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The long-term effect of quetiapine ('Seroquel') on weight in patients with schizophrenia

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Running Header: Long-term effect of quetiapine on weight

Abstract

Quetiapine ('Seroquel') is an atypical antipsychotic drug with demonstrated efficacy and tolerability. Although there are differences between compounds, some typical antipsychotics (quetiapine in particular) have a reduced incidence of debilitating extrapyramidal symptoms (EPS). This has led to a greater focus on other side effects, such as weight gain. We report the long-term weight changes observed in two populations of patients with schizophrenia treated with quetiapine. The first comprises 2023 patients who received quetiapine (mean dose 446 mg/day) in controlled, uncontrolled and open-label extension (OLE) trials. However, since these patients were permitted other antipsychotic medications concomitantly during the OLE, a second cohort was studied, comprising 427 patients from controlled and OLE trials who received quetiapine (mean dose 475 mg/day) as their only antipsychotic medication during the OLE.

In the larger cohort, there was a small mean weight increase of 2.07 kg (n=775) over the first 5–6 weeks. Similar mean weight increases were observed over 12 months. Patients receiving quetiapine monotherapy in the OLE showed only minimal weight changes over 12 months of treatment. Mean weight change from baseline was -0.17 kg after 5–8 weeks (n=49); 1.58 kg after 9–13 weeks (n=171); and -1.47 kg after 40–52 weeks (n=37). There was a trend for any weight gain to be greater in those patients with lower baseline BMI. No dose-related effects on weight were observed.

These results indicate that any weight gain associated with long-term quetiapine monotherapy is minimal. Indeed in patients treated with quetiapine monotherapy (mean dose 475 mg/day), there was a net loss of 1.47 kg after 12 months. The weight gain assessed at 9–13 weeks is

25% less than that associated with risperidone at 10 weeks and only 35–40% of that reported with olanzapine and clozapine.

Word count: 292

Abstract (long version)

Quetiapine ('Seroquel') is an atypical antipsychotic drug with demonstrated efficacy and tolerability. Although there are marked differences between compounds, atypical antipsychotics have a reduced tendency to cause debilitating extrapyramidal symptoms (EPS) compared with earlier antipsychotic agents. Quetiapine, for example, has a particularly favourable EPS profile, with an incidence of EPS no different from placebo across the entire dose range. The reduced incidence of EPS has led to a greater focus on other side effects, such as weight gain. We report the long-term weight changes observed in two populations of patients with schizophrenia treated with quetiapine. The first comprises 2023 patients who received quetiapine (mean dose 446 mg/day) in controlled, uncontrolled and open-label extension (OLE) trials. However, since these patients were permitted other antipsychotic medications concomitantly during the OLE, a second cohort was studied, comprising 427 patients from controlled and OLE trials who received quetiapine (mean dose 475 mg/day) as their only antipsychotic medication during the OLE. Weights were grouped using an observed cases approach, within specified time intervals.

In the larger cohort, there was a small mean weight increase of 2.07 kg (n=775) over the first 5–6 weeks. Similar mean weight increases of 2.23 kg (n=165), 2.16 kg (n=454) and 3.05 kg (n=312) were observed at 9–10 weeks,, 6–9 months and 9–12 months, respectively. Patients receiving quetiapine monotherapy in the OLE showed only minimal weight changes over 12 months of treatment. Mean weight change from baseline was -0.17 kg after 5–8 weeks (n=49); 1.58 kg after 9–13 weeks (n=171); and -1.47 kg after 40–52 weeks (n=37). Only one patient in each cohort withdrew as a result of an adverse event of weight gain.

Analysis of data from the clinical trials database showed there was a trend for any weight gain to be greater in those patients with lower baseline BMI. No dose-related effects on weight were observed.

These results indicate that any weight gain associated with long-term quetiapine monotherapy is minimal. Indeed in patients treated with quetiapine monotherapy (mean dose 475 mg/day), there was a net loss of 1.47 kg after 12 months. The weight gain assessed at 9–13 weeks is 25% less than that associated with risperidone at 10 weeks and only 35–40% of that reported with olanzapine and clozapine.

Word count: 380

Key points

- The reduced tendency of atypical antipsychotics to cause extrapyramidal symptoms has led to a greater focus on other side effects, such as weight gain.

- Analysis of weight data from a total of 2450 patients with schizophrenia shows that quetiapine treatment is associated with no or minimal mean weight increase in the first 5–6 weeks of treatment with little further mean change observed over 12 months. In patients receiving quetiapine monotherapy (n=427), there was a net weight loss of 0.17 kg after 5–8 weeks' treatment, with a net gain of only 1.58 kg after 9–13 weeks' treatment. After 12 months' monotherapy with quetiapine, patients experienced a net weight loss of 1.47 kg.

- Quetiapine used in monotherapy has a weight-gain profile lower than that of risperidone and less than half that of olanzapine or clozapine, and is associated with only minimal changes in weight in the long-term treatment of schizophrenia.

- The combination of efficacy, good tolerability and only minimal effects on weight suggests that quetiapine has a favourable benefit–risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

Key words

Atypical antipsychotics — quetiapine — schizophrenia — weight gain

Introduction

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. For many years, conventional antipsychotic agents have been widely used to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms [EPS]) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment (Van Putten, 1974; Whitworth and Fleischhacker, 1995). Such adverse effects of the older, typical antipsychotics caused a great deal of distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% within 2 years (Perkins, 1999).

Many of the newer, atypical antipsychotic agents have an improved tolerability profile, with a reduced tendency to cause debilitating extrapyramidal symptoms (EPS) compared with earlier antipsychotic agents (see Meats, 1997). However, there are marked differences between compounds — quetiapine, for example, has a particularly favourable EPS profile, with an incidence of EPS no different from placebo across the entire dose range (Arvanitis et al, 1997). With the resulting diminution in prevalence of the very debilitating EPS, more attention is being focused on other side effects of these agents, including a propensity to induce weight gain, seen with most atypical antipsychotics to a greater or lesser degree (Wirshing et al, 1999). In some cases, this may adversely affect patients' quality of life and possibly treatment compliance.

It has been recognised for more than 40 years that there is an association between antipsychotic medication and weight gain (Mefferd et al, 1958). In the past, weight gain has

been linked to efficacy of antipsychotic medication, with research linking a positive outcome with increased weight. However, more recent research has shown this not to be the case (Umbricht et al, 1994; Bustillo et al, 1996).

Weight gain is associated with increased morbidity and mortality from a wide range of conditions including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnoea and respiratory problems (Solomon and Manson, 1997; National Institutes of Health, 1998). It is also linked with morbidity related to the disease being treated. Studies have shown that weight gain causes relatively more distress than many of the other common side effects associated with antipsychotic medication (Weiden et al, 1986; Weiden, 1999). If weight gain is considered by the patient to be unacceptable, compliance with the antipsychotic may be reduced and a worsening of the psychotic condition may ensue.

The extent to which each antipsychotic agent is associated with weight gain varies considerably (Allison et al, 1999; Wirsching et al, 1999). Weight gains of 4.45, 4.15 and 2.10 kg have been observed following 10 weeks' treatment with clozapine, olanzapine and risperidone, respectively (Allison et al, 1999). Weight changes similar to those seen with risperidone have been reported for quetiapine in a preliminary analysis in 2216 patients with psychotic symptoms (Rak et al, 2000). This analysis included a small proportion of patients (8.7%) with psychoses other than schizophrenia. However, patients were permitted to use other antipsychotics concomitantly with quetiapine in the open-label extensions (OLEs) of the clinical studies, which may lead to problems with interpretation of the results as the possibility that changes in weight were attributable to other agents cannot be excluded.

Since the impact of weight gain during long-term therapy with atypical antipsychotic agents is an important consideration for patients with schizophrenia, the aim of the present analyses was to assess weight changes in patients with schizophrenia during long-term treatment with quetiapine. We report the results of two analyses: the first utilises the data in the preliminary report, including only those patients with schizophrenia, and the second focuses on quetiapine studies where no other antipsychotic medications were permitted during the OLE phase (ie quetiapine as monotherapy). In addition, we have examined the quetiapine clinical trials database to ascertain whether there is any dose-related effect on changes in weight, or any effect of body mass index (BMI) or gender.

Methods

Weight data from controlled and uncontrolled clinical trials of quetiapine and the OLE extensions were analysed. Patients with psychotic symptoms were evaluated for eligibility to enter controlled and uncontrolled studies of quetiapine according to the inclusion and exclusion criteria of the particular study. Following the clinical trial, patients were allowed to enter into an open-label extension phase where appropriate. For the purposes of this study, only data from those patients who had schizophrenia were analysed.

All concomitant antipsychotic medication was stopped prior to entry into the clinical studies. Concomitant antipsychotic medication was allowed in the OLE phase of the first study, whereas no other antipsychotics were permitted in the second.

Patient weight was assessed at baseline and at least once during follow-up. Follow-up differed according to the type of trial, ranging from 6 weeks to beyond 12 months. Patients were not assessed following withdrawal of therapy.

Statistical analyses

Weights were summarised using an observed cases approach within specified time intervals. No formal statistical analysis was performed on these data.

Results

Cohort 1

Weight data were analysed from 2023 patients with schizophrenia from Phase II and III controlled, uncontrolled and OLE studies. Out of the original 2216 patient cohort, 193 who had a DSM-IV diagnosis other than schizophrenia were excluded from the current analysis. Patient demographics are presented in Table 1.

The overall mean weight change from baseline during the first 5–6 weeks of treatment was 2.07 kg (n=775). Similar mean weight increases from baseline of 2.23 kg (n=165) at 9–10 weeks, 2.16 kg (n=454) at 6–9 months, and 3.05 kg (n=312) at 9–12 months were observed. The mean daily dose of quetiapine for patients with schizophrenia was 446 mg at 9–12 months. A plot of mean weight increase against treatment duration is presented in Figure 1. Weight gain for olanzapine over a similar time period is presented in Figure 2 for comparison (Kinon et al, 1998).

Cohort 2

Weight data were analysed from 427 patients with schizophrenia from Phase IIIb controlled and OLE studies. These patients were allowed only quetiapine as their antipsychotic medication throughout the course of the study and the open-label extension phase. Patients received a mean daily quetiapine dose of 475 mg at completion of the open-label trial. Patient demographics are presented in Table 1.

Minimal weight changes were observed over 12 months of treatment with quetiapine. Mean weight changes from baseline were -0.17 kg after 5–8 weeks (n=49); 1.58 kg after 9–

13 weeks (n=171); 0.29 kg after 14–26 weeks (n=153); 1.73 kg after 27–39 weeks (n=128); and -1.47 kg after 40–52 weeks (n=37). A plot of mean weight increase against treatment duration is shown in Figure 3.

Withdrawals due to weight gain

Only one patient withdrew from each cohort (0.22% and 0.05%, respectively) as a result of an adverse event of weight gain.

Effect of quetiapine dosage

Review of short-term data from a dose-ranging study in patients with schizophrenia (Trial 13; Arvanitis et al, 1997) and from patients with schizophrenia in the overall database indicates that increasing dose does not result in an increase in mean weight gain (Table 2) — ie any effects on weight are not dose-related.

Effect of body mass index

Relative changes in weight over the 12-month treatment period are presented in Table 3, for patients with low, medium or high baseline BMI values, respectively These reveal a trend for any weight gain to be greater in those patients with lower baseline BMIs.

Effect of gender

There was no clinically relevant difference in the mean weight gain between male and female patients with schizophrenia at any of the time periods recorded, although the increase was numerically greater for males compared with females (Table 4).

Discussion

Our analysis of weight changes in a large cohort of patients permitted concomitant antipsychotic therapy shows that quetiapine treatment was associated with only a modest mean increase in weight (2.07 kg at 5–6 weeks and 2.23 kg at 9–10 weeks). This is considerably less than that recently reported for clozapine and olanzapine, and similar to that associated with risperidone (Allison et al, 1999). This increase in weight occurred predominantly in the first few weeks of treatment. The mean weight gain at 5–6 weeks was similar in those patients receiving quetiapine treatment for <3 months, 3–6 months and >6 months, indicating that any acute weight gain in patients permitted concomitant antipsychotic therapy did not appear to predict long-term increases. Patients with lower BMIs (<23 kg/m^2) had a numerically greater weight gain compared with those with normal (23–27 kg/m^2) or high BMIs (>27 kg/m^2). There was no clinically relevant difference in the mean change in weight between male and female schizophrenic patients.

Although interpretation of weight changes in this cohort is not straightforward, in that patients were permitted concomitant antipsychotic medications during the OLE phase of the trials, the mean weight gain was still modest and similar to that seen with risperidone. However, without a parallel comparator or placebo group it is difficult to ascribe the extent to which any weight change is directly attributable to any individual agent. The results of our second analysis suggest that factor(s) other than quetiapine treatment itself may contribute to the weight gain observed in the large cohort. In clinical studies where no other antipsychotic medications were permitted during the OLE phase of treatment, quetiapine was associated with only minimal changes in weight, both in the short term and over the course of the analysis, with a net weight loss of 1.47 kg after 52 weeks' treatment. Based on this analysis,

any weight gain associated with quetiapine treatment (1.58 kg at 9–13 weeks) is 25% less than that associated with risperidone (2.10 kg at 10 weeks) and 35–40% of that reported with olanzapine and clozapine (4.15 and 4.45 kg, respectively, at 10 weeks) (Allison et al, 1999). Furthermore, at 5–8 weeks, there was a small net loss in weight (of 0.17 kg). Weight changes occurring in the first weeks of treatment, particularly in patients who have previously been untreated, have important implications for compliance with long-term antipsychotic medications (Wetterling and Mussigbrodt, 1999). In this regard, therefore, quetiapine would appear to have a significant advantage over other antipsychotics such as clozapine and olanzapine. Indeed, in a recent study of patient satisfaction with quetiapine, the combination of efficacy and a favourable tolerability profile were reflected in high levels of patient satisfaction and acceptance of long-term treatment (Hellewell et al, 1999).

Weight gain with certain antipsychotics (eg clozapine, olanzapine) can be associated with the development of diabetes (Sussman and Ginsberg, 1999). Interestingly, the addition of quetiapine to on-going clozapine therapy in 65 patients initially treated with clozapine for 6 months (during which time the mean weight gain was 6.5 kg) resulted in a mean weight loss of 4.2 kg over 10 months (Reinstein et al, 1999). Furthermore, glycaemic status improved significantly with the addition of quetiapine in the 20% of patients who developed diabetes while on clozapine therapy. During the first 5–6 months of combination clozapine–quetiapine therapy, insulin requirements decreased and insulin was later discontinued, being replaced by a regimen of oral glibenclamide (glyburide) at 3–4 mg/day. Glycosylated haemoglobin levels returned to normal (HbA_{1c} <7%), and three patients were able to discontinue oral hypoglycaemic therapy completely and remained metabolically stable on a normal diet (Reinstein et al, 1999).

The precise mechanism(s) involved in the induction of weight gain by atypical antipsychotic agents has not been fully elucidated, although various theories have been proposed. It may be that this is a multifactorial process and serotonergic, histaminergic and/or adrenergic neurotransmission may be involved. Olanzapine and clozapine, which appear to be associated with comparatively large increases in weight (Allison et al, 1999), have been shown to increase circulating leptin levels (Bromel et al, 1998; Kraus et al, 1999) which correlate positively with increased BMI.

Further examination of weight changes with quetiapine suggests that any weight gain appears to be more prevalent in those patients with a low baseline BMI. Thus, any weight gain was more likely to occur among patients who were below their ideal body weight, which is perhaps a reflection of the disease process.

Some antipsychotics show a dose-related association with increase in weight, eg chlorpromazine, olanzapine and risperidone (reviewed in Baptista, 1999), with increases of up to 12 kg after 1 years' treatment being observed with olanzapine at a dose of 15 mg/day (Beasley et al, 1997). Antipsychotics also vary in the time course of their effect on weight gain. In a retrospective analysis of records from participants in a number of clinical studies of different antipsychotics, risperidone-treated patients reached a weight plateau after approximately 12 weeks, whereas clozapine- and olanzapine-treated patients show a continued weight increase over a longer period (20 weeks) (Wirshing et al, 1999). In contrast to the above, the present analyses demonstrate that quetiapine shows only a minimal increase in weight, if any, mainly during the first 6 weeks of treatment; thereafter, a plateau is reached. The weight change does not appear to be dose-related, nor does it appear to affect compliance. Given the association of weight gain with increased morbidity and mortality

from hypertension and macrovascular disease (Solomon and Manson, 1997; National Institutes of Health, 1998) and its detrimental impact on patients' well-being (Weiden et al, 1986; Weiden, 1999), quetiapine's minimal effect on weight has important implications for patients' compliance with treatment, their overall health, and for health care costs in general.

The present analyses, including studies in which quetiapine was the only antipsychotic permitted as well as those in which concomitant antipsychotic therapy was also allowed in the OLE, enable us to present a more cohesive interpretation of quetiapine's effects on weight. Perhaps more importantly, they allow us to position quetiapine relative to other antipsychotics. Our analyses demonstrate that any weight gain with quetiapine in monotherapy is 25% less than that of risperidone and about 35–40% that of olanzapine or clozapine. Indeed, after 12 months' treatment, quetiapine monotherapy resulted in a net weight loss of 1.47 kg. These results support and extend the findings of others in which the weight-gain profile of quetiapine is described as being similar to that of risperidone and considerably better than those of olanzapine or clozapine (Collaborative Working Group on Clinical Trial Evaluations, 1998; Goldstein, 1999; Maixner et al, 1999).

In conclusion, weight changes in patients treated long term with quetiapine — whether as monotherapy or in combination with other antipsychotics — are minimal and do not appear to raise potential medical concerns relating to significant weight increases as seen with other atypical antipsychotic agents. Quetiapine's balanced efficacy and tolerability profile, with only minimal effects on weight, suggest that quetiapine has a favourable benefit–risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

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Table 1. Patient demographics

	Cohort 1	Cohort 2
Number of patients (n)	2023	427
Male/female (n)	1433/590	277/150
Age, years (mean ± SD)	37.31 ± 11.05	37.3 ± 10.8
Age distribution		
<65 years	1983	425
≥65 years	40	2
Weight, kg (mean ± SD)	76.31 ± 16.46	**[AZ: please supply]**
Weight distribution (n)		**[AZ: please supply]**
Data not collected	9	
<50 kg	43	
50–70 kg	775	
71–90 kg	846	
>90 kg	350	

Table 2. Mean weight change in patients with schizophrenia receiving different dosages of quetiapine

Trial 13 — Dose-ranging study		Overall database		
	Mean change in weight (kg)		Mean change in weight (kg)	
Daily dose (mg)	6 weeks	Daily dose (mg)	5–6 weeks	9–12 months
75	0.9	<125	1.17	-0.20
150	2.9	125–225	2.95	1.06
300	2.0	>225–450	2.13	3.98
600	2.6	>450–675	1.94	2.76
750	2.3	>675	2.03	2.52

Table 3. Mean weight change from baseline in patients with schizophrenia during controlled and uncontrolled Phase II and III studies of quetiapine and open-label extensions, according to body mass index (BMI)

	Mean change in weight (kg)			
BMI (kg/m^2)	**5–6 weeks**	**9–10 weeks**	**6–9 months**	**9–12 months**
<23	2.56	5.04	2.45	4.20
23–27	3.12	1.38	3.12	2.35
>27	1.08	1.89	1.12	2.89

Table 4. Mean weight change from baseline in male and female patients with schizophrenia during controlled and uncontrolled Phase II and III studies of quetiapine and open-label extensions

	Mean change in weight (kg)			
	5–6 weeks	9–10 weeks	6–9 months	9–12 months
Female	1.55	0.12	0.67	2.49
Male	2.29	2.98	2.81	3.30

Figure legends

Figure 1. Mean change in weight from baseline during quetiapine treatment in Cohort 1 (concomitant antipsychotic therapy permitted) (n=2023).

Figure 2. Mean change in weight from baseline during 12 months' olanzapine treatment (Trial HGAJ: Kinon et al, 1998). **[from ACNP poster]**

Figure 3. Mean change in weight from baseline during quetiapine-only treatment in Cohort 2 (n=427). **[AZ: suggest adding SDs]**

Figure 1.

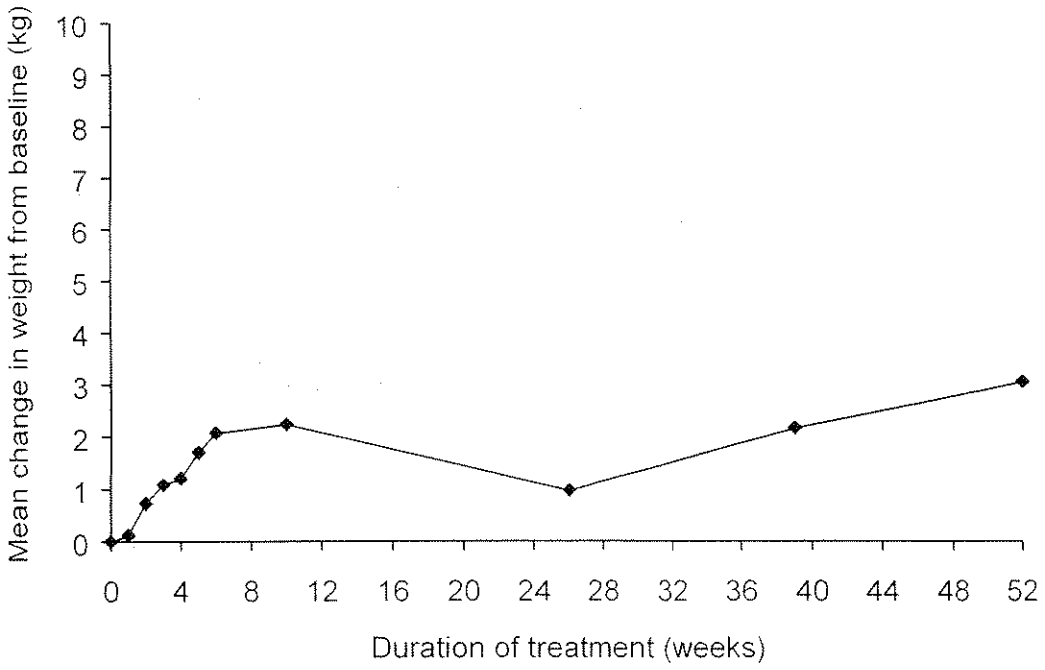
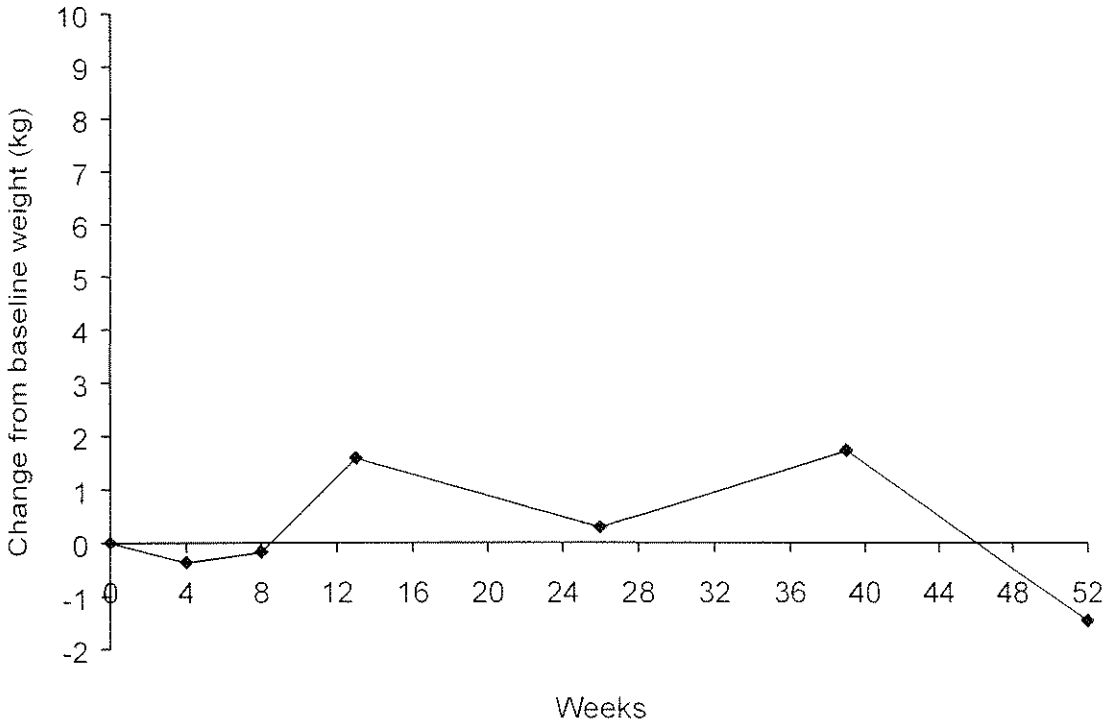

Mean change in weight from baseline (kg)
10
9
8
7
6
5
4
3
2
1
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Duration of treatment (weeks)

Figure 2.

[from ACNP poster]

Figure 3.


Change from baseline weight (kg)
10
9
8
7
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5
4
3
2
1
0
-1
-2
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Weeks