Weight Reduction and Maintenance with IQP-PV-101: A 12-Week Randomized Controlled Study with a 24-Week Open Label Period

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Objective: The safety and efficacy of IQP-PV-101, a proprietary extract of *Phaseolus vulgaris*, on weight management in two phases was evaluated here. The weight loss (WL) phase was conducted over 12 weeks and the weight maintenance (WM) phase took 24 weeks.

Design and Methods: In the double-blind WL phase, subjects were randomized to receive either IQP-PV-101 or placebo. All subjects adhered to a mildly hypocaloric diet. Body weight and other body composition parameters were measured at baseline and every 4 weeks thereafter.

During the single arm, open label WM trial, energy intake was ad libitum. Efficacy parameters were measured at baseline, week 12 and week 24.

Results: At the end of the WL study, the IQP-PV-101 group lost a mean of 2.91 ± 2.63 kg in body weight compared with 0.92 ± 2.00 kg in the placebo group ($P < 0.001$). During the WM phase, 36 out of 49 subjects (73.5%) were able to maintain their weight, even without dietary restrictions.

No serious or related adverse events were reported over the combined period of 36 weeks.

Conclusions: Results indicate that IQP-PV-101 is safe and effective for weight loss and maintenance.

Introduction

It was only in recent decades that obesity and being overweight were considered epidemic issues (1). From 1980s to the 1990s, the prevalence of obesity increased sharply in the United states of America (USA), Europe, and Asia Pacific (2-4). By 2008, it was estimated that about half a billion adults were obese globally (5).

It is commonly known that there are health risks that come with being overweight or obese. The occurrence of insulin resistance and the risk factors for cardiovascular diseases are greatly increased in overweight or obese individuals (6,7).

According to the European Clinical Practice Guidelines for the management of obesity in adults, the first step in attempting to bring body weight down to target is with regular physical activity and by reducing energy intake by 500-1,000 kcal a day (8).

If diet, physical activity and behavioral modification are not sufficiently successful, pharmacological interventions are considered.

The evolution of anti-obesity drugs is an interesting one: from centrally acting sympathomimetics such as phentermine in the 1950s, to serotonin-releasing agents such as fenfluramine in the 1980s, to sibutramine (dual monoamine reuptake inhibitor), rimonabant (cannabinoid CB1 receptor antagonist), and orlistat (lipase inhibitor) in the 1990s. All of these, with the exception of orlistat, have either declined in use in some regions or been withdrawn from the market due to a common issue: safety concerns (9). The two recent high profile cases of market withdrawal imposed by the European Medicines Agency are rimonabant in 2008 due to psychiatric side effects (10), and sibutramine in 2010 due to cardiovascular side effects (11).

Amidst concerns on the safety of pharmacological agents, there is active interest in seeking a safe and effective weight management treatment from natural sources. Different plants have been shown to have an effect on lipase inhibition, food intake suppression, energy expenditure stimulation, inhibition of adipocyte differentiation, and regulation of lipid metabolism (12). There is, however, very limited

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clinical evidence, even less so from randomized placebo-controlled trials over intermediate or long periods of exposure.

Carbohydrates are a main source of dietary calories in the over-weight and obese (13). In order to be absorbed by the body, carbohydrates are broken down into monosaccharides. Two major enzymes catalyze this process: amylase and glucosidase. Amylase converts complex carbohydrates such as starch into oligosaccharides; the glucosidase enzymes further break these down to monosaccharides. Common beans (*Phaseolus* spp.) contain amylase inhibitors in three forms, namely, alpha-A1, alpha-A12, and alpha-AIL (14). These glycoproteins bind to alpha-amylase noncovalently, mainly through hydrophobic interaction, inhibiting starch digestion (15).

Phaseolus vulgaris, commonly known as white kidney bean, has been the subject of several clinical studies. In studies conducted by Celleno et al. (16) and Wu et al. (17), subjects on *Phaseolus vulgaris* extracts lost significantly more body weight compared to subjects on placebo, over 30 days and 60 days, respectively. However, in the first study, chromium was added to the *Phaseolus vulgaris* extract (16), whereas the second study was conducted in an Oriental Asian population (17). Udani et al. found a weight loss (WL) trend with a water-extract of *Phaseolus vulgaris* after 8 weeks but the results were not significant; this could be due to the small sample size and the short treatment period (18).

The investigational product (IP) in our studies, IQP-PV-101 (marketed globally under the Phase 2, Starchlite and PhaseLite brands), contains extracts of *Phaseolus vulgaris*. We aimed to demonstrate the safety and efficacy of IQP-PV-101 in weight management in obese and overweight Caucasian adults, in two phases. The WL phase was a 12-week randomized, double-blind, placebo-controlled study where all subjects followed a strict diet plan; the second phase was the weight maintenance (WM) study over 24 weeks, where the subjects' energy intake was ad libitum.

Methods and Procedures

Subjects
Both studies were conducted in 2 centers in Berlin, Germany, from May 2011 to May 2012. The protocols were approved by the ethics committee of the Charité Universitatsmedizin before trial initiation. All subjects provided written informed consent before any trial-related procedures were carried out.

Screening
The inclusion criteria of the WL study included: 1) aged 18–60 years, 2) BMI between 25 and 35 kg/m^2, 3) accustomed to three main meals a day, 4) stable body weight 3 months before study enrolment, 5) commitment to adhere to diet and to avoid the use of other WL products during study, 6) females' agreement to use appropriate birth control methods during the active study period, and 9) written informed consent. The exclusion criteria included 1) known sensitivity to the ingredients of the IP, 2) history of diabetes mellitus, 3) clinically relevant excursions of safety parameter(s), 4) presence of acute or chronic gastrointestinal disease, 5) history of eating disorders within 12 months before enrolment, 5) active use of medication(s) that could influence gastrointestinal functions, 6) pregnant or nursing, 7) active use of any medication or products for the

treatment of obesity, and 8) participation in other studies within 4 weeks before enrolment.

After completing the WL study, subjects from both the active and placebo arms who lost at least 3% of their body weight at the screening visit were classified as responders and were invited to participate in the WM study, which was an open label extension to the WL study. Other inclusion and exclusion criteria for the WM study were similar to the WL study.

Study intervention
In the WL study, all subjects who fulfilled inclusion and exclusion criteria entered a 2-week run-in period. The basal daily energy requirement for each subject was calculated based on their body weight, gender, age, and activity index. The subjects were then assigned to diet plans that were slightly hypocaloric (500 kcal less than their basal energy needs per day), providing 40% of the ingested energy as carbohydrates. These plans were available on five energy levels: 1,500, 1,800, 2,000, 2,200, and 2,500 kcal per day. Adherence to the diet plan was recorded in a diary on a daily basis. Only subjects who were compliant to the diet during the run-in period were randomized to either IQP-PV-101 or placebo in a 1:1 ratio. Follow-up visits were conducted on week 4, week 8, and week 12 after randomization.

Subjects who opted to participate in the WM study all received IQP-PV-101. Follow-up visits were carried out at week 12 and week 24 after the start of the study, with telephone follow-ups completed at week 6 and week 18. Subjects were advised to maintain a nutritionally balanced diet but did not adhere to any strict diet plans during the WM study.

Each tablet of IQP-PV-101 contained 500 mg of the active ingredient. The dosage of the IP was 2 tablets, three times a day, before meals, for both studies. IP compliance was measured by calculating the number of tablets returned to the study centers at each visit.

Efficacy parameters
Body weight was measured using calibrated weighing scales (Tanita BC-420 SMA). The same scales also measured the subjects' body fat content using bioelectrical impedance analysis.

For the WL study, the primary endpoint was the difference in weight change from baseline to the end of week 12, between the IQP-PV-101 and placebo groups.

For the WM study, the primary endpoint was the percentage of subjects who maintained their body weight over 24 weeks. A subject was considered to have successfully maintained weight if his/her body weight at the end of the study has not increased by more than 1%, compared with baseline.

Waist circumference (in cm) was measured using a measuring tape at the level midway between the lateral lower rib margin and the iliac crest. Hip circumference (in cm) was measured as the maximal circumference over the buttocks.

Subjects completed the Control of Eating Questionnaire (19,20) during each study visit. The COEQ uses visual analog scales to assess

the feelings hunger, satiety, and cravings in subjects over the past 7 days.

Body weight, body fat content, waist and hip circumference, BMI, and responses were recorded at randomization, week 4, week 8, and week 12 of the WL study. For the WM study, the parameters were recorded at baseline, week 12, and week 24.

Safety parameters

Venous blood samples were obtained at screening and the final visit of the WL study (which also served as the screening visit of the WM study), and the final visit of the WM study. Full blood count, electrolyte level, liver function test, renal function, lipid metabolism, and carbohydrate metabolism were analyzed in a central laboratory.

Adverse events (AEs) were recorded at every visit, including telephone follow-ups during the WM study.

Statistical analyses

Statistical analysis was performed with IBM© SPSS© Statistics, Version 19, Copyright 1989, 2010 SPSS.

For the WL study, the primary endpoint was the difference between the IQP-PV-101 and the placebo groups in the weight change between baseline and week 12. For the open label WM study, the objective was to demonstrate noninferiority in to body weight reduction, i.e., the mean body weight at the end of the study is no more than 1% higher than at baseline.

The testing of the primary endpoint data was performed with the nonparametric Wilcoxon test by analyzing the rank sums.

All primary and secondary endpoints as well as the concurrent and safety variables received an explorative examination and were descriptively assessed. The testing of the primary endpoint data was performed with the nonparametric Mann-Whitney U test by analyzing the rank sums and covariance analysis.

All secondary outcomes and the concurrent variables were also evaluated primarily by using nonparametric procedures. Multiple tests were performed without correction of significance level in explorative analysis.

As the study extended over a long-time period and in this time data were collected at repeated visits, it was necessary to examine the progression of the values over the whole intervention study time using parametric and nonparametric methods of analysis with repeat measurements.

All analyses were performed on the intent-to-treat (ITT) population. For the primary endpoints, an analysis was also performed on the per protocol (PP) population.

Results

Demographics

There were 123 and 49 subjects in the ITT population of the WL and WM studies, respectively (Figure 1).

All subjects in the studies were Caucasians. For the WL study, the mean age was 46.0 ± 10.1 years, and 74.0% of the subjects were female. Baseline characteristics were similar between the two groups.

In the WM study, the mean age was 46.5 ± 9.9 years and 89.8% of subjects were female.

Energy intake

During the WL study, there was no significant difference between the two groups in daily energy intake. The mean for all subjects was $2,337 \pm 392$ kcal per day.

Energy intake was not recorded in the WM study.

Investigational product compliance

Subjects in both studies generally complied with the IP administration instructions. In the WL study, there was no significant difference in the percentage of compliance between subjects on IQP-PV-101 and subjects on placebo ($P = 0.154$). In the WM study, subjects achieved a mean compliance rate of $96.83 \pm 6.20\%$ through the 24 weeks.

Efficacy

Body weight. The mean body weight at the start of the WL study was 85.0 ± 11.3 kg in the IQP-PV-101 group and 85.9 ± 10.1 kg in the placebo group ($P = 0.660$). After 12 weeks, subjects in the IQP-PV-101 group lost significantly more weight than those in the placebo group (mean 2.91 ± 2.63 kg vs. 0.92 ± 2.00 kg, $P < 0.001$); the difference between the groups in body weight change was already significant from week 4 onward (Figure 2). After 12 weeks, the mean body weight of subjects in the IQP-PV-101 was 96.5 ± 3.2 % of baseline weight, whereas the mean body weight of the placebo group was $99.0 \pm 2.3\%$ of baseline weight ($P < 0.001$). Significantly more subjects in the IQP-PV-101 group lost at least 5% of their baseline body weight compared with the placebo group (30.6% vs. 8.2%, $P < 0.001$).

The mean body weight at the start of the WM study was 80.4 ± 12.1 kg. The mean weight of the subjects at week 24 was $99.34 \pm 2.96\%$ of baseline weight. Thirty-six out of 49 subjects (73.5%, CI: 58.9–85.1%) successfully maintained their body weight at the end of the study (Figure 3).

For the WL study, analysis was carried out for the change in body weight in the subgroups of overweight subjects and obese subjects.

Of the 66 overweight subjects in the WL study, 32 were randomized to the IQP-PV-101 arm and 34 to the placebo arm. The IQP-PV-101 group lost significantly more body weight than the placebo group after 12 weeks of intervention (2.81 ± 2.30 kg vs. 0.68 ± 1.66 kg, $P < 0.001$).

There were 57 obese subjects in the WL study, of which 30 were in the IQP-PV-101 group and 27 in the placebo group. There was also a significant difference in the weight change between the two groups; the IQP-PV-101 group lost a mean of 3.02 ± 2.97 kg, and the placebo group lost a mean of 1.22 ± 2.36 kg ($P = 0.027$).
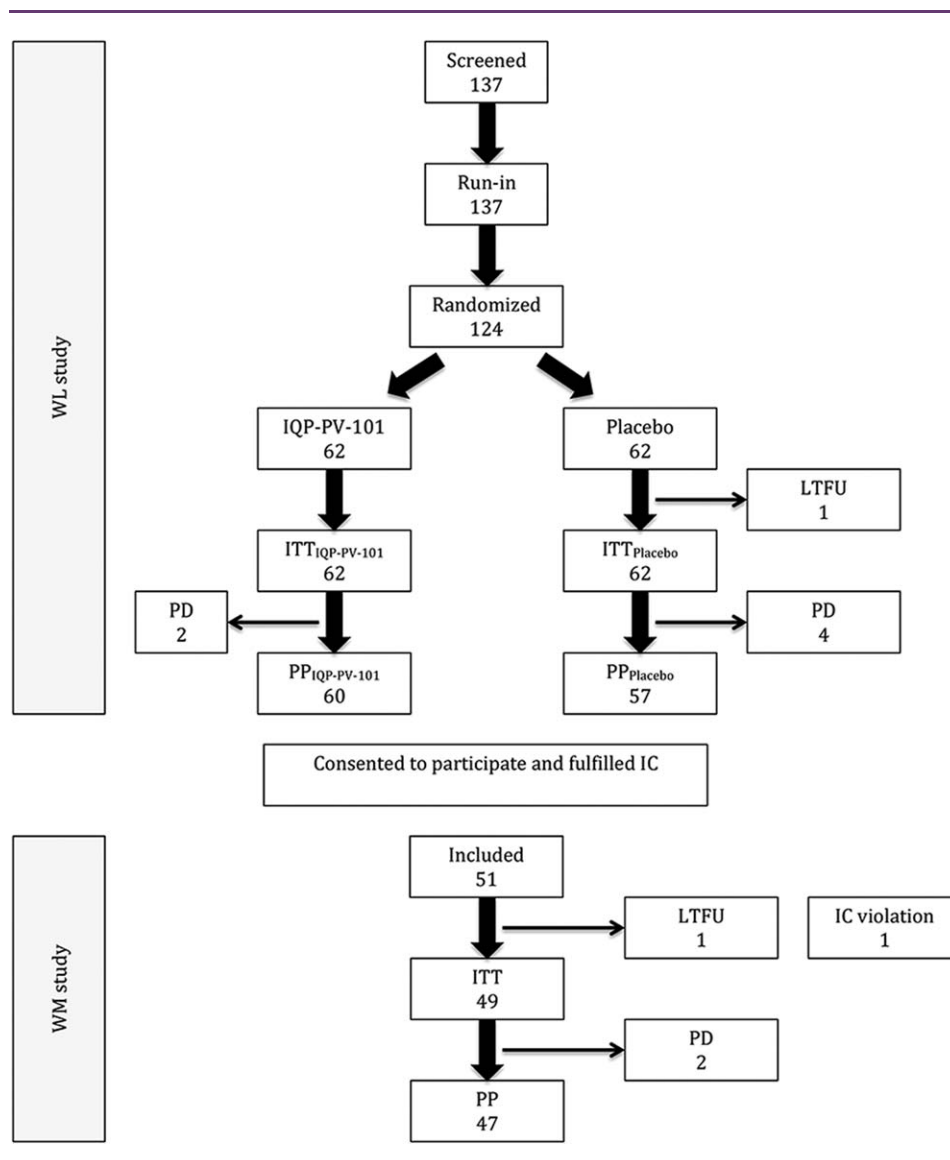
FIGURE 1 Subject recruitment and follow-up. LTFU, lost to follow-up; PD, protocol deviation; IC, inclusion criteria; ITT: intent-to-treat; PP: per protocol.

Body fat mass. The mean body fat mass at the start of the WL study was 31.9 ± 7.3 kg in the IQP-PV-101 group and 31.9 ± 7.3 kg in the placebo group ($P = 0.992$). After 12 weeks, the IQP-PV-101 group lost 2.23 ± 2.16 kg of body fat mass, compared with a reduction of 0.65 ± 2.33 kg in the placebo group ($P < 0.001$); the difference was also significant at week 4 and week 8.

At the end of the WM study, the subjects experienced a slight increase in body fat mass that was not statistically significant (mean $101.5 \pm 7.9\%$ of baseline, $P = 0.200$).

BMI. In the WL study, from week 4 onward, the BMI of the IQP-PV-101 group decreased significantly compared with placebo. By week 12, subjects on IQP-PV-101 experienced a mean BMI reduction of 1.05 ± 0.97 kg/m^2 compared with 0.32 ± 0.69 kg/m^2 in subjects on placebo ($P < 0.001$). After initial WL, there was no signifi-

cant decrease in BMI during the WM study, with a mean reduction of 0.19 ± 0.86 kg/m^2 ($P = 0.119$).

Waist circumference. In the WL study, the waist circumference reduction of subjects on IQP-PV-101 was significantly more pronounced than the placebo group at week 8 and week 12. At week 12, the IQP-PV-101 group lost a mean of 2.50 ± 2.25 cm compared with 0.90 ± 2.13 cm in the placebo group ($P < 0.001$). The waist circumference of subjects continued to decrease in the WM study; after 24 weeks the reduction in waist circumference was statistically significant with a mean of 1.00 ± 2.25 cm ($P = 0.003$).

Body fat mass, BMI, and waist circumference data are summarized in Table 1.

COEQ. At baseline and week 12 of the WL study, there was no significant difference between the two arms in the response to all
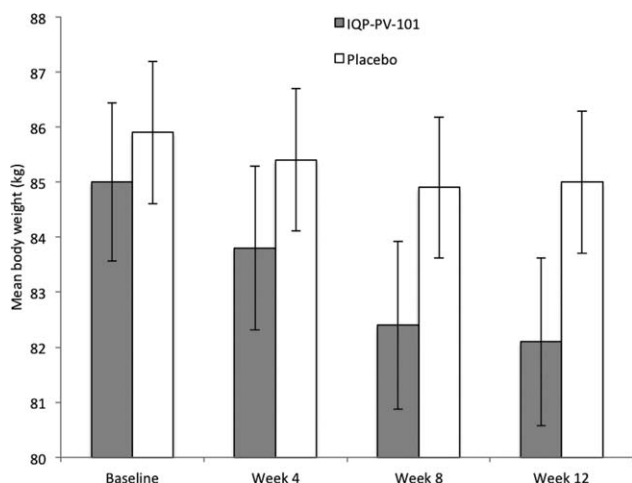
FIGURE 2 Weight reduction from baseline to week 12 for the WL study. Error bars show one standard error of mean.
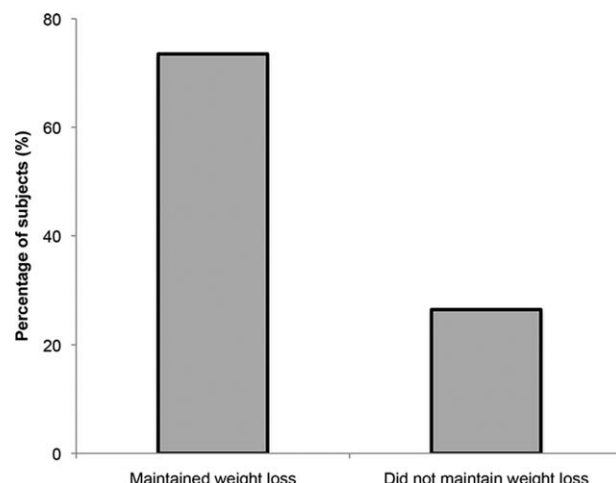

FIGURE 3 Proportion of subjects who maintained and did not maintain weight in the WM study.

the COEQ questions. After 12 weeks, the IQP-PV-101 arm in the WL study experienced a statistically significant decrease in desire for sweet food; frequency and strength of food cravings; the difficulty in resisting food cravings; the frequency of succumbing to food cravings; frequency of cravings for chocolates, other sweet foods, fruit, or fruit juices; the difficulty in controlling eating; and the difficulty to resist eating a particular type of food. The placebo group showed a significant increase in the difficulty in resisting a particular type of food.

In the WM study, there was a significant increase in the subjects' response from baseline to week 24 for the extent of feeling happy and the extent of feeling alert. On the other hand, there was a significant decrease in the response to the strength of cravings.

Safety and tolerability

AE. All the AEs in the two studies were not severe, not serious, and not related to the IP (Table 2).

Laboratory. The investigators did not report any clinically significant changes in the laboratory parameters from both studies.

Discussion

The effects of *Phaseolus vulgaris* extract on WL and glycemic control were reviewed in detail by Barrett and Udani (14). At the time of writing, and to our knowledge, the WL trial was the largest study in terms of sample size and the WM study was the longest single clinical study conducted on *Phaseolus vulgaris* extract. Both studies were performed with the recommendations of the European Food Safety Authority on trials pertaining to weight management in mind (21).

In the WL study, all subjects adhered to a mildly hypocaloric diet and were therefore expected to lose some body weight gradually. From as early as week 4, subjects who were on IQP-PV-101 lost significantly more weight than their placebo counterparts. The same trend was observed in the body fat mass measurements: The IQP-PV-101 group showed a significantly more marked reduction compared with the placebo group at weeks 4, 8, and 12. From this data, we conclude that the reduction in body weight was due to the loss of fat mass, instead of muscles. Improvement in body composition was also shown in the significant reduction in waist measurement in the IQP-PV-101 group, compared with the placebo group. As an indicator of central obesity, waist measurement has also been shown

TABLE 1 Secondary efficacy parameters for the WL and WM studies

| Parameter (unit) | WL study | | | | |
	IQP-PV-101	Placebo	P value[a]	WM study	P value[b]
Body fat mass (kg)	2.23 (2.16)	0.65 (2.33)	<0.001	−0.06 (2.90)	0.892
BMI (kg/m^2)	1.05 (0.97)	0.32 (0.69)	<0.001	0.19 (0.86)	0.119
Waist circumference (cm)	2.5 (2.25)	0.90 (2.13)	<0.001	1.00 (2.25)	0.003

Numbers shown as mean (SD) reduction from baseline to end of study; a negative value denotes an increase.
[a]Comparison between the two arms at week 12 of the WL study.
[b]Comparison between week baseline and week 24 of the WM study.

TABLE 2 List of adverse events

Study phase	Adverse event	Frequency	
		Placebo	IQP-PV-101
WL	Upper respiratory tract infection	1	1
	Toothache	1	n/a
	Hand fracture	1	n/a
	Total	3	1
WM	Upper respiratory tract infection	n/a	2
	Acute back pain	n/a	1
	Ankle sprain	n/a	1
	Tonsillitis	n/a	1
	Gastrointestinal infection	n/a	1
	Sinusitis	n/a	1
	Bronchitis	n/a	1
	Finger cut	n/a	1
	Total	—	9

n/a = not applicable.

to correlate to risks of diabetes mellitus, cardiovascular diseases, and dyslipidemia (22,23).

In weight management, the long-term maintenance of WL is always a question. Even though the specifics in the definition of weight cycling has not been established, the term is generally understood to describe situations where an individual goes through repeated cycles of intentionally losing a substantial amount of body weight, only to regain it. The prevalence of weight cycling appears to be ranging from 18% to 42% in men, and 29% to 56.8% in women (24,25). In a comparison of diets with different compositions, Sacks et al. (26) found that WL in dieters mostly took place in the first 6 months, after which body weight was slowly regained. A meta-analysis revealed that orlistat, until recently the only drug approved by the FDA for long-term management of obesity, was not significantly different than placebo in its WM effect after the 2nd year (27).

Subjects in the WM study were advised to maintain a nutritionally balanced diet, but there were no restrictions to food and energy intake. There was also no intensive investigator supervision during the WM phase: subjects had scheduled visits at weeks 12 and 24, and telephone follow-ups at weeks 6 and 18. Over 24 weeks, 73.5% of subjects managed to maintain their weight. This is encouraging evidence that the WM effects of IQP-PV-101 can be replicated in a noncontrolled setting, mimicking daily life. In the WM study, the dosage was standardized at 2 tablets, three times a day, so that data analysis can be done on a population who were on homogenous intervention. In real life, during WM, the dosage of IQP-PV-101 could possibly be adjusted based on individual needs, based on target weight and carbohydrate intake.

While there was a significant decrease in the ratings for a number of COEQ questions in the WL study, there was generally no significant difference in the response between the IQP-PV-101 and placebo groups. The mostly insignificant findings in the COEQ ratings in both studies were unsurprising, as we did not expect IQP-PV-101 to exert its effects by satiety enhancement. However, the COEQ response did confirm that in both studies, subjects did not experience a surge in hunger and cravings while on the diet that was compulsory during the WL study, leading to the high compliance rate. The validation of the COEQ was not extensively documented; this could be a limitation to the studies.

Another limitation was that energy intake was self-reported. Even though steps were taken by the investigators to ensure compliance to the subjects' diet during the WL phase, the variance in self-reported food intake in the obese has been reported to be high (28,29).

Product safety has rarely been an issue with *Phaselous vulgaris* in reported studies (14). Over a combined period of 36 weeks, we did not encounter any AE that was serious or related to the IP.

We conclude that IQP-PV-101 is effective and safe in WL and WM, even with unrestricted energy intake. O

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