide cohort (ITT matched population). There were no statistically significant differences between the groups in the proportion of patients with low or normal IGF-1 levels at any time point. Of the 32 patients in the lanreotide cohort who had high IGF-1 levels at baseline and had post-baseline IGF-1 results, seven (22%) and 12 (38%) patients had low or normal IGF-1 results at 6 months and 12 months, respectively. For the 37 octreotide-treated patients with high IGF-1 levels at baseline who had post-baseline IGF-1 results, 11 (30%) and 16 (46%) had low or normal IGF-1 results at 6 months and 12 months, respectively.

Safety Data:
The incidence of treatment emergent adverse events was higher in the lanreotide group (52% and 45% in the lanreotide and octreotide cohorts, respectively); while serious adverse events (6% and 8%, respectively) and adverse events leading to withdrawal (2% and 4%, respectively) was lower in the lanreotide cohort as compared to the octreotide cohort. The majority of adverse events were mild or moderate in severity. The most common adverse events at the system organ class level were gastrointestinal disorders, which were reported by 20% and 8% of lanreotide- and octreotide-treated patients, respectively. The most frequently reported adverse event (by preferred term) was diarrhea, which was reported by 13% of patients in the lanreotide group and by 2% of patients in the octreotide group. The incidence of GI disorders was 2.5 times higher and the incidence of diarrhea was 6.5 times higher in the lanreotide cohort as compared to the octreotide cohort in this study. The other most common adverse events were headache and

hypertension, cholelithiasis and abdominal pain. These events were reported by less than 5% of patients in the overall population and were reported at a similar incidence in each treatment group.

Table 10.1.3.4 Summary of Treatment Emergent Adverse Events (Safety Population)

No of patients with:	Lanreotide N=107	Octreotide N=118	Total N=225
	n (%)	n (%)	n (%)
Any adverse event	56 (52%)	53 (45%)	109 (48%)
Any serious adverse event	6 (6%)	9 (8%)	15 (7%)
Any treatment related adverse event	21 (20%)	12 (10%)	33 (15%)
Any adverse events leading to withdrawal[a]	2 (2%)	5 (4%)	7 (3%)
Adverse event leading to death	0	1 (<1%)	1 (<1%)

Source: Sponsor's Tables 14.1.5 and 14.3.1.1 to 14.3.1.4

Deaths

One death was reported on-treatment during the study. Patient 7030004, a 47-year-old female in the octreotide cohort, died of cardiorespiratory arrest 70 days after experiencing severe cranial trauma and multiple fractures following a road traffic accident. Following hospitalization for this event, the patient was found to have a malignant astrocytoma. None of these events were considered to be related to treatment with study medication.

Serious Adverse Events

A total of 20 serious adverse events were experienced by 15 patients during the study. Six patients experienced six serious adverse events in the lanreotide cohort and nine patients experienced 14 serious adverse events in the octreotide cohort. In the lanreotide cohort, two patients had events (colitis and aortic aneurysm, respectively), that were considered possibly related to treatment by the investigator and in the octreotide one patient had an event (biliary colic) that was considered possibly related to treatment by the investigator. Study medication was continued in all three cases and all three patients recovered without sequelae.

Table 10.1.3.5 Serious Adverse Events (Safety Population)

Cohort/ Patient	Age/Sex	Start Day	AE preferred term (verbatim term)	Relationship	Action taken with study drug	Withdrawn from study?	Outcome
Lanreotide							
4010004	42/Female	231	Colitis (Colitis)	Possible	Continued	No	Recovered without sequelae
4070002	60/Male	1	Aortic aneurysm (Aortic aneurysm)	Possible	Continued	No	Recovered without sequelae
6010001	50/Male	145	Neoplasm recurrence (Tumoral recidive)	Not related	Continued	No	Not yet recovered
6010006	32/Female	—	Pregnancy (Pregnancy)	Not related	Discontinued	Yes	—
7010001	35/Female	347	Pregnancy (Pregnancy)	Not related	Discontinued	Yes	Not yet recovered[a]
8040001	46/Female	176	Pyelonephritis (Suspect pyelonephritis)	Not related	Continued	No	Recovered with sequelae
Octreotide							
0020004	72/Female	192	Optic nerve infarction (Infarction in nervus opticus)	Not related	Continued	No	Not yet recovered
		280	Optic nerve infarction (Infarction in nervus opticus)	Not related	Discontinued	Yes	Not yet recovered
4050003	66/Female	155	Asthma (Acute asthma episode)	Not related	Continued	No	Recovered without sequelae
4070003	44/Male	104	Hypotension (Hypotension)	Not related	Continued	No	Recovered without sequelae
		108	Malaise (Malaise)	Not related	Continued	No	Recovered without sequelae
7010026	66/Female	156	Myocardial infarction (Inferior myocardial infarction)	Not related	Continued	Yes	Recovered without sequelae
7030004	47/Female	39	Multiple fractures (Multiple fractures of upper extremity and pelvis right and left arms)	Not related	Discontinued	Yes	Not yet recovered
		39	Traumatic intracranial haemorrhage (Traumatic intracranial haemorrhage)	Not related	Discontinued	Yes	Not yet recovered
		—	Astrocytoma malignant (Malignant astrocytoma)	Not related	Discontinued	Yes	Not yet recovered
		109	Cardio-respiratory arrest (Cardiac respiratory arrest)	Not related	Discontinued	Yes	Fatal
7080003	41/Female	—	Pregnancy (Pregnancy)	Not related	Continued	No	Recovered without sequelae
8010002	72/Female	—	Biliary colic (Biliary colic)	Possible	Continued	No	Recovered without sequelae
9010003	62/Female	174	Colon cancer (Carcinoma of the sigmoid)	Not related	Continued	Yes	Not yet recovered
9010006	71/Male	142	Pituitary tumour benign (surgery for pituitary adenoma)	Not related	Discontinued	Yes	Recovered without sequelae

Source: Sponsor Table 24, Vol 75, pg 76
[a]Follow-up information provided after database lock indicated that Patient 7010001 had a normal pregnancy and birth.

Adverse Events that Led to study Withdrawal
All adverse events leading to treatment withdrawal were serious.

Table 10.1.3.6: Number (%) of Treatment Emergent AEs Associated with Withdrawal (Safety Population)

BODY SYSTEM/ PREFERRED TERM	LANREOTIDE	OCTREOTIDE	TOTAL
NO. OF PATIENTS	107	118	225
NO. OF PATIENTS WITH A TREATMENT EMERGENT AE ASSOCIATED WITH WITHDRAWAL	2 (2%)	5 (4%)	7 (3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	3 (3%)	3 (1%)
ASTROCYTOMA MALIGNANT	0	1 (<1%)	1 (<1%)
COLON CANCER	0	1 (<1%)	1 (<1%)
PITUITARY TUMOUR BENIGN	0	1 (<1%)	1 (<1%)
CARDIAC DISORDERS	0	2 (2%)	2 (<1%)
CARDIO-RESPIRATORY ARREST	0	1 (<1%)	1 (<1%)
MYOCARDIAL INFARCTION	0	1 (<1%)	1 (<1%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	2 (2%)	0	2 (<1%)
PREGNANCY	2 (2%)	0	2 (<1%)
EYE DISORDERS	0	1 (<1%)	1 (<1%)
OPTIC NERVE INFARCTION	0	1 (<1%)	1 (<1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (<1%)	1 (<1%)
MULTIPLE FRACTURES	0	1 (<1%)	1 (<1%)
TRAUMATIC INTRACRANIAL HAEMORRHAGE	0	1 (<1%)	1 (<1%)

An adverse event is considered 'associated with withdrawal' if the patient has withdrawn due to an adverse event and the number of that adverse event has been recorded on the End of Study page of the CRF.
The denominator for the percentages is the number of patients in the Safety population 'N' within each column.
Adverse events have been coded using the MedDRA dictionary.

Sponsor's Table 14.3.1.4, Vol 75

Treatment Emergent Adverse Events

Table 10.1.3.7 Most Commonly Reported Treatment-Emergent Adverse Events by Body System/Preferred Term in Study 721 (Safety Population)

Body System/Preferred Term	Lanreotide (N=107) n (%)	Octreotide (N=118) n (%)	Total (N=225) n (%)
Gastrointestinal System Disorders	**20 (19%)**	**10 (8%)**	**30 (13%)**
Diarrhea	14 (13%)	2 (2%)	16 (7%)
Abdominal pain	2 (2%)	4 (3%)	6 (3%)
Abd pain upper	2 (2%)	2 (2%)	4 (2%)
Nausea	2 (2%)	2 (2%)	4 (4%)
Hepatobiliary Disorders	**3 (3%)**	**4 (3%)**	**7 (3%)**
Cholelithiasis	3 (3%)	4 (3%)	7 (3%)
Biliary colic	0	1 (<1%)	1 (<1%)
Musculoskeletal & Connective Tissue	**5 (5%)**	**4 (3%)**	**9 (4%)**
Arthralgia	2 (2%)	2 (2%)	4 (2%)
General Disorders and Admin Site Conditions	**5 (5%)**	**6 (5%)**	**11 (5%)**
Fatigue	2 (2%)	2 (2%)	4 (2%)
Injection Site Rxn	1 (<1%)	0	1 (<1%)
Respiratory System Disorders	**3 (3%)**	**5 (4%)**	**8 (4%)**
Metabolic & Nutritional Disorders	**5 (5%)**	**4 (3%)**	**9 (4%)**
Diabetes Mellitus	1 (<1%)	1 (<1%)	2 (<1%)
DM inadequate control	1 (<1%)	0	1 (<1%)
DM Non-Insulin-Dep	1 (<1%)	0	1 (<1%)
Cardiac Disorders	**10 (9%)**	**9 (8%)**	**19 (8%)**
AV block, 1st degree	2 (2%)	3 (3%)	5 (2%)
Bradycardia	2 (2%)	0	2 (<1%)
Nervous System	**10 (9%)**	**11 (9%)**	**21 (9%)**
Headache	4 (4%)	6 (5%)	10(4%)
Dizziness	2 (2%)	1 (<1%)	3 (1%)
Anemia	1 (<1%)	1 (<1%)	2 (<1%)

The denominator for the percentages is the number of patients in the Safety Population 'N' within each column.
Dictionary = MedDRA.
Derived from Sponsor's Table 14.3.1.1.1

The most common adverse events at the system organ class level were gastrointestinal disorders, which were reported by 20% and 8% of lanreotide- and octreotide-treated patients, respectively. The most frequently reported adverse event (by preferred term) was diarrhea, which was reported by 13% of patients in the lanreotide group and by 2% of patients in the octreotide group.

Cardiac adverse events were reported by 10 patients (9%) in the lanreotide cohort and nine patients (8%) in the octreotide cohort. The most common cardiac adverse events were first degree atrioventricular block (reported by two lanreotide- and three octreotide-treated patients) and ventricular hypertrophy (reported by one lanreotide- and two octreotide-treated patients).

Table 10.1.3.8 All Cardiac Treatment Emergent Adverse Events, (Safety Population)

Body System/Preferred Term	Lanreotide (N=107) n (%)	Octreotide (N=118) n (%)	Total (N=225) n (%)
Cardiac Disorders	**10 (9%)**	**9 (8%)**	**19 (8%)**
AV block, 1st degree	2 (2%)	3 (3%)	5 (2%)
Ventricular hypertrophy	1 (<1%)	2 (2%)	3(1%)
Aortic valve incompetence	2 (2%)	0	2 (<1%)
Bradycardia	2 (2%)	0	2 (<1%)
Mitral valve incompetence	2 (2%)	0	2 (<1%)
Atrial fibrillation	1 (<1%)	0	1 (<1%)
Bundle branch block left	1 (<1%)	0	1 (<1%)
Cardiomyopathy	1 (<1%)	0	1 (<1%)
Dilatation ventricular	1 (<1%)	0	1 (<1%)
Tachycardia	1 (<1%)	0	1 (<1%)
Bundle branch block right	0	1 (<1%)	1 (<1%)
Cardio-respiratory arrest	0	1 (<1%)	1 (<1%)
Myocardial infarction	0	1 (<1%)	1 (<1%)
Palpitations	0	1 (<1%)	1 (<1%)

Laboratory Parameters
Hematology, biochemistry and urinalysis data were not collected for this study.

Vital Signs
Heart rate, blood pressure, ECG, concurrent disease and concomitant treatments were recorded at the start of the prospective phase and after 6 and 12 months of follow-up.

Of the patients with ECGs at baseline, 22 patients (22%) in the lanreotide cohort and 20 patients (18%) in the octreotide cohort had abnormalities detected. At Month 12 the incidence was 23% in the lanreotide cohort and 13% in the octreotide cohort. The most common ECG abnormalities were conduction defects such as first degree atrioventricular block, left anterior hemiblock and right bundle branch block.

Fifteen patients in each cohort developed newly occurring ECG abnormalities during the study. These were sinus bradycardia (four patients lanreotide and three patients octreotide), sinus tachycardia (three patients in each cohort), first degree AV block (two patients lanreotide and five patients octreotide), left anterior hemiblock (one patient lanreotide and two patients octreotide), complete/incomplete right bundle branch block (two patients octreotide and one lanreotide), T-wave inversion (one patient octreotide), intraventricular conduction defect (two patients lanreotide) and atrial premature complexes (one patient lanreotide).

Special Safety Studies

Echocardiograms

The primary objective of this study is to compare the 2 cohorts on risk of new or worsening valvular regurgitation in any valve in patients with acromegaly. The study was powered to detect a relative risk of 2 with 90% power at the 5% significant level assuming a 25% incidence rate in the octreotide cohort after 1 year, 100 patients per cohort would need to be recruited and 77 completers. The assessments of echocardiography readings for study 721 were performed by two independent board certified cardiologists (Dr. [redacted] with Level III echocardiography experience (minimum of 12 months and at least 1000 echocardiograms). Echocardiographic measurements were taken according to the Guidelines of the American Society of Echocardiography (Guidelines for Quantification of the Left Ventricle by Two-Dimensional Echocardiography; Schiler et al, JASE Vol. 2, No.5, pp.358-367, October 1989). Echocardiograms were read according to established standards for the interpretation of color Doppler of cardiac valve regugitation[30,31] and the standard operating procedures of the [redacted]

It is important to note that the null hypothesis cannot be proved in this trial and that failure to reject a null hypothesis does not mean that it is true. Additionally, cohort studies do not employ randomization of study patients. Therefore, this study is more vulnerable to selection bias compared to a randomized trial. This study as designed is only able to detect a marked difference in the cardiovascular adverse event profiles of the two drugs. This study will not support the cardiac safety of lanreotide, but rather will permit characterization of the valvular changes expected among patients of the type recruited during courses of therapy with lanreotide or octreotide. In the absence of a control group not treated with somatostatin analogue but otherwise matched for variables related to the underlying disease, no inferences will be possible regarding a causal role of drug in any observed valvular changes.

The presence of valvular regurgitation was assessed similarly for all patients by means of an echocardiogram performed using a standardized methodology. Echocardiograms were performed at the start of the prospective phase of the study and at 6 months and 12 months. Each echocardiogram was recorded onto individual videotapes labeled with the date the echocardiogram was performed, the investigators name, patient number, initials and date of birth. Videotapes were then forwarded to [redacted] for logging and tracking. [redacted] sent the echocardiogram videotapes to [redacted] for quality control (QC) and blinding. [redacted] then forwarded the echocardiogram videotapes to [redacted] for reading by blinded central readers. [redacted] sent completed echocardiogram CRFs to [redacted] for data entry.

Echocardiogram tapes were read according to established standards for the interpretation of color Doppler of cardiac valve regurgitation and the standard operating procedures of [redacted] Echocardiographic readings were acquired by cardiologists or echo technicians using a prospectively defined standardized method outlined in the protocol. Echocardiograms were read independently by two cardiologists ('raters') and discrepant readings were resolved by consensus. The cardiologists were blinded to the cohort group of the echocardiograms they reviewed and were also blind to the sequence of each echocardiogram (i.e. baseline, Month 6 or

Month 12). A total of 48 echocardiograms were collected from both 'normal' subjects (subjects with or without acromegaly who had no cardiovascular abnormalities) and those with severe valvular regurgitation to serve as negative and positive controls for the reading and interpretation of the echocardiograms. These were used to validate the accuracy of the central reading and were not used for the statistical analysis. These positive and negative controls were accurately read by the raters and the primary and secondary raters concurred to a high degree. Both readers concurred on 24 cases of absent cardiac valve abnormalities, 19 cases of present cardiac valve abnormalities and 5 cases of negative controls that both readers interpreted as non-evaluable.

Regurgitation, when identified, was categorized into one of the following categories:

- Not evaluable
- None
- Physiological/Trace (for the mitral, tricuspid and pulmonic valves the category 'physiologic' was used. For the aortic valve, the category 'trace' was used.
- Mild
- Moderate
- Severe

Analysis of a change in regurgitation took into account all levels of regurgitation. Any case of moderate or worse than moderate mitral valve regurgitation was classified as significant, and any aortic regurgitation graded as mild or worse than mild was classified as significant. Although there were no established significance levels for tricuspid and pulmonic regurgitation, moderate or worse tricuspid and pulmonic regurgitation were considered significant. 'Significant' regurgitation was used in the secondary analysis.

A LOCF approach was used per valve for missing or non-evaluable Month 12 data when patients had evaluable data for Month 6 (i.e. Month 6 data were carried forward for Month 12). For patients with valves that were non-evaluable at baseline, but were evaluable at both Month 6 and Month 12, the Month 6 assessment was used as a baseline for that particular valve. This procedure was not applicable to *de novo* patients

Centers/countries with small patient numbers were pooled into regions for the primary safety analyses. Sweden, Denmark and the United Kingdom were pooled to form Region 1, on the basis of their similar healthcare systems. All other centers were pooled by individual country, i.e., Belgium (Region 2), Hungary (Region 3), Czech Republic (Region 4), France (Region 5), Spain (Region 6), Italy (Region 7) and Poland (Region 8). The pooling was decided upon by the Sponsor and documented prior to database lock.

The primary safety analysis was based on the ITT matched population. The impact of excluding unmatched patients from this population was evaluated in the supportive ITT population analysis (primary endpoint only).

A summary of valvular regurgitation for all patients (*de novo* and pre-treated combined) is provided in the table below.

Table 10.1.3.9 Valvular Regurgitation Summary – All Patients (ITT Matched Population)

	Lanreotide N=82				Octreotide N=82			
	Baseline		Month 12		Baseline		Month 12	
Mitral								
Total	77	(94%)	78	(95%)	77	(94%)	80	(98%)
None	14	(17%)	27	(33%)	22	(27%)	27	(33%)
Physiologic	36	(44%)	26	(32%)	37	(45%)	35	(43%)
Mild	12	(15%)	18	(22%)	8	(10%)	9	(11%)
Moderate	5	(6%)	3	(4%)	2	(2%)	2	(2%)
Severe	0		0		0		0	
Not evaluable	10	(12%)	4	(5%)	8	(10%)	7	(9%)
Aortic								
Total	77	(94%)	78	(95%)	77	(94%)	80	(98%)
None	49	(60%)	56	(68%)	52	(63%)	55	(67%)
Trace	11	(13%)	9	(11%)	11	(13%)	10	(12%)
Mild	5	(6%)	6	(7%)	6	(7%)	8	(10%)
Moderate	3	(4%)	3	(4%)	3	(4%)	1	(1%)
Severe	0		0		0		0	
Not evaluable	9	(11%)	4	(5%)	5	(6%)	6	(7%)
Tricuspid								
Total	77	(94%)	78	(95%)	77	(94%)	80	(98%)
None	12	(15%)	13	(16%)	13	(16%)	18	(22%)
Physiologic	41	(50%)	41	(50%)	33	(40%)	36	(44%)
Mild	11	(13%)	11	(13%)	11	(13%)	10	(12%)
Moderate	2	(2%)	1	(1%)	1	(1%)	1	(1%)
Severe	0		0		0		0	
Not evaluable	11	(13%)	12	(15%)	19	(23%)	15	(18%)
Pulmonic								
Total	77	(94%)	78	(95%)	77	(94%)	80	(98%)
None	7	(9%)	10	(12%)	9	(11%)	8	(10%)
Physiologic	14	(17%)	15	(18%)	13	(16%)	12	(15%)
Mild	8	(10%)	10	(12%)	13	(16%)	14	(17%)
Moderate	2	(2%)	2	(2%)	2	(2%)	0	
Severe	0		0		0		1	(1%)
Not evaluable	46	(56%)	41	(50%)	40	(49%)	45	(55%)
Any Valve								
Total	77	(94%)	78	(95%)	77	(94%)	80	(98%)
None	6	(7%)	11	(13%)	9	(11%)	10	(12%)
Physiologic	32	(39%)	30	(37%)	33	(40%)	33	(40%)
Mild	21	(26%)	25	(30%)	22	(27%)	26	(32%)
Moderate	11	(13%)	8	(10%)	8	(10%)	4	(5%)
Severe	0		0		0		1	(1%)
Not evaluable	7	(9%)	4	(5%)	5	(6%)	6	(7%)

Source: Sponsor's Tables 14.3.4.2.1 and 14.3.4.2.6

At baseline, mild or moderate mitral valve regurgitation was present for more patients in the lanreotide cohort (21%) than the octreotide cohort (12%). At Month 12, the number of patients in the octreotide group with mild or moderate mitral valve regurgitation remained stable at 13%. At Month 12, the number of patients in the lanreotide group with mild mitral valve regurgitation

increased from 12 (15%) at baseline to 18 (22%) at Month 12; the incidence of moderate mitral valve regurgitation decreased slightly with 5 (6%) at baseline and 3 (4%) at Month 12. For aortic, tricuspid and pulmonic valve regurgitation, the number of patients with mild or greater regurgitation remained largely stable from baseline to Month 12 for both lanreotide and octreotide groups.

The number of patients in the ITT matched population with non-evaluable valvular regurgitation data was higher than expected. In the overall population, 7%, 6% and 16% had non-evaluable data for the mitral, aortic and tricuspid valves, respectively. An even higher proportion of patients had non-evaluable data for the pulmonic valve (52%), however, this was an expected finding, as the pulmonic valve is difficult to image due to its anterior position. The company was asked to justify this rate of non-evaluable valve data. They responded that similar levels of non-evaluable echocardiogram assessments were obtained in the pivotal study 717. The rates of non-evaluable echocardiograms were 17% for the mitral valve, 18% for the aortic valve, 27% for the tricuspid valve and 61% for the pulmonic valve. Therefore, the proportion of patients with evaluable echocardiography readings for study 721 is comparable to the company's previous experience in acromegalic patients. In addition, the proportion of non-evaluable echocardiography assessments is similar to other reported yields. Studies in patients under treatment with fenfluramine and other diet drugs have demonstrated a non-evaluable echocardiographic assessments yield of approximately 15% for the mitral and aortic valves.[32,33]

A summary of valvular regurgitation for only *de novo* patients is provided in the table below. This reviewer concludes that, while the number of de novo patients is small, the de novo patients do not display any clinically worrisome changes in valvular regurgitation with either lanreotide or octreotide during the course of this study.

Table 10.1.3.10 Valvular Regurgitation Summary – De Novo Patients (ITT Matched Population)

	De Novo Lanreotide N=10				De Novo Octreotide N=10			
	Baseline		Month 12		Baseline		Month 12	
Mitral								
Total	10	(100%)	10	(100%)	10	(100%)	10	(100%)
None	2	(20%)	3	(30%)	4	(40%)	4	(40%)
Physiologic	5	(50%)	4	(40%)	6	(60%)	6	(60%)
Mild	1	(10%)	2	(20%)	0		0	
Moderate	1	(10%)	0		0		0	
Severe	0		0		0		0	
Not evaluable	1	(10%)	1	(10%)	0		0	
Aortic								
Total	10	(100%)	10	(100%)	10	(100%)	10	(100%)
None	7	(70%)	6	(60%)	7	(70%)	7	(70%)
Trace	2	(20%)	2	(20%)	1	(10%)	1	(10%)
Mild	1	(10%)	1	(10%)	1	(10%)	2	(20%)
Moderate	0		0		1	(10%)	0	

Severe	0		0		0		0	
Not evaluable	0		1	(10%)	0		0	
Tricuspid								
Total	10	(100%)	10	(100%)	10	(100%)	10	(100%)
None	2	(20%)	3	(30%)	0		1	(10%)
Physiologic	4	(40%)	2	(20%)	6	(60%)	6	(60%)
Mild	2	(20%)	2	(20%)	2	(20%)	2	(20%)
Moderate	0		0		0		0	
Severe	0		0		0		0	
Not evaluable	2	(20%)	3	(30%)	2	(20%)	1	(10%)
Pulmonic								
Total	10	(100%)	10	(100%)	10	(100%)	10	(100%)
None	1	(10%)	2	(20%)	2	(20%)	3	(30%)
Physiologic	1	(10%)	2	(20%)	3	(30%)	1	(10%)
Mild	1	(10%)	1	(10%)	1	(10%)	1	(10%)
Moderate	0		0		1	(10%)	0	
Severe	0		0		0		0	
Not evaluable	7	(70%)	5	(50%)	3	(30%)	5	(50%)

The highlighted areas define the degree of valvular regurgitation that was considered significant. For the mitral, tricuspid and pulmonic valves, 'significant' valvular regurgitation was defined by the sponsor as any case that was moderate or worse than moderate and for the aortic valve it was defined as any case that was mild or worse than mild.

Primary Analyses of Valvular Regurgitation:

The primary endpoint was the odds ratio approximation for the relative risk of new or worsening valvular regurgitation in any valve (mitral, aortic, tricuspid, pulmonic) of lanreotide in comparison to octreotide at 12 months. A patient was counted as worsened if any valve worsened regardless of any improvement. A patient only counted as improved if no valves worsen and at least one improved. Table 10.1.3.11 summarizes this analysis for the ITT matched population.

Table 10.1.3.11. Analysis of New or Worsening Valvular Regurgitation in any Valve at 12 Months (ITT Matched Population)

Any valve:	Lanreotide N=82		Octreotide N=82		Statistical Analyses[a]
	N	(%)	N	(%)	
Number of evaluable patients	82		82		
New valvular regurgitation	17	(21%)	16	(20%)	
Worsening valvular regurgitation	14	(17%)	13	(16%)	
New or worsening valvular regurgitation	28	(34%)	27	(33%)	
Risk difference (95% CI)					0.01 (-0.13, 0.16)
Relative risk (95% CI)					1.04 (0.67, 1.60)
Odds ratio (95% CI)					0.86 (0.41, 1.82)
p-value for odds ratio					0.694

Source: Sponsor's Table 14.3.4.3.1.1

a. An upper confidence limit that is <1 for relative risk, odds ratio <1 or a negative risk difference indicate that lanreotide is significantly better than octreotide.

CI=confidence interval

Valve results were derived using the LOCF approach

Analysis of the primary endpoint indicated that there was no statistically significant difference between the two cohorts in the risk of developing new or worsening valvular regurgitation in any valve at 12 months (odds ratio: 0.86; 95% CI: 0.41, 1.82; p=0.694; ITT matched population). The corresponding relative risk (1.04; 95% CI: 0.67, 1.60) and the risk difference (0.01; 95% CI: -0.13, 0.16) both supported the odds ratio conclusion.

The odds ratio was adjusted for the following confounding factors: age, gender, region, severity/control of disease, history of hypertension, history of cardiovascular disease, history of smoking, previous surgery/radiation and duration of previous treatment. The adjusted odds ratio and relative risk were both close to one, with 95% CI that included one, indicating that there was no statistically significant difference between the two treatments.

These findings were supported by a 'worst case' sensitivity analysis that was performed by the sponsor to assess the effect of including data for patients with missing or not evaluable data at baseline who only had one-post baseline evaluable assessment (other than 'None'). More cases of new, worsening and new or worsening valvular regurgitation were found at 12 months using this worst case approach, however, the results of this analysis (odds ratio: 0.91 [95% CI: 0.48, 1.75]) supported the findings of the primary analysis, which showed no statistically significant difference between the two treatments. The corresponding relative risk was 0.99 (95% CI: 0.71, 1.39) and the risk difference was 0.00 (95% CI: -0.14, 0.13).

Review of the number of *de novo* and pre-treated patients with new or worsening valvular regurgitation at Month 12 did not indicate any notable differences within or between cohorts; however, the number of *de novo* patients in each cohort was too small for meaningful conclusions to be drawn (see Table 10.1.3.10)

Secondary Analyses of Valvular Regurgitation

1. Risk of New/Worsening Valvular Regurgitation in Any Valve at 6 Months

The analysis of the risk of new or worsening valvular regurgitation in any valve for lanreotide in comparison to octreotide at 6 months is summarized in Table 10.1.3.12.

Table 10.1.3.12 Analysis of New or Worsening Valvular Regurgitation in any Valve at 6 Months (ITT Matched Population)

Any valve:	Lanreotide N=82		Octreotide N=82		Statistical Analyses[a]
	N	(%)	N	(%)	
Number of evaluable patients	80		78		
New valvular regurgitation	14	(18%)	14	(18%)	
Worsening valvular regurgitation	11	(14%)	6	(8%)	
New or worsening valvular regurgitation	22	(28%)	19	(24%)	
Risk difference (95% CI)					0.03 (-0.11, 0.17)
Relative risk (95% CI)					1.13 (0.67, 1.92)
Odds ratio (95% CI)					0.97 (0.43, 2.17)
p-value for odds ratio					0.941

Source: Sponsor Table 14.3.4.3.1.1
a. An upper confidence limit that is <1 for relative risk, odds ratio <1 or a negative risk difference indicate that lanreotide is significantly better than octreotide.
CI=confidence interval
Valve results derived using the LOCF approach

These results were consistent with the analysis of the primary endpoint. The overall incidence of new or worsening valvular regurgitation was lower at 6 months than at 12 months.

2. Risk of New/Worsening Valvular Regurgitation by Valve at 6 and 12 Months
The analysis of the risk of new or worsening valvular regurgitation by valve for lanreotide in comparison to octreotide at 6 and 12 months is summarized in Table 10.1.3.13.

Table 10.1.3.13. Analysis of New or Worsening Valvular Regurgitation by Valve at 6 and 12 Months (ITT Matched Population)

	6 Months		12 Months	
	Lanreotide N=82	Octreotide N=82	Lanreotide N=82	Octreotide N=82
	N (%)	N (%)	N (%)	N (%)
Mitral Valve				
Number of evaluable patients	75	69	79	80
New/worsening regurgitation	7 (9%)	10 (14%)	11 (14%)	13 (16%)
Statistical Analyses[a]				
Risk difference (95% CI)	-0.05 (-0.16, 0.05)		-0.02 (-0.13, 0.09)	
Relative risk (95% CI)	0.64 (0.26, 1.60)		0.86 (0.41, 1.80)	
Odds ratio (95% CI)	0.62 (0.22, 1.76)		0.86 (0.34, 2.01)	
p-value for odds ratio	0.369		0.682	
Aortic Valve				
Number of evaluable patients	78	75	82	81
New/worsening regurgitation	7 (9%)	4 (5%)	7 (9%)	3 (4%)
Statistical Analyses[a]				
Risk difference (95% CI)	0.04 (-0.04, 0.12)		0.05 (-0.02, 0.12)	
Relative risk (95% CI)	1.68 (0.51, 5.51)		2.30 (0.62, 8.60)	
Odds ratio (95% CI)	1.87 (0.51, 6.80)		2.75 (0.64, 11.79)	
p-value for odds ratio	0.344		0.172	
Tricuspid Valve				
Number of evaluable patients	71	61	76	74
New/worsening regurgitation	9 (13%)	6 (10%)	8 (11%)	10 (14%)
Statistical Analyses[a]				
Risk difference (95% CI)	0.03 (-0.08, 0.14)		-0.03 (-0.13, 0.07)	
Relative risk (95% CI)	1.29 (0.49, 3.42)		0.78 (0.33, 1.86)	
Odds ratio (95% CI)	1.47 (0.48, 4.50)		0.78 (0.28, 2.14)	
p-value for odds ratio	0.498		0.625	
Pulmonic Valve				
Number of evaluable patients	38	34	45	42
New/worsening regurgitation	5 (13%)	2 (6%)	8 (18%)	5 (12%)
Statistical Analyses[a]				
Risk difference (95% CI)	0.07 (-0.06, 0.21)		0.06 (-0.09, 0.21)	
Relative risk (95% CI)	2.24 (0.46, 10.79)		1.49 (0.53, 4.20)	
Odds ratio (95% CI)	2.33 (0.40, 13.69)		1.43 (0.41, 5.05)	
p-value for odds ratio	0.348		0.575	

Source: Sponsor's Table 14.3.4.4.1.1
a. An upper confidence limit that is <1 for relative risk, odds ratio <1 or a negative risk difference indicate that lanreotide is significantly better than octreotide.
CI=confidence interval
Valve results derived using the LOCF approach

For all four heart valves, statistical analyses indicated that there was no statistically significant difference between the two treatments in the relative risk of new or worsening valvular regurgitation at 12 months. In the lanreotide cohort, the proportions of patients with new or worsening valve regurgitation were lower at 6 months than at 12 months for the mitral and pulmonic valves. In the octreotide cohort, the proportion of patients with new or worsening valve regurgitation was lower at 6 months than 12 months for the mitral, pulmonic and tricuspid valves. For both cohorts, the proportion of patients with aortic valve regurgitation at 6 months was similar to that at 12 months.

The 'each valve' odds ratio analysis was adjusted for the following confounding factors: age, previous surgery/radiation and duration of previous treatment.

3. Significant Valvular Regurgitation at 6 and 12 Months
For the mitral, tricuspid and pulmonic valves, 'significant' valvular regurgitation was defined by the sponsor as any case that was moderate or worse than moderate and for the aortic valve it was defined as any case that was mild or worse than mild. The analysis of significant valvular regurgitation by valve for lanreotide in comparison to octreotide at 6 and 12 months is summarized in Table 10.1.3.14.

Table 10.1.3.14. Analysis of Significant Valvular Regurgitation at 6 and 12 Months by valve (ITT Matched Population)

	6 Months		12 Months	
	Lanreotide N=82	Octreotide N=82	Lanreotide N=82	Octreotide N=82
	N (%)	N (%)	N (%)	N (%)
Mitral Valve				
Number of evaluable patients	76	62	82	82
Significant regurgitation	5 (7%)	1 (2%)	4 (5%)	2 (2%)
Statistical Analyses				
Risk difference (95% CI)	0.05 (-0.01, 0.11)		0.02 (-0.03, 0.08)	
Relative risk (95% CI)	4.08 (0.49, 34.01)		2.00 (0.38, 10.62)	
Odds ratio (95% CI)	4.72 (0.50, 44.49)		1.92 (0.33, 11.04)	
p-value for odds ratio	0.176		0.467	
Aortic Valve				
Number of evaluable patients	77	61	82	82
Significant regurgitation	10 (13%)	7 (11%)	10 (12%)	11 (13%)
Statistical Analyses				
Risk difference (95% CI)	0.02 (-0.09, 0.12)		-0.01 (-0.11, 0.09)	
Relative risk (95% CI)	1.13 (0.46, 2.80)		0.91 (0.41, 2.02)	
Odds ratio (95% CI)	1.34 (0.45, 3.98)		0.90 (0.34, 2.38)	
p-value for odds ratio	0.598		0.827	
Tricuspid Valve				
Number of evaluable patients	71	58	77	77
Significant regurgitation	4 (6%)	1 (2%)	1 (1%)	1 (1%)
Statistical Analyses				
Risk difference (95% CI)	0.04 (-0.02, 0.10)		0.00 (-0.04, 0.04)	
Relative risk (95% CI)	3.27 (0.38, 28.44)		1.00 (0.06, 15.70)	
Odds ratio (95% CI)	4.63 (0.43, 47.56)		1.01 (0.06, 18.01)	
p-value for odds ratio	0.198		0.995	
Pulmonic Valve				
Number of evaluable patients	39	33	50	49
Significant regurgitation	2 (5%)	1 (3%)	2 (4%)	2 (4%)
Statistical Analyses				
Risk difference (95% CI)	0.02 (-0.07, 0.11)		0.00 (-0.08, 0.08)	
Relative risk (95% CI)	1.69 (0.16, 17.84)		0.98 (0.14, 6.68)	
Odds ratio (95% CI)	1.46 (0.11, 18.70)		0.86 (0.11, 6.77)	
p-value for odds ratio	0.771		0.886	
Any Valve[a]				
Number of evaluable patients	78	63	82	82
Significant regurgitation	16 (21%)	9 (14%)	15 (18%)	15 (18%)
Statistical Analyses				
Risk difference (95% CI)	0.06 (-0.06, 0.19)		0.00 (-0.12, 0.12)	
Relative risk (95% CI)	1.44 (0.68, 3.03)		1.00 (0.52, 1.91)	
Odds ratio (95% CI)	1.73 (0.66, 4.53)		0.99 (0.42, 2.36)	
p-value for odds ratio	0.265		0.991	

Source: Table 14.3.4.4.3.1
a A patient was defined as having significant valvular regurgitation in any valve if one or more of their individual heart valves had significant regurgitation. Patients with significant regurgitation in more than one valve are only counted once in the 'Any Valve' analysis.
CI=confidence interval
Valve results derived using the LOCF approach

The number of patients having significant valvular regurgitation at 6 and 12 months for each of the valves was low. Statistical analyses indicated that there was no statistically significant difference between the cohorts in the risk of significant valvular regurgitation.

The sponsor performed a sensitivity analyses to supplement the main analysis for significant valvular regurgitation on the ITT matched population. Patients with significant valvular regurgitation at baseline were excluded from this analysis on a per valve basis. The sensitivity analysis of significant valvular regurgitation by valve for lanreotide in comparison to octreotide at 6 and 12 months is summarized in Table 10.1.3.15.

Table 10.1.3.15. Sensitivity Analysis of Significant Valvular Regurgitation at 6 and 12 Months by valve (ITT Matched Population)

	6 Months		12 Months	
	Lanreotide N=82	Octreotide N=82	Lanreotide N=82	Octreotide N=82
	N (%)	N (%)	N (%)	N (%)
Mitral Valve				
Number of evaluable patients	71	61	76	80
Significant regurgitation	1 (1%)	0	1 (1%)	1 (1%)
Statistical Analyses				
Risk difference (95% CI)	0.01 (-0.01, 0.04)		0.00 (-0.03, 0.04)	
Relative risk (95% CI)	2.58 (0.11, 62.28)		1.05 (0.07, 16.53)	
Odds ratio (95% CI)	2.62 (0.10, 65.42)		1.05 (0.06, 17.15)	
p-value (Fishers Exact test)	1.000		1.000	
Aortic Valve				
Number of evaluable patients	70	55	74	73
Significant regurgitation	3 (4%)	1 (2%)	3 (4%)	2 (3%)
Statistical Analyses				
Risk difference (95% CI)	0.02 (-0.03, 0.08)		0.01 (-0.05, 0.07)	
Relative risk (95% CI)	2.36 (0.25, 22.04)		1.48 (0.25, 8.60)	
Odds ratio (95% CI)	2.42 (0.24, 23.91)		1.50 (0.24, 9.25)	
p-value (Fishers Exact test)	0.630		1.000	
Tricuspid Valve				
Number of evaluable patients	69	57	75	76
Significant regurgitation	3 (4%)	0	0	0
Statistical Analyses				
Risk difference (95% CI)	0.04 (0.00, 0.09)		–	
Relative risk (95% CI)	5.80 (0.31, 110.01)		–	
Odds ratio (95% CI)	6.05 (0.31, 119.66)		–	
p-value (Fishers Exact test)	0.251		–	
Pulmonic Valve				
Number of evaluable patients	36	31	47	47
Significant regurgitation	0	0	1 (2%)	1 (2%)
Statistical Analyses				
Risk difference (95% CI)	–		0.00 (-0.06, 0.06)	
Relative risk (95% CI)	–		1.00 (0.06, 15.52)	
Odds ratio (95% CI)	–		1.00 (0.06, 16.47)	
p-value (Fishers Exact test)	–		1.000	
Any Valve[a]				
Number of evaluable patients	78	63	82	82
Significant regurgitation	7 (9%)	1 (2%)	5 (6%)	4 (5%)
Statistical Analyses				
Risk difference (95% CI)	0.07 (0.00, 0.14)		0.01 (-0.06, 0.08)	
Relative risk (95% CI)	5.65 (0.71, 44.75)		1.25 (0.35, 4.49)	
Odds ratio (95% CI)	6.11 (0.73, 51.07)		1.27 (0.33, 4.89)	
p-value (Fishers Exact test)	0.075		1.00	

Source: Sponsor's Table 14.3.4.4.3.3
Valves that showed significant regurgitation at baseline have been excluded from the sensitivity analysis.
a A significant valvular regurgitation in any valve was defined as one or more of the individual valves having significant regurgitation
CI=confidence interval
Valve results derived using the LOCF approach

For the ITT matched population, the results of the analysis supported the original analysis, indicating that there was no statistically significant difference between the cohorts in the risk of significant valvular regurgitation for each individual valve or for any valve at 6 and 12 months. Similar results were obtained for the Per Protocol matched population, with the exception that the sensitivity analysis of significant regurgitation in any valve at 6 months indicated a higher risk of significant regurgitation in the lanreotide cohort (odds ratio: 12.05 [95% CI: 0.66, 219.32; p=0.031). The corresponding relative risk was 10.87 (95% CI: 0.63, 188.33) and the risk difference was 0.10 (95% CI: 0.02, 0.18).

4. Degree of Worsening

A summary of the degree of worsening (or improvement) in valvular regurgitation at 6 and 12 months compared with baseline is presented in Table 10.1.3.16.

Table 10.1.3.16. Degree of Worsening of Valvular Regurgitation (ITT Matched Population)

	Lanreotide N=82				Octreotide N=82			
	Change from Baseline at:				Change from Baseline at:			
	Month 6		Month 12		Month 6		Month 12	
Mitral								
-2	0		0		0		0	
-1	17	(21%)	25	(30%)	6	(7%)	11	(13%)
0	49	(60%)	42	(51%)	44	(54%)	56	(68%)
1	7	(9%)	12	(13%)	11	(13%)	14	(17%)
2	1	(1%)	1	(1%)	1	(1%)	1	(1%)
3	0		0		0		0	
Aortic								
-2	0		1	(1%)	0		0	
-1	2	(2%)	4	(5%)	2	(2%)	4	(5%)
0	66	(80%)	68	(83%)	55	(67%)	74	(90%)
1	7	(9%)	7	(9%)	4	(5%)	3	(4%)
2	0		0		0		1	(1%)
3	0		0		0		0	
Tricuspid								
-2	0		2	(2%)	0		0	
-1	5	(6%)	10	(12%)	2	(2%)	11	(13%)
0	54	(66%)	54	(66%)	48	(59%)	51	(62%)
1	10	(12%)	8	(10%)	6	(7%)	13	(16%)
2	0		1	(1%)	1	(1%)	1	(1%)
3	0		0		0		0	
Pulmonic								
-2	0		0		1	(1%)	1	(1%)
-1	5	(6%)	7	(9%)	6	(7%)	9	(11%)
0	26	(32%)	26	(32%)	20	(24%)	23	(28%)
1	6	(7%)	11	(13%)	5	(6%)	9	(11%)
2	2	(2%)	3	(4%)	0		3	(4%)
3	0		0		0		1	(1%)

Source: Sponsor's Table 14.3.4.4.1.3.
0: Did not worsen
1: A worsening in class of 1, e.g. 'none' to 'physiologic', 'mild' to 'moderate' etc
2: A worsening in class of 2, e.g. 'none' to 'mild', 'mild' to 'severe' etc
3: A worsening in class of 3, e.g. 'none' to 'moderate', 'physiological' to 'severe'
-1: An improvement in class of 1, e.g. 'physiologic' to 'none', 'moderate' to 'mild' etc
-2: An improvement in class of 2, e.g. 'mild' to 'none', 'severe' to 'mild'

Valve results derived using the LOCF approach

Echocardiography of the mitral valve showed that 30% of patients in the lanreotide cohort and 13% in the octreotide cohort had improvements of at least one level in valvular regurgitation at 12 months and that 16% treated with lanreotide and 18% treated with octreotide had a worsening of at least one level (Table 10.1.3.14).

For the aortic valve at 12 months, 6% of patients in the lanreotide group and 5% in the octreotide group improved by at least one level whereas 9% of lanreotide-treated patients and 5% of octreotide-treated patients worsened by at least one level. One patient in the lanreotide cohort had an improvement in valvular regurgitation of two levels at 12 months. One patient in the octreotide cohort worsened by two levels.

For the tricuspid valve at 12 months, 14% of lanreotide-treated patients and 13% of octreotide-treated patients improved by at least one level whereas 11% of lanreotide-treated patients and 17% of octreotide-treated patients worsened by at least one level. An improvement of two levels in the degree of valvular regurgitation was seen for two lanreotide-treated patients at 12 months. One patient in each cohort (1%) had a worsening of two levels at 12 months. The remaining patients had no change in the level of regurgitation.

With lanreotide, pulmonic valve regurgitation improved in 9% of patients and worsened in 17% and with octreotide, regurgitation in the pulmonic valve improved in 12% of patients and deteriorated in 16%. One octreotide-treated patient had an improvement in valvular regurgitation of two levels at 12 months. Three patients in each cohort (4%) had a worsening of two levels at 12 months. The remaining patients had no change in the level of regurgitation.

In the lanreotide cohort there were a total of 49 (60%) cases of improvements in regurgitation in and 43 (52%) cases of worsening. In the octreotide cohort there were a total of 36 (44%) cases of improvements in regurgitation in and 32 (39%) cases of worsening.

Shift in Valvular Regurgitation from Baseline to Months 6 and 12

Shifts in the severity of valvular regurgitation are summarized in Table 10.1.3.17.

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Table 10.1.3.17. Summary of Number (%) of Patients with Shifts in Valvular Regurgitation from Baseline to Month 12 (ITT Matched Population)

Shift from baseline to Month 12:	Mitral		Aortic		Tricuspid		Pulmonic	
	Lan N=82	Oct N=82	Lan N=82	Oct N=82	Lan N=82	Oct N=82	Lan N=82	Oct N=82
Worsening:								
None to Physiol*	4 (5%)	5 (6%)	4 (5%)	2 (2%)	3 (4%)	4 (5%)	1 (1%)	0
Physiol* to Mild	6 (7%)	4 (5%)	3 (4%)	0	2 (2%)	2 (2%)	1 (1%)	3 (4%)
Mild to Mod	0	1 (1%)	0	0	0	0	1 (1%)	0
Mod to Severe	0	0	0	0	0	0	0	0
No change	31 (38%)	42 (51%)	52 (63%)	59 (72%)	41 (50%)	35 (43%)	12 (15%)	12 (15%)
Improvement:								
Severe to Mod	0	0	0	0	0	0	0	0
Mod to Mild	2 (2%)	1 (1%)	0	1 (1%)	1 (1%)	0	2 (2%)	0
Mild to Physiol*	5 (6%)	4 (5%)	0	0	1 (1%)	2 (2%)	2 (2%)	4 (5%)
Physiol* to None	13 (16%)	5 (6%)	3 (4%)	3 (4%)	5 (6%)	4 (5%)	0	1 (1%)
Not evaluable	9 (11%)	7 (9%)	8 (10%)	5 (6%)	10 (12%)	18 (22%)	44 (54%)	40 (49%)

Source: Sponsor's Table 14.3.4.6.1
Lan=Lanreotide; Oct=Octreotide; Physiol=Physiologic; Mod=Moderate
*Or 'trace' for the aortic valve
Only patients who were evaluable for valvular regurgitation are summarized. No missing valve symptoms are presented.
The denominator for percentages is the number of patients in the ITT matched population within each treatment group.

Review of shift tables indicated that of the patients who were evaluable for valvular regurgitation, the majority had no change in each valve. The proportion of patients in each cohort with shifts that represented either a worsening or improvement in valvular regurgitation was low. Differences between lanreotide and octreotide were noted in the aortic valve were 3 (4%) of lanreotide patients and no octreotide patients, experienced a worsening from 'physiologic' to 'mild' regurgitation, otherwise the two cohorts were similar.

The sponsor was also asked to provide an assessment of concordance between the primary and secondary readers for the ITT matched population echoes at Month 12 with respect to valvular insufficiency for each valve. The tables below demonstrate that the concordance between cardiologists was excellent.

Table 10.1.3.18. Assessment of Concordance between the Primary and Secondary Readers (ITT matched population, Month 12): Mitral Valve

[a]	Cardiologist 2					
Cardiologist 1	Degree of mitral-valve insufficiency					
Degree of mitral-valve insufficiency	None	Physiologic	Mild	Moderate	Severe	Not Evaluable
None	**43**	12	1	0	0	2
Physiologic	10	**49**	2	0	0	0
Mild	0	9	**16**	1	0	0
Moderate	0	0	1	**3**	0	0
Severe	0	0	0	0	**0**	0
Not Evaluable	0	0	0	0	0	**9**

a Consensus assessment in **bold** and highlight

Table 10.1.3.19. Assessment of Concordance between the Primary and Secondary Readers (ITT matched population, Month 12): Aortic Valve

[a]	Cardiologist 2					
Cardiologist 1	Degree of aortic-valve insufficiency					
Degree of aortic-valve insufficiency	None	Trace	Mild	Moderate	Severe	Not Evaluable
None	109	4	0	0	0	2
Trace	3	11	3	0	0	0
Mild	0	2	11	2	0	0
Moderate	0	0	1	2	0	0
Severe	0	0	0	0	0	0
Not Evaluable	0	0	0	0	0	8

a Consensus assessment in **bold** and highlight

Table 10.1.3.20. Assessment of Concordance between the Primary and Secondary Readers (ITT matched population, Month 12): Tricuspid Valve

[a]	Cardiologist 2					
Cardiologist 1	Degree of tricuspid-valve insufficiency					
Degree of tricuspid-valve insufficiency	None	Physiologic	Mild	Moderate	Severe	Not Evaluable
None	23	16	0	0	0	7
Physiologic	6	60	1	0	0	2
Mild	0	10	13	2	0	1
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Not Evaluable	1	3	0	0	0	13

a Consensus assessment in **bold** and highlight

Table 10.1.3.21. Assessment of Concordance between the Primary and Secondary Readers (ITT matched population, Month 12): Pulmonic Valve

[a]	Cardiologist 2					
Cardiologist 1	Degree of pulmonic-valve insufficiency					
Degree of pulmonic-valve insufficiency	None	Physiologic	Mild	Moderate	Severe	Not Evaluable
None	17	1	0	0	0	13
Physiologic	3	21	4	1	0	4
Mild	0	7	17	1	0	1
Moderate	0	0	1	0	0	0
Severe	0	0	0	0	0	0
Not Evaluable	11	7	1	0	1	47

a Consensus assessment in **bold** and highlight

Non-Evaluable Data

For the ITT population, the proportion of patients with non-evaluable data at each visit ranged from 9-11% for the mitral valve, from 9-13% for the aortic valve and from 18-20% for the tricuspid valve. Approximately half of the observations for the pulmonic valve were non-evaluable at baseline, 6 months and 12 months.

For the ITT population, 8% of the patients in the lanreotide and 6% of patients in the octreotide cohort had non-evaluable data for all four valves at baseline. At 6 months, 5% of the patients in the lanreotide and 17% of patients in the octreotide cohort had non-evaluable data for all four valves. At 12 months, 5% of the patients in the lanreotide and 11% of patients in the octreotide cohort had non-evaluable data for all four valves.

Clinically Significant Valvular Regurgitation
Clinically significant valvular regurgitation was defined by the sponsor as moderate or severe dysfunction for the mitral, pulmonic and tricuspid valves and mild or worse for the aortic valve. There were 42 patients in the safety population with significant valvular regurgitation in the consensus reads at any timepoint during the study: 23 receiving lanreotide and 19 receiving octreotide. There were 12 patients (6 lanreotide, 6 octreotide) with significant regurgitation at any follow-up assessment but either no significant regurgitation (5 lanreotide, 3 octreotide) or non-evaluable (1 lanreotide, 3 octreotide) assessment in any valve at baseline.

Echo conclusion for ITT Matched Population:
Seventeen (21%) of lanreotide-treated patients and 16 (20%) of octreotide-treated patients developed new valvular regurgitation. Fourteen (17%) of lanreotide-treated patients and 13 (16%) of octreotide-treated patients developed worsening valvular regurgitation. Twenty-eight (34%) of lanreotide-treated patients and 27 (33%) of octreotide-treated patients developed new or worsening valvular regurgitation. Analysis of the primary endpoint indicated that there was no statistically significant difference between the two cohorts in the risk of developing new or worsening valvular regurgitation in any valve at 12 months (odds ratio: 0.86; 95% CI: 0.41, 1.82; p=0.694; ITT matched population). The corresponding relative risk (1.04; 95% CI: 0.67, 1.60) and the risk difference (0.01; 95% CI: -0.13, 0.16) both supported the odds ratio conclusion.

Analyses of the risk of developing new or worsening valvular regurgitation for each individual heart valve (mitral, aortic, tricuspid and pulmonic) indicated that there was no statistically significant difference in risk between the two cohorts at 6 or 12 months.

The incidence of valvular regurgitation that was mild or greater in any valve was 48 (58%) at baseline for lanreotide and 54 (65%) at 12 months. Increases in events were seen for the mitral valve 17 (21%) at baseline to 21 (26%) at 12 months; aortic valve with 8 (10%) at baseline and 9 (11%) at 12 months and the pulmonic valve with 10 (12%) at baseline and 12 (14%) at 12 months. The tricuspid valve had 13 (15%) of mild or greater regurgitation at baseline which decreased to 12 (14%) at 12 months.

The incidence of valvular regurgitation that was mild or greater in any valve was 46 (55%) at baseline for octreotide and 45 (54%) at 12 months. Increases in events were seen for the mitral valve 10 (12%) at baseline to 11 (13%) at 12 months. Aortic valve regurgitation remained stable with 9 (11%) at baseline and at 12 months. The tricuspid valve had 12 (14%) of mild or greater regurgitation at baseline which decreased to 11 (13%) at 12 months and the pulmonic valve was 15 (18%) at baseline and 14 (17%) at 12 months.

Clinically significant valvular regurgitation was defined by the sponsor as moderate or severe dysfunction for the mitral, pulmonic and tricuspid valves and mild or worse for the aortic valve. For lanreotide, there were 17 cases (20%) at baseline and 15 (18%) at 12 months. For octreotide, there were 14 cases (16%) at baseline and 13 (15%) at 12 months.

Echo assessment for all-treated population:
This reviewer looked at the echocardiography data from all 225 subjects, lanreotide and octreotide, regardless of whether they were in the ITT matched population. There were 100 octreotide and 96 lanreotide subjects with evaluable echocardiograms; there were 29 subjects that only had baseline echos or they were non-evaluable. In the octreotide group, there were 32 subjects (32%) experiencing new regurgitation in 33 valves. Eleven of these valvular episodes were transient, meaning it was only seen in the 6-month visit but was not present at 12 months. Six events were not in the ITT matched population. There were a total of 22 events of new, persistent valvular regurgitation in the octreotide population that occurred in 21 subjects; 18 events occurred in the ITT matched population. Twenty-one (95%) events were likely clinically insignificant (new physiologic mitral, tricuspid, or pulmonic regurgitation or new trace aortic regurgitation). One episode (1/22, 5%) represented a new onset of mild pulmonic valve regurgitation which this reviewer considered potentially clinically significant. This patient (#7020003) was included in the ITT matched population.

Of the 100 subjects in the octreotide group with evaluable echoes, there was a worsening of valvular regurgitation in 16 valves in 11 subjects. Twelve of these events this reviewer considered clinically insignificant (physiologic to mild increase in mitral, tricuspid or pulmonic regurgitation). Four events were potentially clinically significant: one subject had an increase from mild to moderate mitral regurgitation; one subject had an increase from mild to moderate tricuspid regurgitation; one subject had an increase from trace to mild aortic regurgitation; and one subject had an increase from physiologic to severe pulmonic regurgitation (#8050002 in ITT matched group). The sponsor was asked to provide additional information on Patient 805.0002:

> This 46-year-old male Caucasian patient with a history of acromegaly since 1987 was enrolled into Study 721 on 14 August 2003. The patient had undergone prior pituitary surgery on [redacted], but had no radiotherapy for his acromegaly. The patient also had a history of hypertension diagnosed on 01 September 2001, considered by the investigator as no longer active at study entry. The patient demonstrated significant pulmonic valve regurgitation at 12 months with a change from physiologic at baseline (08 September 2003), to severe at month 12 (23 August 2004). This patient did not experience any adverse event during Study 721. The patient completed the study and the study drug was not discontinued at any stage. Last visit date was on 23 August 2004.

Of the 96 subjects in the lanreotide group with evaluable echoes, there were 24 subjects (25%) experiencing new regurgitation in 27 valves. Six of these valvular episodes were transient, meaning it was only seen in the 6-month visit but was not present at 12 months. Four subjects with a total of 5 valvular events were not in the ITT matched population. There were a total of 21 events of new, persistent valvular regurgitation in the lanreotide population that occurred in 19 subjects. Eighteen (86%) events were likely clinically insignificant (new physiologic mitral, tricuspid, or pulmonic regurgitation or new trace aortic regurgitation). Three episodes (3/21, 14%) represented a new onset of mild pulmonic valve regurgitation (2 cases) and mild tricuspid

regurgitation (1 case) which this reviewer considered potentially clinically significant. These 3 patients (#3010007, 4040007, and 4040011) were included in the ITT matched population.

Of the 96 subjects in the lanreotide group with evaluable echoes, there was a worsening of valvular regurgitation in 21 valves in 14 subjects. Fourteen of these events this reviewer considered clinically insignificant (physiologic to mild increase in mitral, tricuspid or pulmonic regurgitation). Seven events were potentially clinically significant: one subject had an increase from mild to moderate mitral regurgitation; one subject had an increase from mild to moderate pulmonic regurgitation; three subjects had an increase from trace to mild aortic regurgitation; one subject had an increase from physiologic to moderate mitral regurgitation (#8050004 in ITT matched group); and one subject had an increase from moderate to severe aortic regurgitation (#7010020 not in ITT matched group). The sponsor was asked to provide additional information on Patient 805.0004 and Patient 701.0020:

> Patient 805.0004 This 73 year old female Caucasian patient with a history of acromegaly since March 1985 was enrolled onto Study 721 on 19 August 2003. The patient had undergone prior pituitary surgery on [redacted], but did not receive radiotherapy for her acromegaly. The patient had no reported history of hypertension or cardiovascular disease. The patient demonstrated significant mitral valve regurgitation at 12 months with a change from physiologic at baseline (15 September 2003), to moderate at month 12 (07 September 2004). This patient presented with one cardiac AE, left anterior hemiblock of mild intensity and considered unrelated to the study drug. The patient was reported as not recovered from this adverse event at the end of the study. During the course of the study the patient presented with 6 adverse events which included; left anterior hemiblock, tiredness, breathless, nausea, headache and inner ear noise, all of mild intensity and unrelated to the study drug. The patient was reported as not recovered from each adverse event at the end of the study. The patient completed the study on 07 September 2004 and the study drug was not discontinued at any stage.
>
> Patient 701.0020: This 74 year old male Caucasian patient with a history of acromegaly since 27 February 1996 was enrolled onto Study 721 on 27 October 2003. The patient had undergone neither prior surgery nor received radiotherapy for his acromegaly and had no record of any significant previous medical or surgical history prior to enrollment. The patient demonstrated significant mitral valve regurgitation and aortic valve regurgitation at 12 months with worsening of mitral valve regurgitation from mild at baseline (22 December 2003), to moderate at month 12 (09 December 2004), and worsening of aortic valve regurgitation from moderate at baseline (22December 2003) to severe at month 12 (09 December 2004). This patient presented with one adverse event during Study 721: a single episode of mild atrial fibrillation unrelated to the study drug from which the patient recovered without sequelae. The patient completed the study and the study drug was not discontinued at any stage. Last visit date was on 09 December 2004.

This reviewer agrees with the sponsor that echocardiographic evaluation did not demonstrate a meaningful difference in the risk of developing new or worsening valvular regurgitation or significant regurgitation in patients treated with lanreotide compared to octreotide. Clinically significant valvular regurgitation was defined for this study as moderate or severe dysfunction for the mitral, pulmonic and tricuspid valves and mild or worse for the aortic valve.

Sponsor's Conclusions:
Lanreotide was found to be safe and well-tolerated over a 12 month period in the treatment of *de novo* and pre-treated patients with acromegaly. The incidence of regurgitation in any valve was consistent with published data and with the known safety profile in both cohorts. Little change in incidence was seen over 12 months and most cases of regurgitation were categorized as being physiologic or mild in severity. Echocardiographic evaluation did not demonstrate a significant

difference in the risk of developing new or worsening valvular regurgitation or significant regurgitation in patients treated with lanreotide compared to octreotide.

The occurrence of clinically significant mitral regurgitation (i.e. moderate or severe in intensity) or of clinically significant aortic regurgitation (i.e. at least in mild intensity) was low in both groups of patients throughout the study. Only 6% of patients in the lanreotide group had clinically significant mitral regurgitation at baseline compared with 4% at Month 12. The corresponding prevalence in the octreotide group was 2% at both assessments. Clinically significant aortic regurgitation was present in 10% to 11% of patients in both treatment groups at the baseline and Month 12 assessments.

Review of the incidence of valvular regurgitation by previous treatment status (*de novo* or pre-treated) did not indicate any difference, however, the number of *de novo* patients included in the study was too small to allow any clear conclusions to be drawn. One observation during this study was the high proportion of patients in both cohorts with non-evaluable valve data.

Analysis of the primary endpoint, the odds ratio approximation for the relative risk of new or worsening valvular regurgitation in any valve of lanreotide in comparison to octreotide at 12 months, showed no statistically significant difference between the two treatments for the ITT matched population. A set of confounding factors was assessed in order to judge their impact on the primary endpoint. The confounding factors that were found to have an impact on the primary endpoint were age, gender, region, severity/control of disease, history of hypertension, cardiovascular disease, smoking, previous surgery/radiation and duration of previous treatment. The odds ratio was adjusted for these factors.

Medical Officer's Conclusions:

Efficacy (exploratory endpoint):
The proportion of patients with low or normal IGF-1 results at baseline, 6 months or 12 months was 61%, 63% and 71%, respectively, in the lanreotide cohort and 55%, 65% and 67%, respectively, in the octreotide cohort (ITT matched population). There were no statistically significant differences between the groups in the proportion of patients with low or normal IGF-1 levels at any time point. Of the 32 patients in the lanreotide cohort who had high IGF-1 levels at baseline and had post-baseline IGF-1 results, seven (22%) and 12 (38%) patients had low or normal IGF-1 results at 6 months and 12 months, respectively. For the 37 octreotide-treated patients with high IGF-1 levels at baseline who had post-baseline IGF-1 results, 11 (30%) and 16 (46%) had low or normal IGF-1 results at 6 months and 12 months, respectively.

Safety:
The incidence of treatment emergent adverse events was higher in the lanreotide group (52% and 45% in the lanreotide and octreotide cohorts, respectively); while serious adverse events (6% and 8%, respectively) and adverse events leading to withdrawal (2% and 4%, respectively) was lower in the lanreotide cohort as compared to the octreotide cohort. The most common adverse events at the system organ class level were gastrointestinal disorders, which were reported by 20% and 8% of lanreotide- and octreotide-treated patients, respectively. The most frequently reported

adverse event (by preferred term) was diarrhea, which was reported by 13% of patients in the lanreotide group and by 2% of patients in the octreotide group. Thus the incidence of GI disorders was 2.5 times higher and the incidence of diarrhea was 6.5 times higher in the lanreotide cohort as compared to the octreotide cohort in this study. The other most common adverse events were headache and hypertension, cholelithiasis and abdominal pain. These events were reported by less than 5% of patients in the overall population and were reported at a similar incidence in each treatment group. Two (2%) of lanreotide subjects vs. 0 (0%) of octreotide subjects reported bradycardia as a treatment emergent adverse event in this trial.

This study was a multicenter, prospective, controlled observer blinded cohort study that was powered to detect a relative risk of 2 in valvular regurgitation between the two somatostatin analogues, lanreotide and octreotide. The primary endpoint for this study was the odds ratio approximation for the relative risk of new or worsening valvular regurgitation in any valve (mitral, aortic, tricuspid, and pulmonic) of lanreotide in comparison to octreotide at 12 months. Analysis of the primary endpoint indicated that there was no statistically significant difference between the two cohorts in the risk of developing new or worsening valvular regurgitation in any valve at 12 months (odds ratio: 0.86; 95% CI: 0.41, 1.82; p=0.694; ITT matched population). The corresponding relative risk (1.04; 95% CI: 0.67, 1.60) and the risk difference (0.01; 95% CI: -0.13, 0.16) both supported the odds ratio conclusion. The odds ratio was adjusted for the following confounding factors: age, gender, region, severity/control of disease, history of hypertension, history of cardiovascular disease, history of smoking, previous surgery/radiation and duration of previous treatment.

There was a higher than expected number of non-evaluable echo data. For the ITT population, the proportion of patients with non-evaluable data at each visit ranged from 9-11% for the mitral valve, from 9-13% for the aortic valve and from 18-20% for the tricuspid valve. Approximately half of the observations for the pulmonic valve were non-evaluable at baseline, 6 months and 12 months.

Twenty-eight (34%) of lanreotide-treated patients and 27 (33%) of octreotide-treated patients developed new or worsening valvular regurgitation. The incidence of valvular regurgitation that was mild or greater in any valve was 48 (58%) at baseline for lanreotide and 54 (65%) at 12 months. Increases in events were seen for the mitral valve 17 (21%) at baseline to 21 (26%) at 12 months; aortic valve with 8 (10%) at baseline and 9 (11%) at 12 months and the pulmonic valve with 10 (12%) at baseline and 12 (14%) at 12 months. The tricuspid valve had 13 (15%) of mild or greater regurgitation at baseline which decreased to 12 (14%) at 12 months. The incidence of valvular regurgitation that was mild or greater in any valve was 46 (55%) at baseline for octreotide and 45 (54%) at 12 months. Increases in events were seen for the mitral valve 10 (12%) at baseline to 11 (13%) at 12 months. Aortic valve regurgitation remained stable with 9 (11%) at baseline and at 12 months. The tricuspid valve had 12 (14%) of mild or greater regurgitation at baseline which decreased to 11 (13%) at 12 months and the pulmonic valve was 15 (18%) at baseline and 14 (17%) at 12 months.

The occurrence of clinically significant mitral regurgitation (i.e. moderate or severe in intensity) or of clinically significant aortic regurgitation (i.e. at least mild in intensity) was low in both