IDE #G030242

Investigational Device Exemption

for the Pilot Study of the

Energex Systems, Inc. Hemo-Modulator™

for

Reducing Viral Load in

Patients with Chronic Hepatitis C (CHC)

Annual/Final Report

August 9, 2007

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1. Basic Elements

IDE Number

IDE #G030242 (Supplements 8 through 20 are related to this study, Pilot 2)

Device Name and Indications for Use

Energex Systems Inc. Hemo-Modulator Device for the Reduction of Viral Load in Patients with Chronic Hepatitis C (CHC) Virus

Sponsor Information

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2. Study Progress

Introduction

The final report for Pilot Study #1 for the Energex Systems Inc. Hemo-Modulator for the Reduction of Viral Load in Patients with Chronic Hepatitis C (CHC) was submitted on May 12, 2005 as Supplement #5. There is no additional information to report on Pilot #1.

Pilot Study #2 for the Energex Systems Inc. Hemo-Modulator for the Reduction of Viral Load in Patients with Chronic Hepatitis C (CHC) began in April 2006 under the IDE protocol approved by FDA in Supplement 8 on February 21, 2006, and approved by the Warren Hospital Institutional Review Board (IRB) on March 16, 2006, and reapproved on March 1, 2007. (The IRB approval letter is provided as Attachment 3 to the first Annual Report, Supplement 14, and the reapproval letter is provided in Appendix 6 to this document.) This annual/final report covers the study progress and completion of Pilot Study #2.

Summary of the study progress in relation to the investigational plan

The study is limited to twelve subjects (Supplement 16, approved by FDA 11/03/06). Eleven subjects have been enrolled, and there will be no further enrollment. Of the eleven subjects who were enrolled, nine have completed the treatment regimen, while two were discontinued from completing the treatment regimen as follows:

- Subject 04-009-1-020: It was discovered after the first treatment that the patient was taking a medication believed to be photosensitizing. Patient was discontinued from further treatment.
- Subject 04-009-1-014: Patient arrived for Session 3/Treatment 3 (13th treatment overall) and was diagnosed with atrial fibrillation and acute coronary syndrome. The patient is a 60 year old male who is morbidly obese, and who has a history of hypertension, uncontrolled diabetes, and chronic joint degeneration. The Investigator

has classified the event as "not related to [Hemo-Modulator] treatment." The event was reported to FDA as Supplement 15, with a copy provided to the IRB.

Two additional subjects were consented, but were not enrolled because the pre-screening evaluation determined that the patients did not meet the study inclusion criteria.

In addition, FDA approved use of the device for one Compassionate Use case (Supplement 18, approved by FDA on 1/9/07); however, due to concerns about the patient's ability to comply with the treatment protocol, it was ultimately decided not to treat this patient.

Number of investigators/investigational

The Principal Investigator is Shanker Mukherjee, M.D. Dr. Mukherjee's Co-Investigator is Barry Herman, M.D. There are no other investigators. Dr. Mukherjee's office addresses are:

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The single investigational site is Warren Hospital, 185 Roseberry Street, Phillipsburg, NJ 08865. Telephone: 908-859-6700. There are no other investigational sites.

IRB Information

This study is overseen by the Warren Hospital Institutional Review Board. The IRB Chairman is Frank Gilly, MD. Dr. Gilly's mailing address is Warren Hospital, 185 Roseberry Street, Phillipsburg, NJ 08865. Telephone: 908-859-6700. The IRB gave its annual reapproval of this study on March 1, 2007. See Appendix 6 for approval letter.

Number of subjects enrolled (by indication or model)

Eleven subjects have been enrolled using the single model employed in the study, and enrollment is now closed.

Number of devices shipped/Device accountability

Two units of the Hemo-Modulator were delivered to the investigational site for use in this study. The Sponsor retrieved the two Hemo-Modulator devices from the investigational site once patient 04-009-1-025 had completed the last study treatment.

In addition, 150 of the associated administration sets were used in the study: nine patients had 15 Hemo-Modulator treatments each and used 135 administration sets (9 x 15 = 135); one patient (04-009-1-014) had 12 Hemo-Modulator treatments and used 12 administration sets (1 x 12 = 12); and one patient (04-009-1-020) had one Hemo-Modulator treatment and used one administration set. In addition two administration sets were opened but discarded:

- One administration set was opened in anticipation of patient 04-009-1-014's 13th treatment, but was discarded when patient -014 was discontinued due to an UADE just before receiving his 13th treatment.
- One was opened for patient 04-009-1-024, but was discarded because the tubing assembly was noted to be defective, and was returned to the manufacturer for investigation.

Brief summary of results

Nine patients completed the treatment regimen. The data from these patients are presented as the primary data set. Since patient 04-009-1-014 completed twelve of the planned fifteen treatments, this patient's data is included in several of the analyses as well. Patient 04-009-1-020 completed only one treatment, and did not return for follow-up. Therefore, his data is not included in the analyses. Section 3.2.6.1 of the study protocol presented the success/failure criteria for the study. Each of the pre-established success criteria are shown in bold italics, and an analysis of the study results against these criteria follows:

1. The primary effectiveness measurements of UBI treatment with the Energex Systems Hemo-Modulator include a comparison of the baseline viral burden to the viral burden at 6 months following the last treatment for each subject measured by RT-PCR. Clinical success is defined as at least 10% of the patients treated (on an intent-to-treat basis) achieving an undetectable HCV-RNA level (<100 copies/IU) at the end of treatment (Week 22) and maintaining that undetectable level 6 months after the last treatment, and no patient demonstrating a significant worsening in histological severity on biopsy at Week 46.

With respect to the primary effectiveness criteria stated above, no patient achieved an undetectable HCV-RNA level at the end of treatment (Week 22) or at any time recorded throughout the study. Liver biopsies have been completed for the nine patients who completed the treatment regimen. Eight of the patients have had their pre- and post-study biopsies reviewed by a panel of three pathologists. The results of the biopsy evaluation are discussed in the *Biopsy Evaluations* section on page of this report. Details regarding the biopsy evaluation protocol and the results are presented in Appendix 4. The ninth patient began the study later than the rest of the patients, and this patient's post-study biopsy was not available in time to undergo review by the three pathologists at the same time as the other eight patients' biopsies. Therefore, only the initial assessment by the

on-site pathologist at Warren hospital is available for the ninth patient (04-009-1-025) at this time, and review by the second pathologist (and, if there is disagreement between the first two readers, by a third pathologist) will occur as soon as it can be scheduled.

2. A secondary assessment of effectiveness will be performed at the end of the study. Secondary indicators of effectiveness include comparisons of individual and overall percentage improvements in viral load and in liver function tests (AST and ALT) after each treatment, versus the baseline liver function test values. A qualitative comparison of the subjects' responses on the quality of life survey, baseline versus the forty-six and forty-eight week follow-up, will also be performed. The following endpoints will also be reported:

- ***Percentage of patients achieving a negative HCV RNA level at each follow-up point,***
- ***Percentage of patients achieving negative HCV RNA at week 22, who maintain undetectable levels through week 46, and***
- ***Percentage of patients achieving normal Liver Function Tests at each follow-up point.***

Energex has looked at each of the planned secondary effectiveness measures, and presents the following findings.

Individual percentage improvements in viral load

Appendix 1 contains graphs of each patient's viral load measurements over time. The lines/bars on each graph correspond with each treatment session. Note that a tenth patient (04-009-1-014, who completed 12 of the 15 treatments) is included in this analysis. None of the patients (0%) achieved a negative HCV RNA level at any follow-up point; however, several patients experienced large reductions in HCV RNA levels.

Table 1 shows the time-averaged change from baseline in viral load and in log viral load for each subject. Five patients had overall reductions in the time-averaged change in viral load during the course of the study (04-009-1-013, -016, -023, -024, -025).

Table 1: Time-Averaged Mean Change from Baseline* in Viral Load (x1,000,000) & Log Viral Load

Subject Number	Time-Averaged Change in Viral Load	Time-Averaged Change in Log Viral Load
040091013	-0.408	-0.165
040091014	1.495	0.104
040091015	0.666	0.207
040091016	-0.811	-0.245
040091018	0.306	0.142
040091019	0.405	0.051
040091021	0.656	0.032
040091023	-0.199	-0.253
040091024	-0.965	-0.181
040091025	-0.730	-0.097

* Baseline is the average of Day -14 and Day 0 visits.

Table 2 shows the percentage change in viral load from the baseline average (Day -14 and Day 0) to the post-study average (24-week-post-treatment and 26-week-post-treatment average) for each patient.

Table 2: Percentage change in viral load - baseline average versus post-study average

Patient ID	Pre-baseline Average Viral Load IU/ml	Post-Week 24 and 26 Average Viral Load IU/ml	% Change
040091013	1560000	535000	-65.71%
040091014	5665000	5630000*	-0.62%
040091015	1028500	1107500	7.68%
040091016	2530000	518000	-79.53%
040091018	739500	1050500	42.06%
040091019	3010000	2925000	-2.82%
040091021	3140000	2730000	-13.06%
040091023	657500	313500	-52.32%
040091024	3095000	2685000	-13.25%
040091025	4040000	2525000	-37.50%

* Patient -014 was discontinued after 12th treatment; therefore, his last viral load recorded at Session 3/Tx1 is used here.

Several patients ended the study with viral loads markedly lower than their pre-study viral loads (04-009-1-013, -016, -023, and -025), as calculated by comparing the post-study average to the pre-baseline average, with the largest % reduction seen in patient 04-009-1-016.

Overall improvements in viral load

The analysis in Table 3 was performed to look at changes in viral load for the overall study group over time. The results show paired t tests for the mean changes, and signed rank tests for the median changes. Due to the small number of patients in this series, a p-value <0.10 was considered a reasonable indicator for statistical significance. The mean and median changes that were statistically significant (p-value <0.10) occurred at Study Days 20, 259, 323, and 327. Note that a tenth patient (04-009-1-014, who completed 12 of the 15 treatments) is included in this analysis.

Table 3: Mean & Median Change From Baseline* in Viral Load (x 1,000,000)

Day	Mean Change	Mean P-Value	Median Change	Median P-Value
10	0.109	0.686	0.186	0.695
20	-0.402	0.072	-0.210	0.049
56	-0.197	0.433	-0.178	0.492
70	0.447	0.162	0.570	0.184
80	0.249	0.459	0.245	0.432
90	0.435	0.283	0.313	0.375
126	0.668	0.114	0.730	0.160
140	0.740	0.247	0.078	0.557
150	0.868	0.255	0.171	0.301
160	0.263	0.709	-0.072	0.820
245	-0.390	0.300	-0.487	0.203
259	-0.939	0.010	-1.000	0.031
323	-0.525	0.079	-0.470	0.098
327	-0.678	0.079	-0.470	0.098

* Baseline is the average of Day -14 and Day 0 visits.

Table 4 shows the mean change from baseline in log viral load. Due to the small number of patients in this series, a p-value <0.10 was considered a reasonable indicator for

statistical significance. The mean changes that were statistically significant (p-value <0.10) occurred at Study Days 20, 126, 259, and 323). Note that a tenth patient (04-009-1-014, who completed 12 of the 15 treatments) is included in this analysis.

Table 4: Mean Change From Baseline in Log Viral Load

Day	Mean Change	Mean P-Value
10	-0.007	0.902
20	-0.076	0.082
56	-0.037	0.601
70	0.076	0.259
80	0.031	0.658
90	0.034	0.599
126	0.127	0.092
140	0.092	0.191
150	0.064	0.521
160	0.016	0.837
245	-0.136	0.223
259	-0.344	0.032
323	-0.141	0.092
327	-0.241	0.105

Individual improvements in liver function tests

Appendix 2 contains graphs of each patient's liver function tests (AST/SGOT, ALT/SGPT, and direct bilirubin) over time. Note that a tenth patient (04-009-1-014, who completed 12 of the 15 treatments) is included in these analyses.

The reference range for normal was defined as 24-38 IU/l for AST/SGOT, and 24-50 IU/l for ALT/SGPT. Patient 04-009-1-015 had SGOT values in the normal range at pre-baseline, and maintained normal SGOTs at most timepoints throughout the study, but had abnormal SGPTs before the study, which persisted throughout the study. Patient 04-009-1-018 began the study with abnormal SGOTs, but dropped into the normal range at several points throughout the study. Patient -018's SGPTs were abnormal at pre-baseline, and remained abnormal throughout the study. Patient 04-009-1-019 began the study with normal SGOT and SGPT values, and remained in the normal range for SGOT and SGPT for most study intervals. Patient 04-009-1-025 began the study with

normal SGOTs, but dropped below the normal range at several intervals. Patient -025 began the study with abnormal SGPTs, but dropped into the normal range at several intervals. All other patients began the study with abnormal (high) SGOTs and SGPTs, and did not experience values within the normal ranges for SGOT or SGPT at any study timepoints.

Table 5 provides the time-averaged mean change from baseline in liver function tests for each subject.

Table 5: Time-Averaged Mean Change from Baseline in Liver Function Tests

Test	Subject Number	Time-Averaged Change
DirectBili	040091013	-0.080
	040091014	0.000
	040091015	-0.090
	040091016	0.013
	040091018	-0.001
	040091019	-0.025
	040091021	-0.034
	040091023	-0.003
	040091024	-0.155
	040091025	-0.058
SGOT	040091013	-22.124
	040091014	1.595
	040091015	-0.350
	040091016	-5.353
	040091018	-6.588
	040091019	-0.002
	040091021	-27.068
	040091023	26.494
	040091024	1.599
	040091025	-8.585
SGPT	040091013	-38.183
	040091014	-9.423
	040091015	-9.238
	040091016	-5.036
	040091018	-6.265
	040091019	-3.576
	040091021	-60.450
	040091023	15.300
	040091024	18.543
	040091025	-12.658

Table 5 shows that SGPT (ALT) decreased in every patient except two (-023, and -024) during the course of the study. Since elevated SGPT (ALT) is thought to be released from

hepatocytes when they undergo cell death from the cellular immune response, patients with higher SGPT may have more hepatocyte death during the chronic phase of the infection. If we use a cutoff for baseline SGPT of 100, 4 patients (-013, -021, -023, and -024) had baseline SGPT values above this cutoff. Of these 4, two (-013, and -021) had the most marked declines in SGPT in comparison with the remainder of the patients. The time averaged change in SGPT for these two patients is –38 and –60, which is ~ 3 and 5 fold higher than the patient with the next highest decrease (-13, subject 25).

The same pattern occurred for SGOT (AST), although not to the same degree (subjects -013 and -021 had time avg changes of –22 and –27, respectively). The next closest change occurred in subject 25 who had a change of –9. ALT is more specific for liver cell death in hepatitis C than is AST. If we assume that high baseline ALT indicates higher hepatocyte turnover, then marked reductions in ALT might suggest that these patients had decreased hepatocyte turnover after the treatments.

Energex finds the marked declines in SGPT and SGOT in the patients cited above to be very encouraging. The marked declines cited were durable for 5.5 months, although they did not result in patients achieving values in the normal reference ranges. The data suggests, however, that the Hemo-Modulator had an effect in some patients that, with an optimized maintenance-type therapy regimen, could have continued to reduce their SGOT and SGPT levels, eventually bringing SGPT and SGOT values to within the normal reference ranges.

Overall improvement in liver function tests

Figure 1 shows the graph of the mean liver function tests for the overall study group over time. The graph does not suggest any significant worsening in liver function tests for the overall group, and may suggest some improvement in overall liver function, particularly with regard to SGPT.

Figure 1: Mean Liver Function Tests

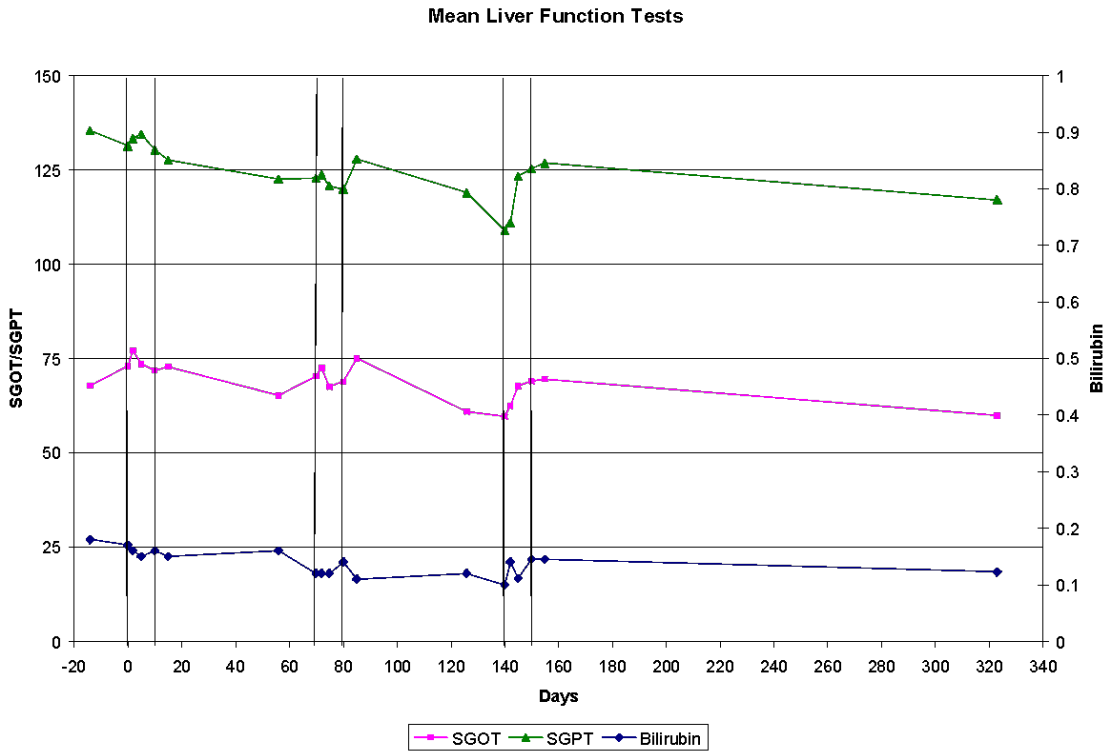

Table 6 shows the mean and median changes from baseline for the overall group for liver function tests: AST/SGOT, ALT/SGPT, and direct bilirubin. The results show paired t tests for the mean changes, and signed rank tests for the median changes. Due to the small number of patients in this series, a p-value <0.10 was considered a reasonable indicator for statistical significance. The mean and median changes that were statistically significant (p-value <0.10) are highlighted yellow in the table.

Table 6: Mean & Median Change From Baseline in Liver Function Tests

Test	Day	Mean Change	Mean P-Value	Median Change	Median P-Value
DirectBili	2	-0.015	0.394	0.000	0.500
	5	-0.025	0.397	0.000	0.500
	10	-0.015	0.520	0.000	0.453
	15	-0.025	0.322	0.000	0.500
	56	-0.015	0.685	0.000	0.563
	70	-0.055	0.003	-0.050	0.016

	72	-0.055	0.012	-0.075	0.023
	75	-0.055	0.093	-0.075	0.078
	80	-0.035	0.111	-0.025	0.125
	85	-0.065	0.009	-0.050	0.016
	126	-0.055	0.003	-0.050	0.016
	140	-0.075	0.012	-0.100	0.023
	142	-0.035	0.191	0.000	0.281
	145	-0.072	0.026	-0.100	0.047
	150	-0.039	0.154	0.000	0.156
	155	-0.039	0.228	0.000	0.313
	323	-0.061	0.002	-0.050	0.016
SGOT	2	6.800	0.121	3.750	0.154
	5	3.100	0.470	-1.500	0.939
	10	1.500	0.593	2.250	0.734
	15	2.500	0.545	1.000	0.695
	56	-5.200	0.341	-6.750	0.111
	70	0.000	1.000	-3.500	0.432
	72	2.100	0.556	0.250	0.484
	75	-2.900	0.421	-0.750	0.570
	80	-1.500	0.696	-2.750	0.287
	85	4.600	0.244	1.250	0.248
	126	-9.400	0.045	-9.750	0.047
	140	-10.700	0.016	-4.750	0.002
	142	-7.900	0.054	-5.000	0.045
	145	-3.500	0.228	-4.000	0.199
	150	-2.278	0.625	-1.000	0.734
	155	-1.722	0.801	-5.000	0.547
	323	-11.389	0.203	-13.500	0.203
SGPT	2	-0.100	0.984	-3.000	0.680
	5	1.000	0.848	-0.500	0.922
	10	-3.100	0.485	-3.000	0.432
	15	-5.700	0.428	-0.500	0.578
	56	-10.800	0.217	-6.000	0.064
	70	-10.600	0.178	-12.000	0.186
	72	-9.700	0.082	-10.500	0.064
	75	-12.600	0.013	-11.500	0.010
	80	-13.500	0.032	-9.000	0.037
	85	-5.500	0.352	-4.250	0.154
	126	-14.400	0.075	-13.250	0.049
	140	-24.400	0.007	-15.000	0.004
	142	-22.400	0.008	-12.500	0.002
	145	-11.056	0.103	-7.500	0.051
	150	-8.944	0.168	-7.500	0.184
	155	-7.611	0.323	-5.500	0.516
	323	-17.278	0.334	-16.000	0.359

It is interesting to note that significant changes in SGPT (ALT) occurred during the second and third treatment sessions (days corresponding with first, second, and third treatment sessions are highlighted in pink). While the first 4 SGPT values obtained between days 2 and 15 were not significantly different from baseline, almost all subsequent values, especially those obtained on days 56 through 145 were significantly decreased compared with the baseline value.

Biopsy Evaluations

During the course of the investigation, the Sponsor determined that the comparison of pre-study and post-study biopsies required a detailed analysis and would benefit from a review protocol that could minimize potential reviewer bias and the minimize the effect of day-to-day reviewer variability. Therefore, Energex developed a biopsy review protocol (See Appendix 4) that involved review by a panel of three liver pathologists, all of whom were blinded to the pre- or post- status of the liver specimen pairs. The reviewers used the Modified Histology Activity Index (HAI, also called the Ishak Score) System.

The pairs of pre- and post-study biopsy specimens for each patient were labeled with ID numbers that identified them as pairs, but that did not identify the patient or the pre- or post-study status of the individual specimens to the reviewers. The first reviewer (Initial Reviewer) was the pathologist at the study site. The second reviewer (Independent Reviewer) was a liver pathologist at a site not involved in this study. The third reviewer (Adjudicating Reviewer) was another liver pathologist at a site also not involved in the study. All reviewers were asked to read all the specimens in a single session. (The specimens for the last subject, 04-009-1-025, who lagged several weeks behind the rest of the study group, were to be evaluated in a separate session due to time constraints.) The Adjudicating Reviewer was asked to make a final determination in any case where the Initial and Independent Reviewers disagreed. As the Initial and Independent Reviewers disagreed in their assessments of at least one of each of the eight pairs of specimens, the Adjudicating Reviewer evaluated all eight specimen pairs.

The results of the analyses by each reviewer are shown in the two-by-two tables in Appendix 4.3. These tables show how many patients moved from one grade to another (pre- versus post-study) and how many patients moved from one stage to another (pre-versus post-study). The results are summarized in the report in Appendix 4.2 by the medical monitor, Andrew Talal, MD. Appendix 4.4 shows the actual results for each

patient assigned by each reviewer. (Note that only the review by the Initial Reviewer had been completed for patient 04-009-1-025 as of the date of this report; therefore, these results are shown in Appendix 4.4, but patient -025's results were not included in the report in Appendix 4.2 or in the two-by-two tables in Appendix 4.3, because review by the Independent Reviewer, and by the Adjudicating Reviewer have not been completed for this patient.)

With regard to improvement in liver inflammation, according to the adjudicating reviewer's assessment, two patients (04-009-1-016 and -024) demonstrated a significant improvement of at least three points in grade/inflammation. The other two reviewers also assigned significant improvement in grade/inflammation to patient -024. In the case of patient -016, one of the other reviewers (independent reviewer) assigned significant improvement in grade/inflammation to patient -016, while the original reviewer assigned only a one-point improvement to patient -016.

With regard to deterioration in liver inflammation, according to the adjudicating reviewer's assessment, two patients (04-009-1-015 and -023) demonstrated a significant deterioration of at least three points in grade/inflammation. One of the other two pathologists (the original reviewer) agreed with the adjudicating reviewer's assessment of a 3-point change in subject -015; while the other reviewer (independent reviewer) assessed only a 1-point deterioration for this patient. With regard to patient -023, neither of the other two reviewers assigned significant deterioration in grade/inflammation to patient -023. All pathologists agreed that patient -015 and -023 specimens exhibited heavy (3+/4+) hepatic iron, suggestive of confounding factors.

In terms of fibrosis, the adjudicating pathologist indicated that fibrosis had improved by one point in 3 patients (04-009-1-016, -019, -024) and worsened by one point in 1 patient (04-009-1-023). In the case of subject -023, all pathologists concurred that the patient had worsened. In the case of -016, the original reviewer agreed with the adjudicating

reviewer's assessment of improvement. In the case of -019, the second reviewer agreed with the adjudicating reviewer's assessment of improvement. In the case of -024, neither of the first two reviewers agreed with the adjudicating reviewer's assessment of improvement. In summary, with regard to fibrosis changes, three pathologists agreed that one patient (-023) had worsening of fibrosis, and at least two of three pathologists agreed that two patients had improvement of fibrosis (-016, and -019). Please see the report in Appendix 4.2 by the medical monitor, Andrew Talal, MD, for further discussion of the biopsy results.

Energex believes that these results, which show that some patients had an improvement in stage or grade of liver disease, indicates a beneficial effect of Hemo-Modulator treatment in patients with chronic HCV. Energex believes that the expected clinical progression in these study patients with chronic HCV is gradual deterioration in liver stage (fibrosis) and grade (inflammation). Therefore, the results of this pilot study, wherein two patients were seen to have marked improvement in liver inflammation (at least a 3 point improvement) after treatment with the Hemo-Modulator, suggests that the Hemo-Modulator may reduce inflammation in the liver. This potential effect of the Hemo-Modulator (reduction of inflammation) has also been suggested by other clinical results: In this study, two patients had resolution of symptoms associated with inflammatory responses. As described in the *Additional Findings* section of this report, one patient experienced resolution of a long-term psoriatic rash, and one patient experienced resolution of long-term night sweats in this Pilot. An additional patient in the first pilot study (04-008-1-012) was also reported to have experienced resolution of drenching night sweats that had persisted for years after Hemo-Modulator treatment. Energex considers the results of the liver biopsies to be the most important information gained from this Pilot, and is considering a clinical study proposal to further investigate whether the Hemo-Modulator is effective at slowing, halting or reversing liver damage in patients with chronic HCV.

Comparison of SF-36 scores: baseline versus last visit

Appendix 3 contains the graphs of each patient's SF-36 mental component score (MCS) and physical component score (PCS) over time. Because of the variability of the date from patient to patient, and because of the small sample size, it was determined that averaging the patients' results together would not be meaningful. A review of the graphs does not suggest that Hemo-Modulator treatment was associated with marked improvements or deteriorations in quality of life as measured by this tool. A few of the patients (04-009-1-016, -023, -024) seemed to experience a decline in the MCS during the active treatment phase, but recovered during the follow-up phase. (Note that the graphs in Appendix 3 were calculated from the database as of 4-13-07, and did not contain the final post-24 week and post-26-week visit SF-36 results for patients -024 and -025.)

SF-36 survey question #2 ("Compared to one year ago, how would you rate your health in general now?") is not calculated as part of the summary scores, and the responses to this question are therefore presented separately in Table 7.

Table 7: Responses to SF-36 Question 2
Compared to one year ago, how would you rate your health in general now?

Response	# of patient who selected this response
Much Better	0
Somewhat Better	1
About the Same	7
Somewhat Worse	1
Much Worse	0

Results reflect response at 26-week-post-treatment visit for each patient, except for patient -025, who did not have a 26-week-post-treatment SF-36, and whose response therefore reflects the 24-week-post-treatment SF-36.

These responses correlate well with the summary scores, indicating that Hemo-Modulator treatment does not appear to have been associated with marked improvement or worsening in this quality of life measure. The Sponsor believes that these results indicate

that the treatment was well tolerated by patients. This belief is further supported by the observation that no patient voluntarily withdrew from the study or missed any of their scheduled 15 Hemo-Modulator treatments. Energex believes that this level of patient compliance considered with the SF-36 data indicates that the treatment is well tolerated by patients.

Summary of anticipated and unanticipated adverse effects

Serious and/or Unanticipated Adverse Events	Number
Acute Coronary Syndrome	1
Vasovagal Episode	1
Porphyria Cutanea Tarda (PCT)	1
Adverse Events	
Headache	1
Hot-flashes	3*
Body Rash	1
Urinary Tract Infection	1
Hematoma at post treatment lab access site	1

** All three for same patient04-009-1-019*

Serious AEs/UADEs:

The following serious AEs have occurred during the course of the study:

- Subject 04-009-1-014: Patient arrived for Session 3/Treatment 3 (13th treatment overall) and was diagnosed with atrial fibrillation and acute coronary syndrome. The Investigator considers the event not device related. The event was reported to FDA as a UADE in Supplement 15, with a copy provided to the IRB.
- Subject #04-009-1-016 had a vasovagal episode which occurred post completion of venipuncture at initiation of blood harvesting. The patient was cool, clammy and had a decrease in blood pressure. The patient was placed in supine position, oxygen was

applied via nasal cannula at 3L and a cool compress applied to his forehead. The vasovagal response resolved, and the patient completed the treatment without further complication. The patient reported having a similar episode in the past during venipuncture. Dr. Mukherjee was informed and reports the event as being not related to the Hemo-Modulator treatment. This event was reported to FDA as a UADE in Supplement 11, with a copy provided to the IRB.

- Subject 04-009-1-016 reported to the Study Coordinator that he was diagnosed with Porphyria Cutanea Tarda (PCT) after developing areas of scaly and blistered skin on his hands and arms. The patient was subsequently treated with phlebotomy. It is the Principal Investigator's opinion and the Medical Monitor's opinion that the patient's diagnosis of PCT is not related to the Hemo-Modulator treatments. Nevertheless, since patients with PCT are susceptible to photosensitivity reactions, it is possible that exposure to the ultra-violet blood irradiation of the Hemo-Modulator treatment may have contributed to the patient's dermatological symptoms; although exposure to sunlight seems a more likely cause. This patient had completed the treatment phase of the study, and information about the patient's diagnosis of PCT was received during the post-treatment follow-up phase. The patient was followed according to the protocol. In response to this information, the Sponsor modified the protocol and the Informed Consent form to cite photosensitivity reactions in patients with PCT as a possible adverse event. While the protocol and Informed Consent already advised that photosensitivity reactions may occur in patients taking certain medications, the warning was expanded to explain that photosensitive reactions may also occur in patients with PCT. Potential subjects who have been diagnosed with PCT was added as an exclusion criteria. This was reported to the FDA as a UADE in Supplement 19, with a copy provided to the IRB.

Adverse Events:

Other adverse events have included the following:

- Subject 04-009-1-015: Headache on 4/5/06 - Moderate; resolved after taking Tylenol on 4/5/06.
- Subject 04-009-1-019: Hot Flash - Reported having two hot flashes at home on 4/12/06 that resolved spontaneously without complication. Patient also reported slight hot flash during treatment on 4/21/06, which resolved spontaneously.
- Subject 04-009-1-023: Hematoma at phlebotomy site - onset 7/5/06 at post treatment lab access site. By 7/18/06, the AE was totally resolved, with no visible ecchymosis noted.
- Subject 04-009-1-016: Patient came in for his 24-week post-treatment visit and reported that he had a urinary infection and was taking Cipro.
- Subject 04-009-1-019: Body rash - Patient reported he developed a full body rash. Patient was examined by primary care provider on 2/23/07. Patient was treated with decreasing steroid dose and OTC benadryl and pepcid. At the advice of the Principal Investigator, Dr Mukherjee, the patient was tested for pophyria cutanea tarda (PCT), but the test results were negative for PCT.

Finally, an Adverse Event case report form was completed for Subject 04-0009-1-014, although the Study Coordinator and Principal Investigator did not classify the event as an adverse event. The Study Coordinator reported, "There was no adverse event. General practitioner ordered hospitalization due to continued non-compliance with diabetes medical regimen and hypertension. June 27, 2006 subject admitted to hospital [and was] discharged on June 28, 2006." This is the same patient who was eventually discontinued from the study as a result of acute coronary syndrome requiring treatment incompatible with further Hemo-Modulator treatments (as discussed in section Serious AEs/UADEs above and reported to FDA in Supplement 15).

Energex believes that the adverse events profile exhibited in this pilot study further supports the safety of the Hemo-Moduator. Side effects were generally mild and resolved on their own or with minimal medical attention. Compared with the often intolerable side effects profiles exhibited by current drug treatment therapies for HCV,

the side-effects profile of the Hemo-Modulator would represent a real benefit for patients if effectiveness is proven. Energex believes that the compliance of the patients in this trial, who all completed all 15 treatment visits on schedule, even though some had to travel long distances, further demonstrates that Hemo-Modulator treatments are very well tolerated by patients.

Additional Findings

The Principal Investigator noted that several patients experienced unanticipated health and quality of life improvements as follows:

- One patient (04-009-1-013) had complete remission of a psoriatic skin rash which had been present for several years. The symptoms resolved during treatment, reappeared briefly after treatment cessation, and then completely resolved for the duration of the follow-up period. As this patient is a regular patient of Dr. Mukherjee, Dr. Mukherjee is able to report that the patient continues to be free of psoriasis as of June 2007, which is 9+ months from his last Hemo-Modulator treatment.
- One patient (04-009-1-025) had bothersome night sweats for approximately two years. During an interview with Dr. Mukherjee, the patient reported complete remission of this symptom during and after the study. (It should be noted that one patient from the first pilot study 04-008-1-012 also reported drenching night sweats for 4 years that completely resolved during the study.)
- One patient (04-009-1-015) reported he routinely gets “cold attacks” each year, but did not get one this year.

It is interesting to note that resolution of long-term night sweats (which can be associated with many inflammatory disorders) and psoriasis in these patients coincided with their Hemo-Modulator treatment regimens. These results may indicate avenues for future research.

Discussion of Results

A review of viral loads over time, liver function tests over time, SF-36 results over time, and reported adverse effects continue to support the general safety of Hemo-Modulator treatments. The study results did not demonstrate the anticipated effect of reduction in viral load over time to undetectable levels; however, Energex believes that the falling SGPT/ALT levels in several patients, and the observation of two patients with significantly improved signs of liver inflammation are encouraging results that will direct future research.

Description of any deviations from the investigational plan by investigators

Over the course of the entire Pilot 2 study, there have been several deviations from the investigational plan; however, none are considered to affect the scientific soundness of the study. They are summarized below.

1) Five patients (Patient ID#s: 04-009-1-013, -014, -015, -016, -018) received additional lab work at the Session 2/Treatment 1 visit. The deviation involved drawing an extra blood sample for CRP, total hemolytic complement, and T-cells subtype testing. The study protocol calls for blood to be drawn at the Session 2/Treatment 1 visit for various lab tests (including, for example, RT-PCR, Blood Chemistries and others); however, the protocol did not require the additional sample for CRP/Total hemolytic complement/T-Cells subtype at this visit. The error was due to a discrepancy between the protocol and a Sponsor-provided document, the "Pilot Study Treatment Schedule." This schedule document incorrectly listed the CRP/Total Hemolytic Complement/T-cells Subtype test as occurring at the Session 2/Treatment 1 visit. The Study Coordinator noticed that the schedule did not agree with the protocol, and brought this to the Sponsor's

attention. The Sponsor corrected the error that caused these deviations from the protocol, and reported the incident to the IRB in a letter dated June 21, 2006.

2) An extra blood draw (for CRP, Total hemolytic complement, and T-Cells subtype) was taken for four patients at the following intervals due to an oversight by the person drawing blood:
   - Patients 04-009-1-013, -015, -018: Visit Session 1, Treatment 4
   - Patient 04-009-1-014: Visit Session 1, Treatment 1
3) Patient 04-009-1-025's lab value for CH50 is not available for Session 2, Treatment 3, because of an accident at the laboratory.
4) Patient 04-009-1-019 developed a body rash during the 6-month, post-treatment follow-up period. His primary care physician treated the patient with decreasing steroid dose and over-the-counter benadryl and pepcid. The Study Coordinator reported this as a protocol deviation because exclusion criteria #9 stated, "Has the subject taken anti-coagulants or photosensitizing drugs within 7 days prior to study enrollment or may the subject require such medications during the course of study participation [Excluded drugs include: antihistamines, prescription non-steroidal anti-inflammatory drugs (NSAIDs), phenothiazine…and digitalis.]?" The Sponsor does not consider this event a significant protocol deviation because the exclusion criteria was a safety measure intended to avoid potential photosensitization reactions related to Hemo-Modulator treatment exposure. Since the patient had completed all Hemo-Modulator treatments, and was in the follow-up phase, the Sponsor does not anticipate any impact on study results or endpoints. Furthermore, as reported to FDA in the June 2006 Annual Report (Supplement 14, pages 19-20), the Sponsor had previously modified the protocol to state that during the intersession treatment intervals (approximately 55 days long) and during the post-treatments follow-up interval (6 months), patients could take short-term photosensitizing medications such as non-steroidal anti-inflammatories, antibiotics, and antihistamines, under the following conditions:

a. The investigator authorizes the use of the medication,
b. The patient may not begin taking these photosensitizing medications until 2 days following the last Hemo-Modulator treatment in the session.
c. The patient must stop taking the medication 7 days before beginning the next Hemo-Modulator treatment/session.

5) Subject 04-009-1-018 was contacted by telephone by the Study Coordinator prior to the additional/supplemental blood draws described in Supplement 17. The patient expressed willingness to undergo the additional blood draw procedure, but—because the subject lives far from the investigational site—was permitted to have the blood draw performed at a local off-site laboratory and to have the sample shipped to Warren Hospital. The patient did not sign the Addendum to the Consent Form before undergoing the additional blood draw (viral load determination). This deviation was noted during a monitoring visit. The Study Coordinator contacted the patient again, and the patient agreed to sign a statement acknowledging that she had been informed of the content of the Addendum to the Informed Consent related to the additional/supplemental blood draws. This documentation is provided as Appendix 7. The IRB was also informed of this error. Please note that this deviation does not involve use of the investigational device on a patient not properly consented. The patient had been consented prior to enrollment in the study and was already in the follow-up phase. The Addendum to the Informed Consent was related to the additional blood draw performed during the follow-up interval.
6) Subject 04-009-1-018 missed the second additional/supplemental blood draw described in Supplement 17 and scheduled for ~104 days from final treatment (second of two supplemental blood draws for viral load assessment scheduled to occur mid-way through the follow-up period).
7) Subject 04-009-1-014 missed Session 3/Treatment 3 due to a UADE, and was discontinued from further treatments. The subject did not complete the last three treatments.

8) Subject 04-009-1-016: The lab lost the specimen needed for absolute CD4 and CD8 counts for pre-baseline/Session 2.
9) Subject 04-009-1-020: After Session 1/Treatment 1 it was discovered that the patient was taking digitalis, which is not permitted under the protocol. The patient was discontinued from further Hemo-Modulator treatments.

In addition, there were two sponsor-authorized deviations from the protocol

10) In a letter to the IRB and Principal Investigator dated 12-22-2006, the Sponsor authorized a deviation to open the visit window for seven patients for their 90-day and 104-day post-final-treatment evaluations, because FDA approval on these additional visits, granted under Supplement 17, was not received until after several patients missed the time frame requested in Supplement 17. As subjects 04-009-1-013, -015, -016, -018, -019, -021, -023 were unable to complete the 90-day and 104-day post-final-treatment evaluations (because FDA approval of these additional tests was not received soon enough), the Sponsor allowed the following deviation from the protocol: Patients 04-009-1-013, -015, -016, -018, -019, -021, -023 received the 90 day post-final-treatment viral load assessment as soon as practical (following FDA's approval and IRB approval). These patients received the next viral load assessment 14 days (+/- 2 days) from the 90 day post-final-treatment assessment. The Sponsor determined that this deviation to open the time window for these evaluations did not affect the scientific soundness of the study, or the rights, safety, or welfare of the patients.
11) Subject 04-009-1-024: The Sponsor authorized a deviation that allowed this subject to be enrolled according to the protocol even though his first Hemo-Modulator treatment began several weeks after the first set of pre-baseline tests. The patient was consented and had blood drawn for pre-baseline testing on May 3, 2006. The patient was scheduled to begin H-M treatments on May 17, 2006. The patient was admitted to Warren Hospital the weekend of May 6-7 for cellulitis of the right foot. The patient injured his foot while kickboxing. He was

given IV vancomycin and Zosyn. Due to the patient's injury, participation in the H-M study was postponed. The patient was re-scheduled to begin treatment on June 7, 2006. To confirm study eligibility, the patient underwent liver biopsy and repeated the other pre-baseline tests needed to complete CRFs 4,5,6, and 7 on May 24, 2006 (2 weeks prior to new anticipated treatment start date). On June 7, 2006, the patient presented for first treatment, and had blood drawn for the pre-Treatment 1 RT-PCR according to the protocol. He then informed the Study Coordinator that he was taking Naproxyn. The patient was informed that he could not begin treatment while taking Naproxyn, because the protocol excludes patients who have taken photosensitizing medications within seven days prior to beginning Hemo-Modulator treatments. The patient stopped taking Naproxyn, and was rescheduled to begin treatment on June 14, 2006. The patient was permitted to enter the study if he had been off Naproxyn for seven days preceding treatment initiation, and if the pre-baseline data from the blood tests drawn on May 24th, and the more recent RT-PCR test results from June 7th, confirmed his eligibility. CRF 1 (Inclusion/Exclusion Criteria) was completed within 2 weeks prior to the patient beginning H-M treatment, using pre-baseline blood test values from samples drawn on May 24th (except for RT-PCR, which used the more recent June 7 data). The Sponsor believed that it was in the patient's best interests to use the pre-baseline test results obtained May 24th (which is 3 weeks from treatment start rather than 2 weeks from treatment start as indicated in the protocol), rather than to have the patient repeat the pre-baseline blood work during the 2 week window preceding treatment start. The Sponsor believed that this decision was best for the patient, and did not affect the scientific soundness of the study. Dr. Mukherjee agreed with the Sponsor's determination.

3. Risk Analysis

Summary of any new adverse information (since the last progress report) that may affect the risk analysis

As discussed under the summary of adverse effects, subject 04-009-1-016 was diagnosed with Porphyria Cutanea Tarda (PCT). It is the Principal Investigator's opinion and the Medical Monitor's opinion that the patient's diagnosis of PCT is not related to the Hemo-Modulator treatments. Nevertheless, since patients with PCT are susceptible to photosensitivity reactions, it is possible that exposure to the ultra-violet blood irradiation of the Hemo-Modulator treatment may contribute to dermatological symptoms in patients with PCT. Therefore, the Sponsor modified the protocol and the Informed Consent form to cite photosensitivity reactions in patients with PCT as a possible risk. While the protocol and Informed Consent already advised that photosensitivity reactions could occur in patients taking certain medications, the warning was expanded to explain that photosensitive reactions may also occur in patients with PCT. Finally, a diagnosis of PCT was added as an exclusion criteria. This was previously reported to the FDA as Supplement 19, with a copy provided to the IRB.

Reprints of any articles published from data collected from this study

No articles have been published from the data collected from this study.

New risk analysis, if necessary, based on new information and on study progress

Supplement 12 added vasovagal reaction to the list of possible adverse effects and Supplement 19 added photosensitivity reactions in patients with PCT to the list of possible adverse effects. The study data does not suggest the need for any further modifications to the risk analysis.

4. Other Changes

Summary of any changes in manufacturing practices and quality control:

The Sponsor has made no significant changes in manufacturing practices and quality control procedures. The Sponsor has made no changes to the Hemo-Modulator device. One change was made to the associated disposable administration sets used with the Hemo-Modulator device: the length of the tubing between the drip tube and the stopcock was changed from 24" to 42". At the request of the study nurses, additional length was added to the tubing in the administration sets to: 1) allow the nurses to handle and move the reservoir bag more easily without pulling on the patient's access device, 2) allow the bag to be hung at a greater distance from the patient to facilitate a quicker return flow, thus shortening the overall length of treatment time, and 3) more easily position the patient within a reachable distance from the Hemo-Modulator machine.

Summary of all changes in the investigational plan not required to be submitted in a supplemental application

Since the last Annual Report, several changes in the investigational plan have been reported to FDA and/or the IRB as follows:

Supp #	Date	Subject
15	9/6/06 submitted to FDA	UADE for patient -014. Patient discontinued from further treatment. No response received from FDA. IRB copied on FDA correspondence.
16	10/6/06 submitted to FDA 11/3/06 FDA response	Request 12th patient. Approved by FDA. Approved by IRB 12/7/06. (Twelfth patient not enrolled.)
17	11/17/06 submitted to FDA 12/18/06 FDA response	Request for additional viral load samples mid-way through follow-up period approved by FDA. IRB Chair confirmed IRB approval on 12/07/06.

18	12/8/06 submitted to FDA 1/9/07 FDA response	Compassionate Use for Patient, AH, approved by FDA. Approved by IRB 2/1/2007. Sponsor decided not to treat AH.
19	12/20/06 submitted to FDA.	Additional Exclusion criteria for Porphyria CutaneaTarda (PCT) added. Submitted as change being effected. No FDA response received. IRB notified.

In addition to the changes described in Supplements 15 through 19, the following changes to the investigational plan, which did not require submission to FDA, have also been implemented:

Windows on Post-24-week and Post-26-week Visits

The protocol did not specify windows for post-24 week and post-26-week visits. Therefore, the Sponsor clarified via email to the Study Coordinator that the post-24 week visit could be done post 24 weeks (-2 days, +2 weeks) to allow adequate time for scheduling a biopsy, with the post-26 week visit occurring 2 weeks from post 24-week visit (± 2 days).

Biopsy Review Protocol

The original investigational plan called for a review of liver biopsies taken before the study and at 24 weeks after the final treatment; however, the plan did not provide a specific protocol for evaluation of the liver biopsy specimens. Therefore, the Sponsor added a biopsy evaluation protocol specifying the methods by which biopsy specimens were to be evaluated. As advised by the Medical Monitor, the protocol included a second, independent review of the specimens by a pathologist trained in liver pathology. This independent reviewer, who was not otherwise involved in the study, was blinded to patient identification and to whether each specimen was from the pre- or post-study interval. The protocol also provided for adjudication by a third reviewer if the results of the original and independent reviewers differed. Finally, the biopsy review protocol included the methods for labeling the specimens, so that the privacy of the patients continued to be protected. The biopsy review protocol only specified how to evaluate the

specimens that were already being collected under the original protocol. It did not require any additional tests or specimens to be collected from the patients, or any additional visits by the patients. The IRB Chair was informed via a letter on May 15, 2007 of the biopsy evaluation plan and of the Sponsor's methods for protecting the confidentiality of the study subjects. The IRB Chair informed the Sponsor via email on May 15, 2007 that IRB approval was not required to implement these changes. The biopsy review protocol is provided in Appendix 4. A copy of the email from the IRB Chairman, Dr. Frank Gilly, is provided as Appendix 5.

5. Future Plans

Progress toward product approval, with projected date of PMA or 510(k)

The current study was a small pilot study. A review of viral loads over time, liver function tests over time, SF-36 results over time, and reported adverse effects further demonstrated that Hemo-Modulator treatments are safe and well-tolerated by patients. The study results did not demonstrate the anticipated effect of reduction in viral load over time to undetectable levels; however, Energex believes that the reduced viral loads in some patients, falling SGPT/ALT levels in several patients, and the observation of two patients with significantly improved signs of liver inflammation are encouraging results that will direct future research. Energex is considering another study protocol to evaluate the potential effect of the Hemo-Modulator device in slowing, halting, or reversing liver damage in patients with chronic HCV. Energex is currently evaluating the particular treatment regimen, patient population, and clinical endpoints that would be appropriate for future clinical investigation, and will submit an IDE Supplement to FDA as soon as these determinations have been made and the new protocol has been developed. Energex anticipates that the next IDE Supplement application will be for a pilot study poised to move directly into a pivotal trial.

Appendices

1: Viral load graphs over time for each patient

2: SGOT, SGPT, and direct bilirubin graphs over time for each patient

3: SF-36 summary score graphs over time for each patient

4: Biopsy review protocol, report, and results

5: Email from IRB Chair stating no IRB review required for biopsy review protocol clarification.

6: IRB Approvals: Approvals for 11th and 12th patients in response to FDA Approval Letters for Supplements 13 and 16. Additional IRB approval demonstrating annual re-approval.

7: Documentation of deviation related to Subject 04-009-1-018's failure to sign the Addendum to the Informed Consent prior to the additional/supplemental blood draw.

Appendix 1: Viral Load Graphs

Appendix 2: SGOT, SGPT, Direct Bilirubin Graphs

Appendix 3: SF-36 Graphs

Appendix 4: Biopsy review Information

Appendix 4.1: Biopsy Review Protocol

Appendix 4.2: Dr. Talal's Report, *Liver Biopsy Interpretation for Energex Hemomodulator Study*

Appendix 4.3: Two-by-Two Tables Summarzing findings of Three Reviewers

Appendix 4.4: Detailed Biopsy Review Spreadsheet

Appendix 5: Email from IRB Chair stating no IRB review required for biopsy review protocol clarification.

Appendix 6: IRB Approvals for Supplements 13 and 16, and for annual reapproval on March 1, 2007.

Appendix 7: Documentation of deviation related to Subject 04-009-1-018's failure to sign the Addendum to the Informed Consent prior to the additional/supplemental blood draw.