

# A Relatively Low Nicotine Strength E-Liquid that Reduces the Urge to Smoke as much as Cigarettes

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## Abstract

A pharmacokinetic and pharmacodynamic evaluation of a new 3 and 6 mg/ml nicotine e-liquid (OG Blue from Liquid Labs LLC) was conducted comparing the new products to own brand cigarettes and 4 mg Nicorette nicotine gum. The randomized, open label, crossover clinical study was completed in 27 smokers to measure nicotine plasma levels and subjective effects of product use. Subjects used the products under controlled conditions and blood was collected prior to and for up to 180 minutes following use. The ability of the products to satisfy the urge to smoke over the short term was assessed using the “Urges to Smoke” question in the Tobacco/Nicotine Withdrawal Questionnaire (TNWQ), and positive effects were assessed using the “Is the product ‘Pleasant’ right now?” question in the Direct Effects of Product Questionnaire (DEPQ); both were administered as 100-point VAS. Peak (C<sub>max</sub>) and overall (AUC) nicotine exposure for the 2 e-liquids was less than the 4 mg nicotine gum and significantly lower than own-brand cigarettes. Overall, the 3 mg and 6 mg products were rated to be similarly pleasant and effective in reducing the urge to smoke compared with own-brand cigarette, despite significantly lower nicotine exposure.

## Methods

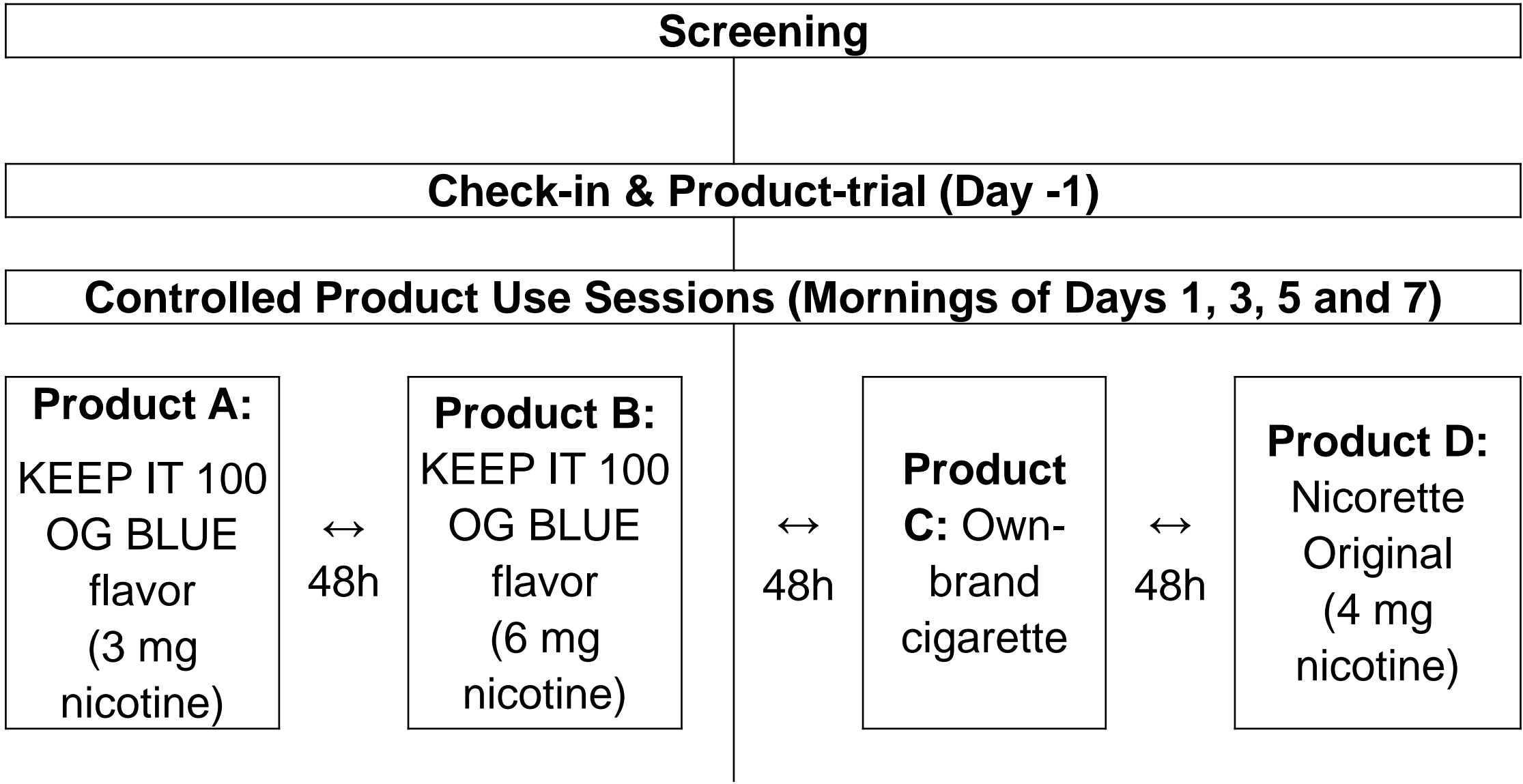
This was a randomized, open-label, crossover study designed to evaluate the nicotine pharmacokinetics and pharmacodynamics of KEEP IT 100® brand OG-Blue e-liquid (Figure 1) produced by Liquid Labs LLC compared to own brand cigarettes and Nicorette 4 mg nicotine gum in healthy adult male and female smokers. The OG Blue e-liquid was tested at nicotine concentrations of 3 and 6 mg mg/mL. The formulas were similar except for the concentration of nicotine. Each subject was provided with an Aspire Nautilus tank-system atomizer equipped with a 1.8 ohm coil. The airflow was set to 1.1 mm. The battery was set to 12 watts. Subjects vaped 10 times (maximum 3 ± 2 seconds per puff) at approximately 30 ± 5-second interpuff intervals. Subjects also puffed their own brand cigarette 10 times at 30 second intervals. Original flavor Nicorette gum (4 mg nicotine) was chewed for 30 minutes as per label instructions (“chew and park” method).

Subjects participated in a standard Screening Visit and a Confined Assessment Phase, which included a Product Trial Session on Day -1 and Product Use Sessions, which consisted of morning Controlled Product Use Sessions. Subjects were required to have a history of smoking an average of ≥10 cigarettes daily for at least 1 year and had to have tested positive for urine cotinine (≥200 ng/mL) at Screening. Each study day of product use was separated by approximately 48 hours. Subjects vaped the study products, puffed their own brand cigarette or chewed the gum in a random order. Blood samples were collected within 5 minutes of start of product use and at 2, 5, 10, 15, 30, 45, 60, 90 and 180 minutes after product administration. **Figure 2** shows the study design.

Figure 1. OG BLUE



Figure 2. Study Design



## Results

A total of 27 subjects were randomized and 21 subjects completed the study. The subjects ranged in age from 27 to 56 years, with a mean age of 42.1 years. Most subjects were male (74.1%), White (81.5%), and not Hispanic or Latino (100.0%). The subjects reported smoking 15.6 cigarettes per day for a mean duration of 26.0 years.

Nicotine plasma levels were measured after controlled product use. **Figure 3** shows the baseline adjusted plasma nicotine concentrations of each product and **Table 1** shows the derived nicotine PK parameters. Own-brand cigarette nicotine time to C<sub>max</sub> (T<sub>max</sub>) was 6 minutes with a C<sub>max</sub> of 18.7 ng/mL. The 3 and 6 mg/mL OG Blue also showed an early T<sub>max</sub>, at 5 and 6 minutes, respectively, but with markedly lower peak concentrations of 2.6 and 3.9 ng/mL. The 4 mg nicotine Nicorette gum reached a maximum nicotine concentration of 5.9 ng/mL at 45 minutes post-use. While, the OG Blue products showed a similar time course profile as own brand cigarettes; the exposure was only 14% that of the nicotine exposure following use of own brand cigarettes. Mean AUC for own brand cigarettes was 1003 ng/mL/min and 678 for the Nicorette gum. The 3 and 6 mg OG Blue products delivered much less nicotine (150 and 242 ng/mL/min) than both comparators. The rate of nicotine plasma rise (C<sub>max</sub>/T<sub>max</sub>) was greatest for own-brand (3.1 ng/mL/min) followed by 0.5 and 0.7 for the 3 and 6 mg/mL OG Blue. Nicorette gum was slowest at 0.1.

Multiple PD measures were evaluated to determine the subjective effects of the OG Blue products in comparison to the controls (own brand cigarettes and Nicorette gum). Mean Change from Baseline (CFB) scores for Urges to Smoke VAS over time are presented **Figure 4**. Inferential analysis of the maximum CFB scores for urge to smoke (**Table 2**) did not detect a statistically significant difference between both OG Blue products and own brand cigarettes. Nicorette gum was significantly less effective in suppressing the urge to smoke compared with own brand cigarettes.

Inferential analysis of the maximum response for Pleasant VAS (**Figure 5**) did not detect a statistical difference between both OG Blue products and own brand cigarettes. Nicorette gum was significantly less Pleasant than cigarettes.

Table 1. Nicotine Pharmacokinetic Parameters

Parameter Statistic	KEEP IT 100 OG Blue, 3 mg N=27	KEEP IT 100 OG Blue, 6 mg N=27	Own-Brand Cigarette N=27	Nicorette Gum N=27
<b>C<sub>max</sub> (ng/mL)</b>	n=23	n=23	n=22	n=24
Mean (SD)	2.63 (1.58)	3.96 (3.55)	18.66 (10.09)	5.85 (3.12)
Median	2.27	2.62	17.35	5.40
(Min, Max)	(0.37, 5.74)	(0.31, 15.71)	(0.61, 43.13)	(1.88, 13.52)
Geometric mean	2.10	2.73	15.13	5.14
<b>T<sub>max</sub> (minutes)</b>	n=23	n=23	n=22	n=24
Median	5.0	6.0	6.0	45.0
(Min, Max)	(2.0, 180.0)	(2.0, 180.0)	(5.0, 31.0)	(15.0, 180.0)
<b>AUC<sub>(0-4)</sub> (ng*min/mL)</b>	n=23	n=23	n=22	n=24
Mean (SD)	150.23 (65.03)	242.44 (134.75)	1003.47 (348.83)	677.59 (352.66)
Median	157.33	243.34	1044.42	645.10
(Min, Max)	(38.33, 286.36)	(23.41, 551.66)	(25.68, 1667.35)	(235.82, 1517.98)
Geometric mean	134.34	196.79	857.71	593.63

Figure 3. Baseline Adjusted Plasma Nicotine Concentrations

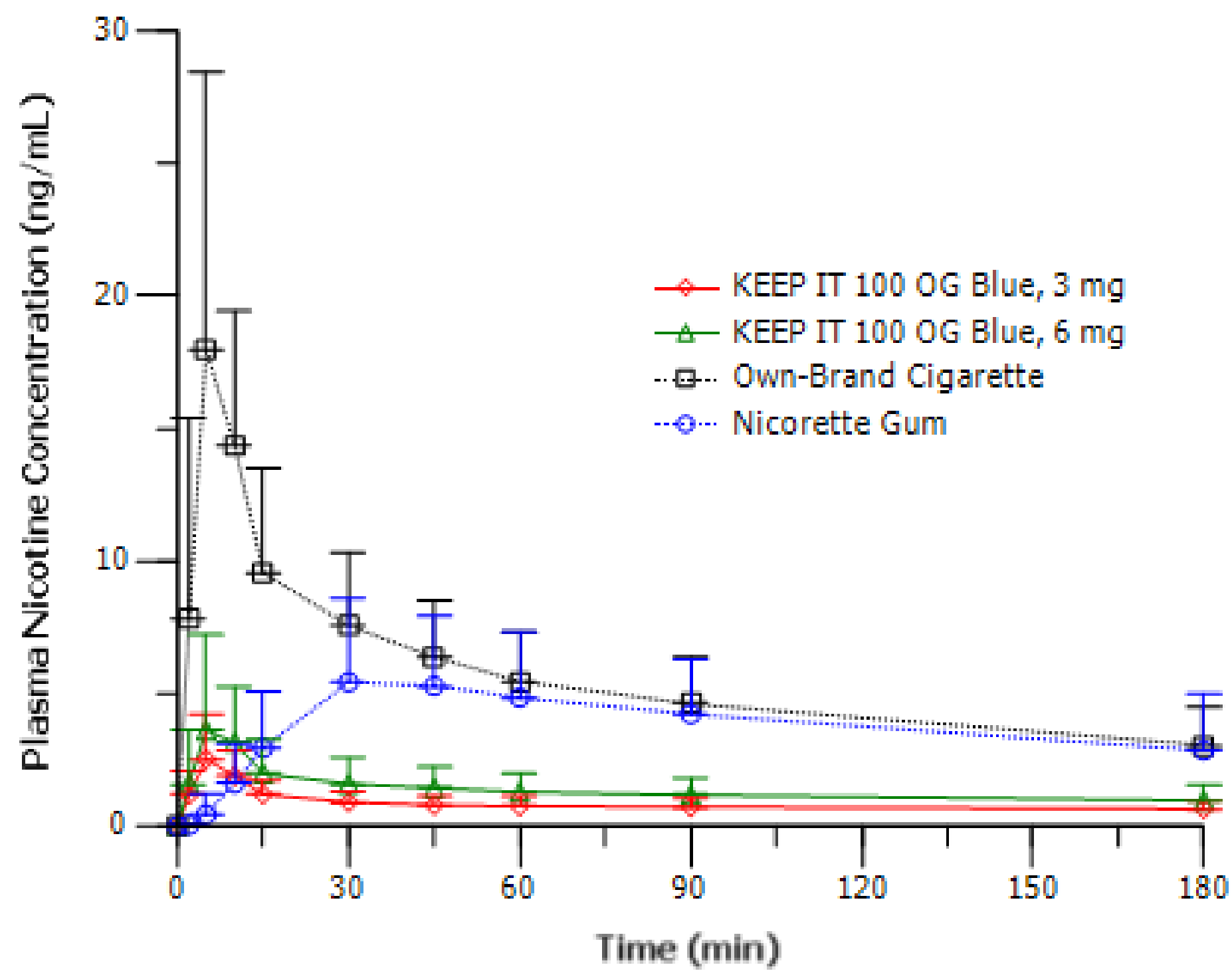


Figure 4. Mean (SE) Urges to Smoke VAS Change from Baseline Scores over Time

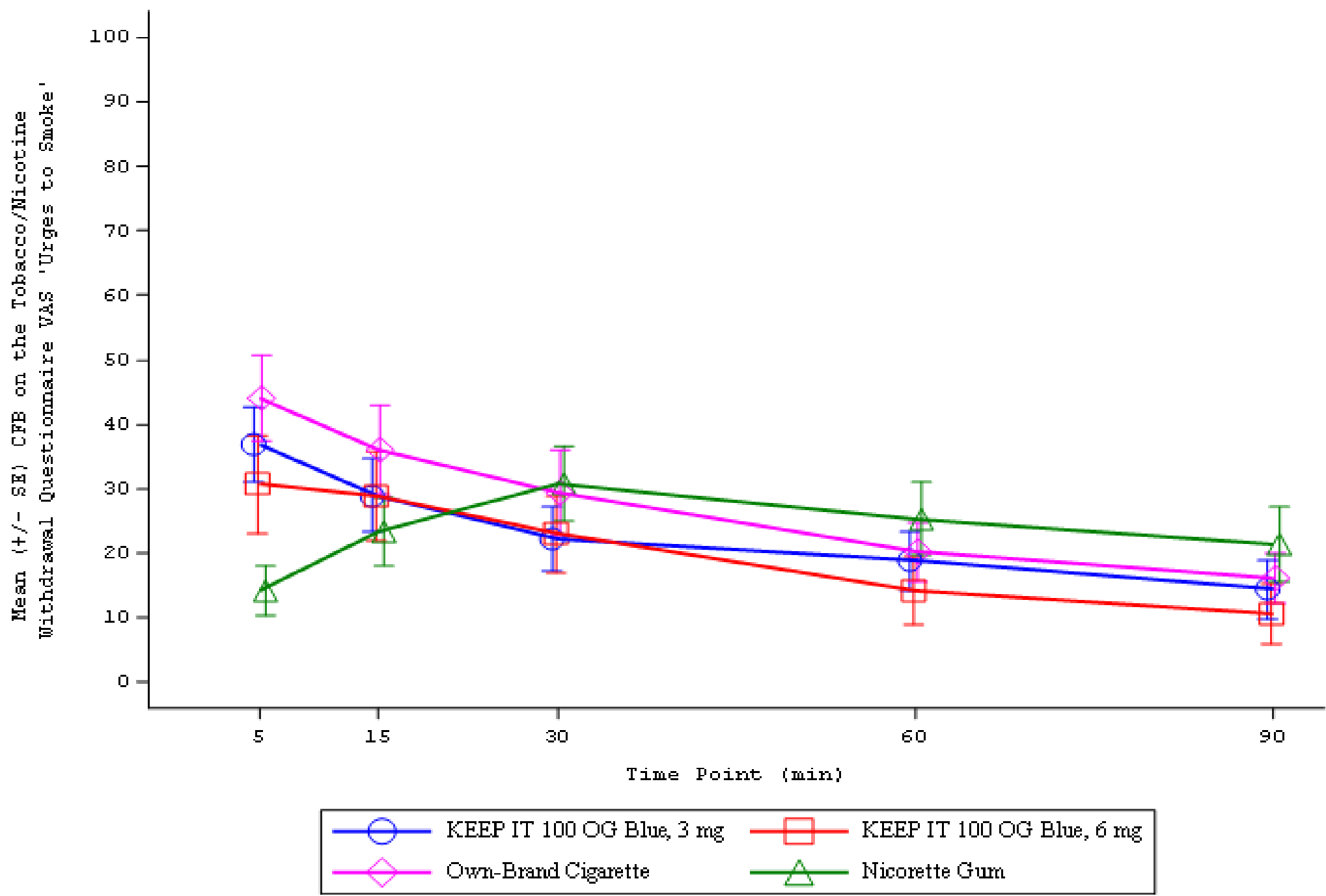
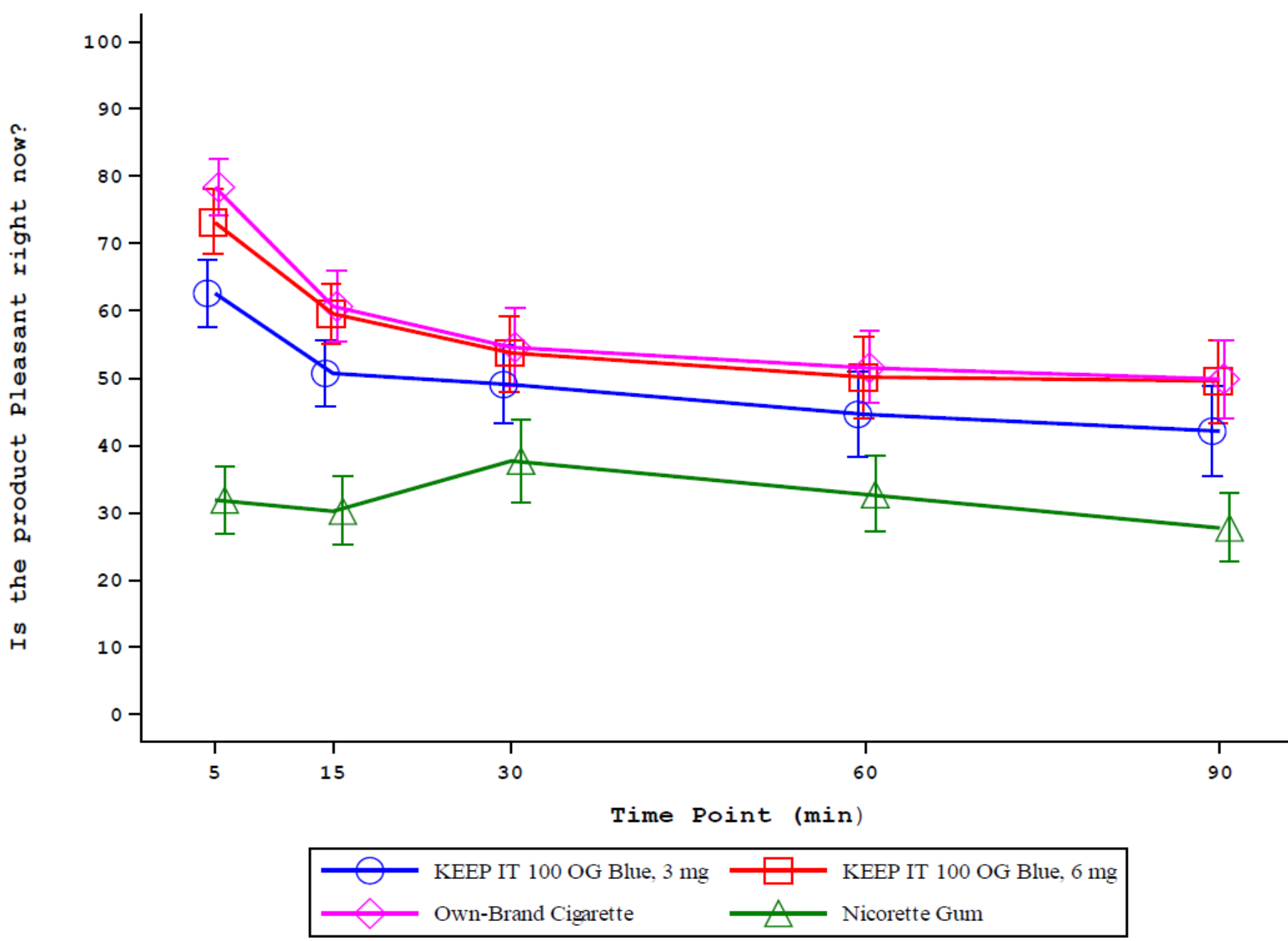


Figure 5. Mean (SD) Pleasant VAS Scores over Time



## Conclusions

Despite lower peak (C<sub>max</sub>) and overall (AUC) exposure to nicotine, KEEP IT 100 OG Blue e-liquid products showed similar peak reductions in urges to smoke and similar ratings of pleasantness when compared with own-brand cigarettes. This is remarkable considering that the OG Blue products delivered less than 15% of the nicotine as own brand cigarettes. KEEP IT 100 OG Blue were also more effective at reducing the urge to smoke and rated more pleasant than Nicorette gum. These results indicate that the abuse liability of KEEP IT 100 OG Blue (3 mg and 6 mg) is not greater than own-brand cigarettes, but greater than Nicorette gum.