IMPROVED GASTROINTESTINAL (GI) TOLERABILITY OF ROCHE NELFINAVIR 625 MG FILM-COATED TABLETS IN COMPARISON WITH NELFINAVIR 250 MG FILM-COATED TABLETS (VIRACEPT®)

AN EVALUATION IN HEALTHY VOLUNTEERS

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Poster 6.4

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Background

Nelfinavir-based highly active antiretroviral therapy (HAART) has been clinically proven to provide potent and durable suppression of HIV replication over at least 4 years of continuous treatment.[1] In addition, it has shown comparable efficacy to novel agents such as atazanavir,[2] abacavir[3] and ritonavir-boosted fosamprenavir (GW433908)[4] in large, randomized clinical trials. Furthermore, nelfinavir allows the future use of boosted protease inhibitors (PIs) through its unique resistance profile.[5]

The effectiveness of antiretroviral therapy is closely related to adherence,[6] which is driven by the convenience of the regimen. To improve its convenience, a novel formulation of nelfinavir (V11), containing nelfinavir 625 mg per tablet, was developed, reducing the pill count of nelfinavir from ten to four pills daily. The new 625 mg formulation has a novel tablet composition to accommodate the high drug load in comparison to the existing formulation.

Adherence is also driven by the tolerability of a regimen.[7] Nelfinavir has excellent tolerability and safety profiles that are characterized by low rates of toxicity-related discontinuations and a lack of major organ toxicities.[1] The side effects of nelfinavir are primarily gastrointestinal (GI) in nature. A study in healthy volunteers was performed to examine the impact of this novel formulation of nelfinavir on GI tolerability.

Study objective

To investigate the GI tolerability of nelfinavir 625 mg (V11), administered as two tablets twice daily, in comparison with the currently marketed 250 mg formulation, administered as five tablets twice daily, in healthy volunteers over a treatment period of 7 days each.

Methods

Subjects

The study included 48 healthy volunteers (HIV seronegative). Subject demographics are summarized in **Table 1**.

Table 1: Demographics

	Subjects n = 48
Gender	
Male	45
Female	3
Race	
Caucasian	45
Black	2
Asian	1
Age (years)	
Mean (range)	27.7 (19–56)
Body mass index (kg/m²)	
Mean (range)	24.1 (20–30)

Study design

- A multiple-dose, randomized, two-period cross-over study in healthy male and female volunteers.
- Participants received nelfinavir 1250 mg twice daily, taken with food, administered for 7 days with each formulation, separated by a 7- to 14-day washout.
- Subjects kept a stool diary throughout the study, including a 3 days run-in period, as well as during the washout and follow-up period.
- Stools were collected over 24 hours on day –1 and over any one day between days 5 and 7 of both treatment periods.
- Nelfinavir plasma concentrations were determined on day 7 of each study period in the morning at trough and 3.5 hours post-dose – close to the previously established t_{max}.
- Adverse events (AEs) were monitored throughout the study until follow-up at 4 to 10 days after the second treatment period. Diarrhoea was not considered to be an AE for this study as this information was already covered in the stool diaries.

During this study, the participants stayed at the treatment centre for the 24 hours stool collection on day –1, and remained at the study centre during the two nelfinavir treatment courses.

Study evaluation

- The primary measure of GI tolerability was the incidence of moderate or severe (or potentially life-threatening) diarrhoea using modified ACTG definitions as shown in **Table 2**. A minimum of 5 days of the stipulated 7-day treatment course was required for the subjects to be included in this evaluation. For subjects completing only the first treatment period, a method of imputation was used whereby the diarrhoea was assumed to occur with the 625 mg formulation twice as frequently as observed in the subject when treated with the 250 mg formulation.[8]

Table 2: Modified ACTG diarrhoea severity table

Grade	Description	Definition
1	Mild	Three or four loose stools per day, not for whole treatment period (excluding day 1)
2	Moderate	Five to seven loose stools per day, **or** diarrhoea for the whole treatment period
3	Severe	More than seven loose stools per day, **or** bloody diarrhoea, **or** orthostatic hypotension, **or** intravenous treatment required
4	Potentially life-threatening	Hypotensive shock, **or** hospitalization required

Table 3: Standardized stool scales

Faecal urgency scale		Bristol stool form scale	
0	No urgency	1	Separate hard lumps, like nuts
1	Normal	2	Like a sausage, but lumpy
2	Slightly more than normal	3	Like a sausage, with cracks
3	Unusually strong, disturbing	4	Like a sausage or snake, easy and smooth
4	Strong urgency, being afraid of not reaching the toilet in time	5	Soft blobs with clear-cut edges (easy to press out)
		6	Fluffy pieces with ragged edges, a mushy stool
		7	Liquid stool, no solid pieces

- As no subjects in the study experienced moderate/severe diarrhoea a *post hoc* analysis of GI upset was performed. GI upset was defined by ≥ 1 occurrence of loose stools (Bristol stool form score 6 or 7) and/or severe faecal urgency (score 3 or 4) as defined in **Table 3**.
- The 24-hour stool collections were analysed for weight, faecal fat, faecal calcium and magnesium content, as well as pH.

Results

Study population

A total of 46 subjects took all the prescribed doses of both treatments. Two subjects withdrew prematurely, one during the washout period after the first treatment period (test formulation), and one on day 7 of the second treatment period (test formulation) prior to the last dose. The first withdrawal was due to a combination of adverse events; furuncle (moderate intensity), arthralgia, vomiting and a sore throat (of mild intensity), all of which were considered by the investigator to be unrelated to study medication. The second withdrew due to abnormal liver function results observed on day 4 of the second period, which continued to rise during nelfinavir treatment.

According to previous definitions, 47 subjects were evaluable for both treatments, and 48 for treatment with the 625 mg formulation. For the one subject who did not start taking the 250 mg formulation, an imputed diarrhoea assessment was used for this treatment as described under Methods.

GI tolerability

- Complete stool diary information was available for all subjects who underwent treatment.
- The majority of stools voided were normal (Bristol stool type < 6).
- Loose stools (type 6 or 7) on > 1 occasion during the study were recorded by approximately 75% of subjects.
- Nine subjects voided three or four loose stools within one day during treatment, washout, or follow-up (= mild diarrhoea).
- None of these reports qualified as moderate or severe diarrhoea as shown in **Table 4**.

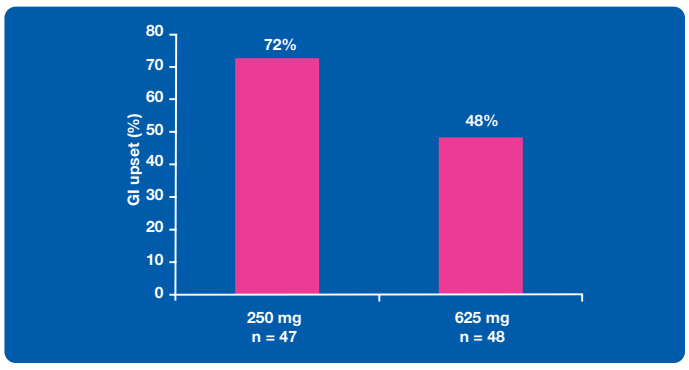
Table 4: Diarrhoea grading for both treatment periods

		Moderate/severe diarrhoea with 625 mg formulation	
		YES	NO
Moderate/severe diarrhoea with 250 mg formulation	YES	0 subjects	0 subjects
	NO	0 subjects	48* subjects

*one case had an imputed result for the standard formulation (250 mg)

For both formulations, the additional analysis of GI upset was performed and is shown in **Figure 1**.

Figure 1: Incidence of GI upset during treatment period including the first day of wash-out or follow-up, respectively



The results of the analyses of the 24 hours stool collections are summarized in **Table 5**. Stool weight and faecal calcium content were, on average, increased during both nelfinavir treatments, if compared with the baseline values from day –1, while faecal magnesium content decreased slightly. However, there was a wide variation across the study population (SD) and no conclusions of significance can be drawn.

Table 5: 24-hour stool collection results

		Change from day –1	
	Day –1	250 mg	625 mg
Weight (g/day)			
n	39	36	37
Mean (SD)	115 (70)	71 (120)	50 (110)
Faecal fat (g/day)			
n	36	28	28
Mean (SD)	3.3 (2.3)	0.1 (3.2)	–0.2 (3.0)
Faecal Ca (mmol/day)			
n	39	36	37
Mean (SD)	25.1 (18.4)	8.6 (23.6)	5.3 (22.6)
Faecal Mg (mmol/day)			
n	39	36	37
Mean (SD)	7.3 (4.5)	–0.4 (4.2)	–0.7 (5.0)
Faecal pH			
n	39	36	37
Mean (SD)	6.6 (0.5)	0.0 (0.6)	0.0 (0.6)

Nelfinavir plasma concentrations

Both formulations showed comparable trough levels, but at 3.5 hours post-dose the mean plasma concentrations of nelfinavir were approximately 30% higher for the 625 mg formulation than for the 250 mg formulation **Table 6**.

Table 6: Summary of nelfinavir plasma concentrations

	250 mg n = 47	625 mg n = 48
Pre-dose (ng/mL)		
Median (range)	1,350 (401–4,350)	1,380 (576–6,380)
Mean	1,622	1,602
CV%	53.8%	60.8%
3.5 hours post-dose (ng/mL)		
Median (range)	2,820 (759–6,310)	3,510 (1,010–6,660)
Mean	2,780	3,600
CV%	45.1%	36.0%

Safety

- Both formulations were generally well tolerated **Table 7**.
- A large proportion (> 40%) of reported AEs were considered by investigators to be unrelated to study medication, and the majority resolved before the end of the study.
- Flatulence was the most common AE considered to be related to study treatment, which occurred in 9% and 6% of patients with the 250 mg and 625 mg formulations, respectively.
- There were no AEs of severe intensity.

Table 7: Summary of all adverse events that occurred with a frequency of greater than 5% in either arm

Adverse event	250 mg n = 47	625 mg n = 48
Flatulence	4 (9%)	3 (6%)
Abdominal pain	4 (9%)	1 (2%)
Dyspepsia	0	3 (6%)
Headache	2 (4%)	5 (10%)

Discussion

Nelfinavir, at a dose of 1250 mg twice daily was given to healthy volunteers in two formulations. Forty-eight subjects received a new 625 mg formulation (V11), while 47 also received the commercially available 250 mg formulation (Viracept®). One subject was withdrawn from the study after the first treatment course due to AEs unrelated to the study medication, and one subject before the very last dose of the second treatment course due to abnormal laboratory values.

During treatment with both formulations in this study, only cases of mild diarrhoea were found. There were no occurrences of moderate or severe diarrhoea. Stool analysis demonstrated a similar increase in stool weight during treatment with both formulations, but faecal fat and electrolytes showed little change after the two different formulations, indicating that the new formulation has no additional laxative effect. An additional analysis was performed on the basis of the stool diary data assessing GI upset. Comparing the percentage of subjects experiencing GI upset with each formulation, a clear improvement was seen with the 625 mg tablet formulation (V11).

The 30% higher nelfinavir plasma concentrations measured at 3.5 hours post-dose for the 625 mg formulation as compared with the commercial 250 mg tablet are in line with previous results gained for this V11 formulation. Refinement of this formulation was necessary to obtain the Roche 625 mg V12 tablet for which bioequivalence with the commercial 250 mg Viracept® tablet formulation was established in fed state at a dose of 1250 mg.[9] This successor formulation V12 has also shown improved GI tolerability in HIV seropositive patients.[10]

This new 625 mg formulation of nelfinavir is more convenient than the existing version, with a reduction in the daily pill count from ten to four. In addition, it may offer improved GI tolerability. Enhanced convenience and tolerability could potentially improve adherence, which in turn could result in greater efficacy.

Conclusions

In this study in healthy subjects both the 250 mg and the 625 mg formulation were well tolerated. Both formulations were only associated with mild diarrhoea and there were no cases of moderate or severe diarrhoea. The nelfinavir 625 mg (V11) formulation was associated with markedly less signs of GI upset compared with the commercially available 250 mg formulation. As this formulation provided higher nelfinavir plasma concentrations around C_{max}, as compared with the existing 250 mg formulation, the nelfinavir 625 mg formulation was developed further to achieve comparable exposure with the marketed 250 mg Viracept® tablet.

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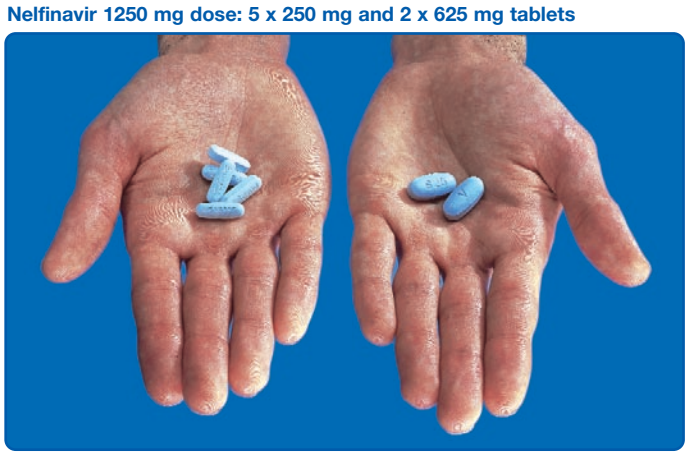
Nelfinavir 1250 mg dose: 5 x 250 mg and 2 x 625 mg tablets



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