

# Clinical effect of nemifitide, a novel pentapeptide antidepressant, in the treatment of severely depressed refractory patients

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Clinical data were evaluated from an open-label, single-center, pilot study in patients with chronic refractory depression. The primary efficacy criterion was the change from baseline using the Montgomery–Asberg Depression Rating Scale. The secondary efficacy criteria were the 17-item Hamilton Depression Rating Scale and the Clinical Global Impression-Improvement scale. Response to treatment (40–240 mg once per day by subcutaneous injection for 10–20 doses) was defined as more than 50% improvement in the Montgomery–Asberg Depression Rating Scale from baseline or Clinical Global Impression-Improvement  $\leq 2$  and lasting for at least two sequential weeks. Patients with a sustained response at the end point in the acute main treatment phase were enrolled for up to 2 years in a maintenance phase of the study to determine duration of response and to initiate retreatments upon relapse. Of the 25 patients with chronic refractory depression, 11 patients showed a response for Montgomery–Asberg Depression Rating Scale and one responded according to the secondary criterion Hamilton Depression Rating Scale. In seven of the 11 responders to Montgomery–Asberg Depression Rating Scale the effects were sustained for the remainder of the acute phase. Two additional sustained responders identified according

to secondary criteria (Hamilton Depression Rating Scale or Clinical Global Impression-Improvement) were also enrolled in the maintenance phase. All nine sustained responders were retreated, as needed, in the maintenance phase of the study, ranging from 71 to 660 days. Mean duration of response following initial treatment and between retreatments was around 2 months. Pharmacokinetic data indicated dose-proportional systemic exposure to the drug. *Int Clin Psychopharmacol* 23:29–35 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2008, 23:29–35

Keywords: antidepressant, efficacy, nemifitide, refractory, safety, treatment-resistant

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Received 25 September 2006 Accepted 15 March 2007

## Introduction

Over the last 25–30 years, there has been impressive progress in depression research methodology in areas such as the genetics (Lesch, 2003) and the pathophysiology (Nemeroff, 2003a) of depression, the neural (Sokoloff, 2003) and genetic (McMahon *et al.*, 2006) mechanisms underlying the therapeutic effect of certain drugs, the biochemical lesion(s) in depression (Leonard, 2000), and functional neuroimaging (Kalin *et al.*, 1997; Leuchter *et al.*, 1997; Mayberg, 2003). There have also been significant strides in the development of new clinical approaches to the treatment of depression, including new antidepressants, psychotherapy (dynamic psychotherapy) interpersonal, behavioral therapy, and electroconvulsive therapy (Montgomery *et al.*, 1992). It is well recognized, however, that many depressed patients (up to 50%) fail either to respond to treatment or to achieve full remission. In addition, many therapies that are initially effective, fail to prevent relapse (Fawcett and Barkin, 1997; Frazer, 1997; Preskorn, 1997; Montgomery, 1999; Thase, 1999; Fava, 2000; Nelson, 2000).

The more difficult clinical situation is observed in acute treatment-resistant depression patients with a history of up to 1 year of resistance to two or more adequate antidepressant trials (Nierenberg *et al.*, 1994; Souery *et al.*, 1999; Posternak and Zimmerman, 2001; Lam *et al.*, 2002). Some new strategies regarding the management of treatment-resistant depression were published recently (Rush *et al.*, 2001a, b; Thase *et al.*, 2002; Nemeroff *et al.*, 2003b). The most serious scientific and clinical gaps are, however, observed now in the treatment of the chronic refractory depression patients defined as those patients with resistance to several antidepressant trials (extensive prior treatments, including augmentation strategy) and duration of trial(s) of more than 12 months (Souery *et al.*, 1999; Dursun and Devarajan, 2001; Alexander and Perry, 2003). It is well known that clinical trials in treatment-resistant depression are rare, but not nearly as rare as in chronic refractory depression. Some algorithms are there for the treatment of chronic refractory depression patients (Phillips and Nierenberg, 1994): augmentation strategy (lithium, thyroid hormone, psychostimulants),

combining an antidepressant strategy (selective serotonin reuptake inhibitor with tricyclics) and switching strategy (one antidepressant class to another or within the same class). No scientific evidence exists regarding any significant advantage of either of these algorithms over the other two and, in practice, the effect of any treatment depends on an evaluation of the clinical status for each individual patient (Lam *et al.*, 2002). Moreover, there is no placebo-controlled clinical trial in a refractory depression population with an adequate sample size to support the efficacy of any of these three algorithms versus monotherapy with a novel antidepressant.

Nemifitide (Hlavka *et al.*, 1997), a synthetic antidepressant pentapeptide, was initially evaluated in placebo-controlled studies as a monotherapeutic drug for the treatment of patients with major depressive disorder and demonstrated remarkable antidepressant activity with rapid onset of action, sustained clinical effect following 5–15 doses, and very good tolerability and clinical safety profile (Kelly *et al.*, 1996; Feighner *et al.*, 2000a,b, 2001, 2002, 2003; Feighner and Sverdlov, 2002; Feighner, 2003; Montgomery *et al.*, 2006). The objective of this study was to determine the safety and relative efficacy and duration of efficacy of nemifitide in treating chronic refractory depression patients who had a well-established history of treatment resistance to multiple therapies for over 3 years.

## Method

This was a single-center, open-label, pilot study ( $N = 25$ ) of nemifitide in men and women outpatients, 18 years of age or older who met *Diagnostic and statistical manual of mental disorders*, fourth criteria for major depressive disorder and who had a well-established psychiatric history of being refractory to multiple prior antidepressant treatment regimens. The primary objective of this study was the safety issue during the whole period of observation and the effect of treatment in the acute phase using a wide range of doses of nemifitide. The secondary objective was the duration and stability of response over time in the long-term maintenance phase up to 2 years.

Entry criteria incorporated all of the following: (i) a Montgomery–Asberg Depression Rating Scale (MADRS) score  $\geq 25$ ; (ii) no or minimal response to repeated treatments with at least three different antidepressants from two of the following four classes: tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI) or atypical antidepressants (ATA) (one of three antidepressants could be replaced by electroconvulsive therapy (ECT); and (iii) failure at one or more attempts of augmentation therapy (AUG) or other mood stabilizers (MST).

The most important items in the exclusion criteria were (i) a history or presence of psychotic symptoms or bipolar I disease, (ii) a bipolar II episode in the past and maintenance on mood stabilizers, (iii) use of ECT within 3 months before screening, (iv) Prozac within 1 month of screening or MAOIs within 14 days of screening or any other antidepressants within 7 days of screening, (v) regular treatment with L-3,4-dihydroxyphenylalanine or other dopaminergic agents (Eldepryl, Parlodel, and so on), and (vi) a history or presence of significant cardiovascular, renal, hepatic, gastrointestinal, endocrine, nervous system or any other conditions that could interfere with the safety of the patients.

The primary efficacy criterion was a change from baseline for MADRS. The secondary efficacy criteria were the 17-item Hamilton Depression Rating Scale (HAMD), Carroll Self-Rating Depression Scale, and Clinical Global Impression-Improvement (CGI-I). Response for MADRS or HAMD was defined as an improvement of  $\geq 50\%$  from baseline or a CGI-I  $\leq 2$  lasting at least two sequential weeks. A sustained response to treatment using the MADRS, HAMD or CGI-I was defined as lasting through to the end point of the acute treatment.

Partial response was defined as improvement  $\geq 33\%$  from baseline for MADRS or HAMD and lasting at least two sequential weeks.

Each patient enrolled received daily subcutaneous injections of nemifitide of 20, 40, 80, 160 and/or 240 mg/day, as determined by the principal investigator. The initial treatment of 2 weeks duration (acute phase) consisted of two 5-day dosing cycles (Monday–Friday) separated by 2 days (Saturday–Sunday), followed 1 week later by one or two optional 5-day dosing cycles (additional acute treatment), if deemed appropriate by the investigator. Patients with a sustained response at the end point in the acute treatment phase, as measured by the primary (MADRS) or any secondary psychometric scores, HAMD, CGI-I, were enrolled in the extension study (maintenance phase) to determine the duration of response and to initiate retreatments upon relapse. The period of observation for the maintenance phase was up to 2 years. During the maintenance phase, responders were evaluated on a monthly basis. According to the judgment of the principal investigator, the patient with a relapse in the maintenance phase could be retreated with nemifitide with a regimen in accordance with the initial treatment as many times as needed until termination from the study. Duration of response in the maintenance phase was calculated as duration of response = (day of relapse – start day of previous response) + 1. If the patient was terminated in the maintenance phase with response at the end of trial day, then the duration of response was calculated as Duration of Response = (End of Trial Day – Start Day of the Last Response) + 1.

The safety profile was evaluated regarding adverse events, concomitant medications and vital signs, ECG, clinical laboratory analysis and physical exams.

The pharmacokinetic profile was evaluated from plasma concentrations of nemifitide measured by using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) assay. Blood samples were collected at 10 min after dosing on day 5 of the first dosing cycles, processed and stored at  $-70^{\circ}\text{C}$  until analyzed (Feighner *et al.*, 2002).

All potential participants in the study provided written informed consent. An institutional review board approved the protocol.

## Results

### Demographic and baseline characteristics

Of the 25 patients enrolled in the study (intent-to-treat population), 22 completed the initial treatment with a minimum of 10 doses of nemifitide. Three patients (one 39-year-old man with current baseline MADRS = 35, one 19-year-old woman with current MADRS baseline = 46, another 48-year old woman with current baseline MADRS = 44) withdrew voluntarily during the main treatment after 7–9 doses of nemifitide because of lack of perceived efficacy but not because of adverse effects.

Of the 25 patients, 16 were women and nine were men. Mean age was 42.2 years (range 19–64 years). All patients were Caucasian. The mean baseline for MADRS was 37.8 (median = 38, range from 31 to 46) and HAMD – 27.2 (median = 28, range from 18 to 35). Mean baseline for Clinical Global Impression, severity of illness, evaluated by the investigator, was 5.4 (range 5–7). The most frequent final dose was 160 mg/day and the majority of patients required an increase of the initial dose of nemifitide from 20 to 80 mg/day to the final doses of 160–240 mg/day.

### History of depression and prior treatments

Mean age at the first episode of depression for the 25 patients enrolled in this study was 22.7 years (range 5–43 years). The enrolled population consisted of 15 patients (60%) with multiple episodes of depression and 10 patients (40%) with a single episode of depression that did not respond to any of the treatments mentioned in the inclusion criteria. Mean length of the current episode was 8.3 years (range: 3–21 years). Ten different classes of treatments were considered for each individual patient before enrollment into this study (Table 1), such as TCA, MAOI, SSRI, ATA, MST (anticonvulsants/antimanics), AUG, anxiolytics, antipsychotics, ECT and other therapy. Each treatment class could include many different types of drugs. The most used frequently were SSRI (25 patients), ATA (25 patients), MST (24 patients),

AUG (23 patients), TCA (22 patients) and anxiolytics (20 patients). The number of treatment classes varied from (minimum of) three classes (one patient) to 10 classes (four patients). The most frequently used SSRI drugs were Prozac, Zoloft, Paxil and, in the ATA class, Effexor and Remeron.

### Safety

In this study, nemifitide demonstrated a good safety profile for all parameters. The most common side effects were as follows: bruising and erythema (edema) at the injection site, itching at the injection site, headache, abdominal cramps/pains and nausea. Most of the side effects reported were mild and transient. The incidence of adverse events for the refractory population after treatment with nemifitide was similar to that reported after treatment of major depression in other studies with the same drug (Feighner *et al.*, 2001, 2003; Montgomery *et al.*, 2006). One dropout occurred because of a serious adverse effect (SAE), a patient with an excellent response to nemifitide who developed an anaphylactic reaction. This patient (who had a history of allergic reaction to multiple drugs and foods) had been retreated every 2 or 3 months to retain remission and developed the anaphylactic reaction after 38 injections, mostly at 160 mg/day, in the acute treatment and maintenance phases. The investigator considered this serious event to be nonlife-threatening, but study drug-related and treatment of this patient was discontinued.

### Efficacy

Table 2 presents the results of responses, partial responses and sustained responses for the three psychometric scores (MADRS, HAMD and CGI-I). Eleven patients responded, as measured by the primary efficacy criterion (MADRS), and one responded, as measured by the secondary criterion HAMD, for a total of 12 responders. Of the 11 responders according to MADRS, nine patients had received 19–20 doses of nemifitide and two patients, 10 doses of nemifitide. The main treatment doses in the group of the 11 responders were 240 mg/day (two patients), 160 mg/day (six patients), 80 mg/day (two patients) and 40 mg/day (one patient).

At the end point of the acute treatment phase of the 11 responders, seven sustained the response according to the MADRS criterion, one by using the HAMD and one by using the CGI-I. These nine sustained responders were enrolled in the maintenance phase of the study. A summary of the maintenance phase is presented in Table 3. The full period of observation starting from the acute phase until the end of trial day varied from 71 to 660 days. Five sustained responders (patients 004, 005, 008, 013 and 022) demonstrated multiple responses after relapses using effective retreatment. These five sustained responders were terminated because of

**Table 1 Summary of history of prior treatment by patient**

Subject no.	Prior treatments (before enrollment into the refractory study)										Total types of treatment before enrollment	Length of current episode in years
	TCA	MAOI	SSRI	ATA	MST	AUG	ANX	APS	ECT	OTH		
001	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8	4
002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10	6
003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9	6
004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8	10
005	Yes	No	Yes	Yes	Yes	No	Yes	No	No	No	5	4
006	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	8	20
007	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9	11
008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	7	19
009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10	7
010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	9	15
011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10	21
012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9	5
013	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7	7
014	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	6	3
015	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9	10
016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10	6
017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9	7
018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8	16
019	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7	10
020	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	No	6	9
021	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	5	10
022	No	No	Yes	Yes	No	Yes	No	No	No	No	3	5
023	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	7	12
024	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	6	5
025	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	6	8
Total patients	22	14	25	25	23	23	20	16	10	12		

ANX, anxiolytics; APS, antipsychotics; ATA, atypical antidepressants; AUG, augmentation strategies; ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitors; MST, mood stabilizers (anticonvulsants/antimanic); OTH, other therapy; SSRI, selective serotonin reuptake inhibitors; TCA, tricycles antidepressants.

**Table 2 Patient response for MADRS, HAMD and CGI-I**

Patient no.	MADRS response			HAMD response			CGI-I response		Enrolled in maintenance phase
	Responder <sup>a</sup>	Partial <sup>b</sup>	Sustained <sup>c</sup>	Responder <sup>a</sup>	Partial <sup>b</sup>	Sustained <sup>c</sup>	Responder <sup>a</sup>	Sustained <sup>c</sup>	
001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
002									No
003		Yes			Yes				No
004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
006									No
007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
008				Yes	Yes	Yes			Yes
009									No
010									No
011									No
012									No
013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
014									No
015									No
016									No
017	Yes	Yes		Yes	Yes				No
018									No
019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
020	Yes	Yes		Yes	Yes		Yes		No
021	Yes	Yes		Yes	Yes		Yes		No
022	Yes	Yes		Yes	Yes		Yes	Yes	Yes
023									No
024									No
025	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total patients (%)	11 (44.0)	12 (48.0)	7 (28.0)	12 (48.0)	13 (52.0)	8 (32.0)	10 (40.0)	8 (32.0)	9 (36.0)

CGI-I, Clinical Global Impression-Improvement; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale.

<sup>a</sup>Means  $\geq$  50% change from baseline for MADRS or HAMD or CGI-I=1 or CGI-I=2 and lasting at least two sequential weeks.

<sup>b</sup>Means  $\geq$  33.3% change from baseline for MADRS or HAMD and lasting at least two sequential weeks.

<sup>c</sup>Means  $\geq$  50.0% change from baseline for MADRS or HAMD or CGI-I=1 or CGI-I=2 and lasting at least two sequential weeks, including through end point on the acute treatment phase.

Table 3 Summary of maintenance phase for sustained responders

Patient no.	Number of doses in acute/maintenance phases	Day of response	Day of relapse	EOT <sup>a</sup> day	Duration of response <sup>b</sup>	Psychometric scores at day of relapse or EOT <sup>a</sup> day				Reason for termination
						MADRS	HAMD	CSRDS	CGI-I	
001	20/10	15	71	–	57	29	19	22	NA	Unsatisfactory therapeutic effect in the maintenance phase after the last relapse
		–	–	92	–	25	11	4	3	
004	20/28	15	131	–	117	21	20	12	3	Unsatisfactory therapeutic effect in the maintenance phase after the last relapse
		148	232	–	85	44	30	20	NA	
		260	288	–	29	26	17	14	NA	
		–	–	316	–	33	27	16	4	
005	10/35	8	136	–	129	32	24	29	3	Administrative reasons <sup>c</sup>
		162	295	–	134	27	20	30	3	
		317	421	–	105	28	22	18	NA	
		435	603	–	169	31	23	24	NA	
007	10/15	610	–	660	51	10	7	3	1	Unsatisfactory therapeutic effect in the maintenance phase after the last relapse
		15	92	–	78	28	23	31	NA	
		–	–	117	–	40	26	34	4	
008	20/10	12	22	–	11	28	18	12	3	Administrative Reasons <sup>c</sup>
		45	130	–	86	18	17	7	3	
		156	–	156	1	22	11	19	3	
013	19/19	29	127	–	99	34	23	25	NA	SAE <sup>d</sup>
		141	162	–	22	24	18	18	3	
		169	197	–	29	31	17	14	2	
		205	–	290	86	20	14	16	2	
019	20/19	22	65	–	44	37	28	34	NA	Unsatisfactory therapeutic effect in the maintenance phase after the last relapse
		–	–	127	–	45	28	24	4	
022	20/30	15	29	–	15	17	12	12	3	Administrative reasons <sup>c</sup>
		36	85	–	50	42	29	31	5	
		197	–	268	72	12	11	9	2	
025	20/7	36	54	–	19	24	16	27	NA	Unsatisfactory therapeutic effect in the maintenance phase after the last relapse
		64	–	71	8	35	23	31	3	

CGI-I, Clinical Global Impression-Improvement; CSRDS, Carroll Self-Rating Depression Scale; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SAE, severe adverse effect.

Sustained Response (MADRS): Patients 001, 004, 005, 007, 013, 019, 025; Sustained Response (HAMD): Patient 008; Sustained Response (CGI-I): Patient 022.

<sup>a</sup>EOT-end of trial day.

<sup>b</sup>Duration of response=(day of relapse – start day of previous response)+1 or (EOT day – start day of the last response)+1.

<sup>c</sup>Study was terminated by the sponsor; not related to efficacy or safety.

<sup>d</sup>Anaphylactic reaction.

unsatisfactory therapeutic effect after the last retreatment. One sustained responder was terminated as a result of a SAE. This patient was reevaluated 23 days after the day of the SAE and the patient still had a response to retreatment. Three sustained responders were terminated from the study by the sponsor for various administrative reasons not related to efficacy or safety. Mean duration of response following initial treatment and between retreatments was around 2 months and varied in the maintenance phase from 8 to 169 days.

### Pharmacokinetics

Systemic exposure to nemifitide was evaluated from plasma concentrations in samples collected as described in the Methods section. The 10 min postdose collection time (observed  $T_{max}$ ) was selected based on our experience from both preclinical and pharmacokinetic clinical studies with nemifitide (Feighner *et al.*, 2002). The samples were collected from most patients (17) enrolled in the study and stored frozen over a long period of time, reflecting the duration of the various, multiple

**Table 4** The magnitude of response for responders for MADRS, HAMD, CSRDS and CGI-I

Patient No.	MADRS		HAMD		CSRDS		CGI-I
	Baseline	Peak effect <sup>a</sup>	Baseline	Peak effect <sup>a</sup>	Baseline	Peak effect <sup>a</sup>	Peak effect <sup>a</sup>
001	37	2	21	2	27	5	1
004	40	1	27	2	36	6	1
005	34	3	26	5	36	4	1
007	39	9	30	7	37	4	1
008 <sup>b</sup>	36	14	27	11	19	3	2
013	46	6	33	6	37	6	1
017	40	11	33	7	35	15	2
019	43	14	32	14	27	10	2
020	35	8	23	5	22	4	2
021	39	10	26	8	36	6	2
022	31	9	22	5	NA	9	1
025	42	6	26	7	NA	8	1

CGI-I, Clinical Global Impression-Improvement; CSRDS, Carroll Self-Rating Depression Scale; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale.

<sup>a</sup>Peak effect in acute main treatment phase of study.

<sup>b</sup>Effect lasted 10 days.

treatments, but all samples were analyzed together. Blood collection for pharmacokinetic evaluation started while the study was in progress (following a protocol amendment) and most samples were, therefore, collected from patients receiving higher doses of nemifitide. The number of samples collected and analyzed was two, 17, 15 and seven from the patients receiving doses of 40, 80, 160 and 240 mg, respectively. The results showed a relatively large inter-patient and intra-patient variability, most likely because of the different storage time of individual samples prior to analysis. Nevertheless, the mean concentrations ( $C_{max}$ ) of nemifitide were 90, 220, 499 and 1081 ng/ml in the patients receiving doses of nemifitide of 40, 80, 160 and 240 mg, respectively, indicating dose proportional systemic exposure to the drug.

## Discussion

All 25 patients enrolled in this study had a long history of depression, with no or minimal response to treatment and, according to our inclusion criteria, met the definition of a chronic refractory depression patient. Upon reviewing the literature, the authors did not find a clinical trial where the patients appeared to be among the same high refractory level as in this study.

Analysis of our data (listed in Table 2) revealed a significant level of correlation between the three psychometric scores (MADRS, HAMD, CGI-I). Patients with a full or partial response demonstrated by one psychometric score (for e.g., MADRS) would have a high probability of response, if measured by the other psychometric scores (HAMD or CGI-I). As seen in Table 2, only two patients responded to one psychometric score without a corresponding response to other psychometric scores. Patient number 008, responded only for HAMD, and patient number 022 showed a sustained response only for CGI-I.

Additional analysis of magnitude of response is presented in Table 4 for responders using MADRS, HAMD, CSRDS and CGI-I for baseline and peak effect in the acute main treatment phase of the study. Table 4 shows a very high magnitude of response for all responders. For example, MADRS at peak effect in the acute phase varied from 1 to 14 (baseline varied from 31 to 46) and for HAMD from 2 to 14 (baseline varied from 21 to 33). Magnitude of response at peak effect in the acute phase measured by CGI-I varied from 1 to 2. The majority of responders (8 of 11) demonstrated peak effect at the end point of the acute main treatment phase (after 20 doses of nemifitide).

As the majority of refractory patients need systematic retreatments over long periods of time, our study design included a maintenance phase to determine duration of response and initiate retreatment upon relapse.

This was the first pilot open-label preliminary study with nemifitide for a refractory population with a relatively small number of patients and without a placebo group. Forty-four percent response rate for MADRS in the acute main treatment phase and multiple responses after relapse and effective retreatment in some patients who entered into the maintenance phase are promising efficacy results for nemifitide in this chronic refractory depression population. The optimal dose, duration, clinical strategy in the maintenance period and a program for preventive treatment need additional clarification. The authors are aware of the practical and ethical difficulties of designing future studies in this population. The strength of the data indicating a marked response to nemifitide in this chronic refractory depression population is, however, the key reason for our plans to proceed with future studies to evaluate further the efficacy and safety of the drug.

## Conclusion

The data obtained in this study indicate that nemifitide is a promising, well-tolerated antidepressant for the treatment of chronic refractory depression. Further trials are planned to verify the findings of this study.

## Acknowledgements

The authors express their appreciation for the cooperation and support of this study by the staff of the Feighner Research Institute. We also thank several members of our Scientific advisory board (Drs S. Montgomery, A. Schatzberg, S. Preskorn, S. Stahl, A. Nierenberg) for their help in developing the study design and in the evaluation of the results. The study was funded by Tetrigenex Pharmaceuticals, Inc. All authors represent the interest of Tetrigenex.

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