



Effect of Plumping Hyaluronic Acid Lip Treatment SPF 30 #1020 on enhancing skin volume and redness

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**Objective:** To evaluate the effect of formulation on lip plumping and rubefacient.

**Result Summary**

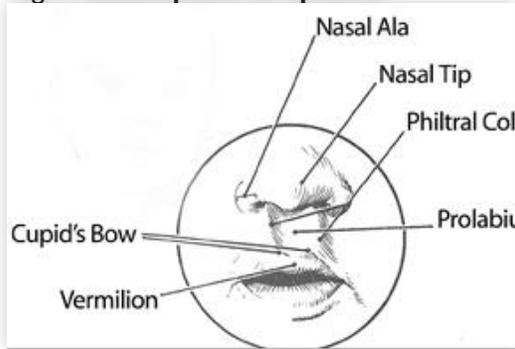
	Baseline	one treatment	One month treatment	One month + 1
<b>Lip Curvature 3D lip profile volume (mm<sup>3</sup>)</b>				
Average	22173.0	22754.0	22310.5	22583.5
Percent change from baseline		2.62%	0.62%	1.85%
Significance (p value)		2.85553E-05	0.45666	0.02052
<b>Average lip pout height increase in mm (volume increase /surface area)</b>				
Average		0.7803	0.1960	0.5155
Percent of subjects improved		90.91%	68.18%	72.73%
<b>Lip Surface area mm<sup>2</sup></b>				
Percent change from baseline		11.85%	1.69%	5.63%
Significance (p values)		1.475E-08	0.1685	0.0006
Percent of subjects improved		95.5%	54.5%	81.8%
<b>Lip redness</b>				
Percent change from baseline		11.732%	0.913%	7.048%
Significance (p values)		1.06E-07	0.582778	3.21E-05
Percent of subjects improved		95.45%	59.09%	86.36%

**Introduction**

It is well known that gravity is not the sole determinant of the aging face, but volume loss, including that of soft tissue and bone, is equally important in the pathogenesis of the stigmata of aging (1-2). It has been widely observed that women who look young for their age have large lips (3). Lips are generally thicker in young subjects than in old persons. Mean labial curvature is larger and more variable in young than in old persons (4).

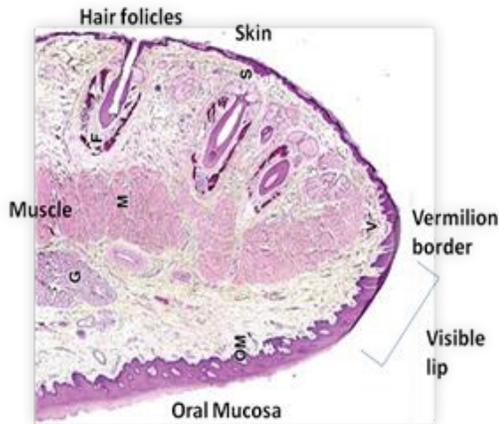
According to (5) the aged look is due to a loss of elasticity and resultant ptosis (drooping) of the upper lip rather than to often-postulated but unproven total volume loss.

**Fig 1: Description of lip area**



Studies by (6)] showed a statistically significant lengthening of the aging upper lip. The prolabium (middle part of the philtrum) is lengthened with age thus decreasing visible upper lip vermilion (lip outline). Iblher at al (2012) observed a decrease in thickness and redistribution towards a length increase with age, but no total volume loss of lips (6).

**Fig 2 Histological section of lip**



Studies by Iblher et al (2012) involving histomorphometric analysis of the upper lip complex of young (< 40 years, n = 10) and old (> 80 years, n = 10), revealed statistically significant thinning of the skin (epidermis+dermis), thickening of the subcutis and a degeneration of elastic and collagen fibers. The orbicularis oris muscle becomes thinner and shows a decrease of the forward curve defining the vermilion border. According to Iblher et al (2012), the main processes of lip aging are redistribution from thickness to length without total volume loss and a decrease of structural components of the lip, which leads to the decrease of pouting, an inversion of the vermilion and a ptosis (drooping) of the lip (6). The perioral soft tissues drop down in older subjects and the soft tissue descends on the entire labial arch (the arch between the upper set of teeth) (7).

In an attempt to obtain a youthful look several approaches have been practiced to enhance the lips. For decades, women have applied lipstick and lip-liner slightly above and below the actual top and bottom of their lips to give their lips a fuller appearance. There is a myriad of devices that claim to increase lip volume by suction (8), percussion or vibration massage(9) . Injection of fillers is the most popular method of lip augmentation however, these procedures are not only expensive, and can have side effects and complications. Use of blood flow enhancers is a much simpler method of lip plumping (10).

Vasodilation from blood flow enhancers cause an increased blood flow causing redness (rubor) of the effective area. Increased permeability of the blood vessels results in an exudation (leakage) of plasma proteins and fluid into the tissue (edema), which manifests itself as swelling (tumor). Controlled manifestations of these processes can be used for plumping of lips as well as a natural reddening. Rubefacients (containing salicylates or nicotinamides) cause localized vasodilation of skin and to cleanse and nourish the affected area as well relieve visceral pain by drawing blood from deeper parts of the body into the skin. They are used mostly today to ease the pain and swelling of arthritic joints and shingles. Capsaicin applied topically can produce a burning sensation at the application site, and has also been grouped with rubefacients, although the mechanism of pain relief is to desensitize nociceptors (sensory receptors that send signals that cause the perception of pain in response to potentially damaging stimulus (11).

The most popular rubefacient include salicylates, with trolamine salicylate (12 -14), diethylamine salicylate (15-16), salicylic acid (17-18), benzydaminesalicylate (19), methyl salicylate (20), glycol salicylate (21), copper salicylate (22), ethylene glycol monosalicylate ester (23), or a mixture of salicylates (24). Other Actives include capsicum oleoresin (24, 21), and adrenal extract (18).

Clinical study CRL2018-0005 was conducted to study the effect of a product on lip plumping and rubefacient. The study was sponsored by Topix Inc and conducted at Clinical Research Laboratories (CRL) in Piscataway, NJ. The following test material was tested:

- Plumping Hyaluronic Acid Lip Treatment SPF 30 #1020

### **Procedure**

This study was conducted in adherence with the principles of Good Clinical Practice as contained in the U.S. Code of Federal Regulations (CFR), Title 21, CFR, Parts 50 and 312 and International Conference of Harmonisation (ICH) Guidelines for Good Clinical Practice: Consolidated Guidance (GCP E-6, April, 1996). Since the study is not invasive, it was not necessary to obtain the approval of an Institutional Board for this study.

All panelists in this study were completely informed about the pertinent details and purpose of this study. Panelists were provided with a copy of the Informed Consent form and were given sufficient time to read the document. The study was explained to each panelist and they were given the opportunity to ask questions prior to signing of the Informed Consent. Written Informed Consent was obtained from each panelist prior to conducting any study procedures. Panelists also signed a Photography Release Form for the capture and use of digital images, if applicable.

A total of 25 subjects were recruited for the study out of which 22 completed the study. Three subjects discontinued due to product unrelated reasons. The subjects were adult women, recruited from the local population. They were females between the ages of 18 and 45 years; of Fitzpatrick Skin Types I-IV with full lips. The subjects were carefully examined to make sure they did not show signs of visible skin disease which might be confused with a skin reaction from the test procedure or material. They were of normal health with no evidence of acute or Chronic disease including dermatologic or ophthalmological problems; even colored skin on the test area (lips and peri-oral) and in good general health. The subjects expressed willingness to cooperate with the investigator and comply to study requirements; and clearly demonstrated the ability to understand the purpose of the study and what is required of her to bring it to a meaningful conclusion as well as risks associated with participation. They Demonstrated the ability to read and understand all the items in the informed consent document; and willingly signed it and the photo release form;

Panelists in ill health or under a doctor's care or taking medication(s) which could influence the outcome of the study were excluded from the study. They were also excluded if they exhibited sunburn, rashes, scratches, burn marks etc., which might interfere with evaluation of test results or systemic illness that could contra-indicate participation. Additionally, the subjects were examined and excluded if they showed dermatological disorders in the test areas including warts nevi, moles, sunburn, suntan, scars and active dermal lesions, infections, burns, cuts, tattoos, visible scars or acne or any form of suspicious lesion or skin cancer on the treatment area. They were also excluded if they had very thin lips or had cosmetic or surgical treatment of the test site including lip fillers and treatment with rubefacient products.

The subjects were not pregnant, lactating or planning to get pregnant for the duration of the study. They were instructed not to participate in any cosmetic or other clinical trials involving the lip area. Panelists were instructed not to use any other topical agents in the test area, or receive any skin treatments, other than the products provided, for the duration of the study. Panelists were instructed to maintain their daily cleansing routine for the duration of the study.

After admission to the study, the panelist could withdraw at any time for any reason. The Investigator was to attempt to determine the reason and report it fairly and accurately.

### **Procedure**

The subjects reported to the testing lab with a clean face devoid of any lip treatment for the baseline measurements. Photographs were obtained using the Clarity Pro 3D system. The subjects were provided with the test material to apply on their lips making sure to stay within the vermilion border of the lips. Ten minutes after treatment photographs were obtained again. The subjects were provided with the test material to apply 4+ times a day for 4 weeks, after which photographs were obtained again with and without product application.

Clarity Pro (BrighTex Bio-Photonics - BTBP LLC) is a facial photography system that uses three cameras that synchronously capture the front, left and right facial profiles. Their software then combines the images to a high density mesh model (20 pixels per millimeter in the X and Y dimensions, less than 4 microns on the Z axis) in three dimensions. Using this system, 3D measure of volume is possible with good accuracy (25, 26).

Using Clarity Pro photographs of the subjects were obtained at the following time points:

- Baseline
- 10 minutes after one treatment
- 4 weeks after treatment
- At the 4 Week visit - 10 minutes after one treatment

#### *Data analysis*

The photographs were analyzed for volume in a 3D system and for lip area (mm<sup>2</sup>) and redness (a\* values) in the 2D system. The 3D data was acquired in pixels, converted to mm<sup>3</sup> as per calculations suggested by BTBP (27).

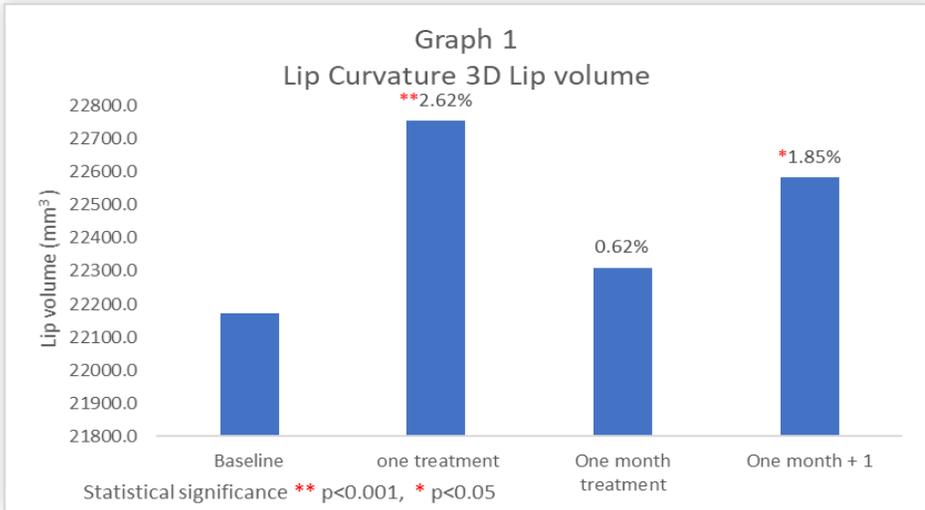
An Excel analysis package was used to assess the statistical significance of the post-treatment data as compared to pre-treatment (baseline) by employing the two-sample paired student's t-test. This test for significance determines the probability that a given results could not have occurred by chance. The probability is called a p-value. Data was evaluated at a 95% (p<0.05) confidence level. In summary, the data is significant when the p-value is less than 0.05 and highly significant if the p-value is less than 0.001 (28-29).

### **Results and discussions**

#### *Lip Curvature 3D Lip Volume*

Three D photography is increasing in popularity with the advent of a myriad of 3D cameras. The ability to capture images in three dimensions has opened up new avenues for observation and has increased the ability to analyze changes after treatments. With two dimensional imaging linear distances, angles, and areas can be determined accurately, however, the human body is a three-dimensional structure and requires manipulation in three planes within the constraints of esthetics, stability, and function.

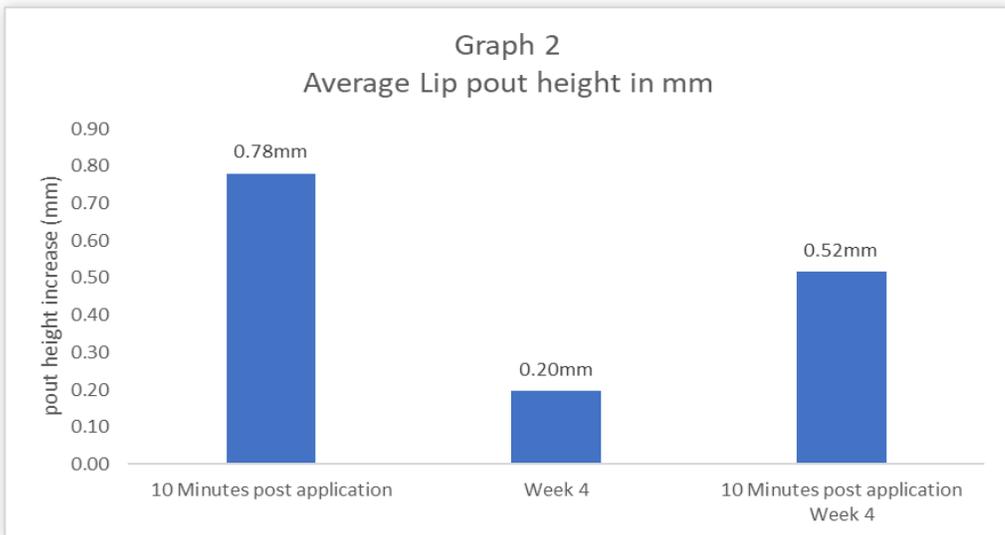
Three dimensional photography is a valuable tool for study of volume of lips for example after enhancement with filler injections (26-27). Graph 1 shows lip curvature using 3D volume analysis (in mm<sup>3</sup>) after treatment with Topix Plumping Hyaluronic Acid Lip Treatment SPF 30.



As observed in graph 1, there was a highly significant ( $p<0.001$ ) increase in lip volume after one treatment Plumping Hyaluronic Acid Lip Treatment SPF 30. Out of 22 subjects 20 showed and improvement. Rossi et al created a visual grading scale and compared with 3D volume measurements. The effect of Topix treatment appears to show almost visually graded change of 0.5-1 (30) in lip size which is quite conspicuous.

The plumping effect of Topix is clearly transient nevertheless, after one month of use there was a slight cumulative. When applied again after one month of use there was once more a significant increase ( $p<0.05$ ) in lip volume.

Graph 2 shows an overall volume increase. Graph 2 exhibits third dimensional “pout” of the lips taking into account the much larger scale of area of lips. Graph 2 shows the pout height increase in mm. On average there was a 0.78mm increase in the lip pout after one treatment; this is about the thickness of a dime, yet very palpable.



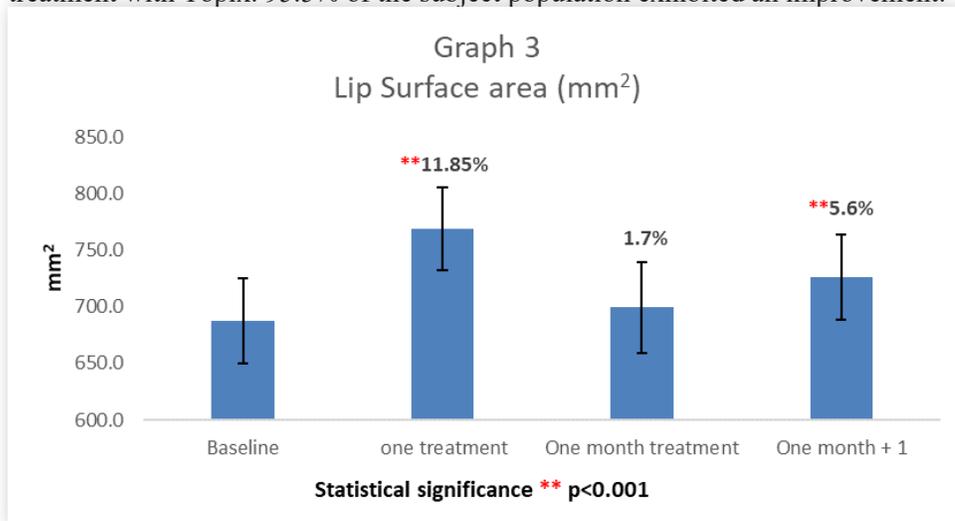


After 1 month treatment there was still an 0.2mm pout that increased to 0.52mm after another treatment with Topix.

Clearly the product is effective when the blood flow is initiated immediately after treatment. As the inflammation resolves the plumping effect also recedes. Multiple treatments did not appear to exhibit an additive effect, on the contrary, the inflammatory reaction was lower after one month use, probably as a result of adaptation.

**Lip Surface area**

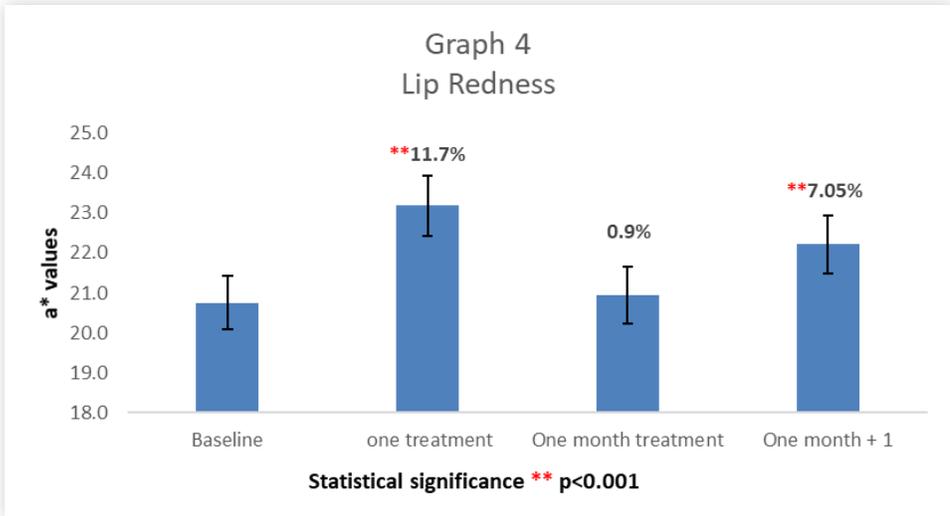
Graph 3 shows 2D area analysis of the lips from the photographs (attached appendix 1). There was a highly significant ( $p < 0.001$ ) increase of 11.85% in lip area after one treatment with Topix. 95.5% of the subject population exhibited an improvement.



After one month treatment there was slight cumulative lip area increase of 1.7% which increased to 5.6% ( $p < 0.001$ ) after another treatment in the lab.

**Rubefacients (Lip Redness - a\* values)**

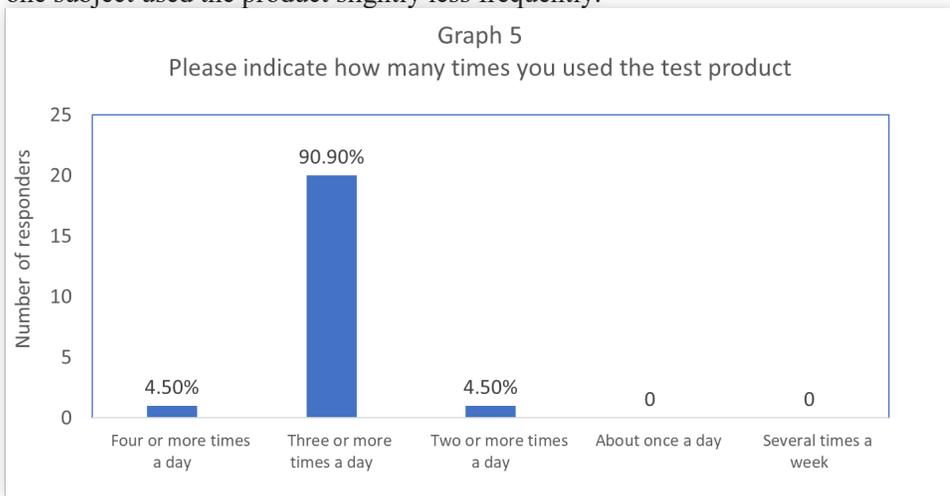
The L\* a\* b\* color space describes mathematically all perceivable colors in the three dimensions; L\* for reflectance and a\* and b\* for the color components green–red and blue–yellow (CIE- L\*a\*b\* 1976 color space). International Commission on Illumination (French Commission internationale de l'éclairage, hence its CIE initialism) describes all the colors visible to the human eye and was created to serve as a device-independent model to be used as a reference. Using image analysis of the Clarity Pro, a\* values were determined from the lip area of the subjects. Graph 4 shows a highly significant ( $p < 0.001$ ) increase in lip redness after one treatment of Topix. 95.45% of the subject population exhibited an improvement.



There was 0.9% cumulative effect of the product after one month use. After another treatment in the lab there was again a significant ( $p < 0.001$ ) increase in lip redness.

**Subject self assessment**

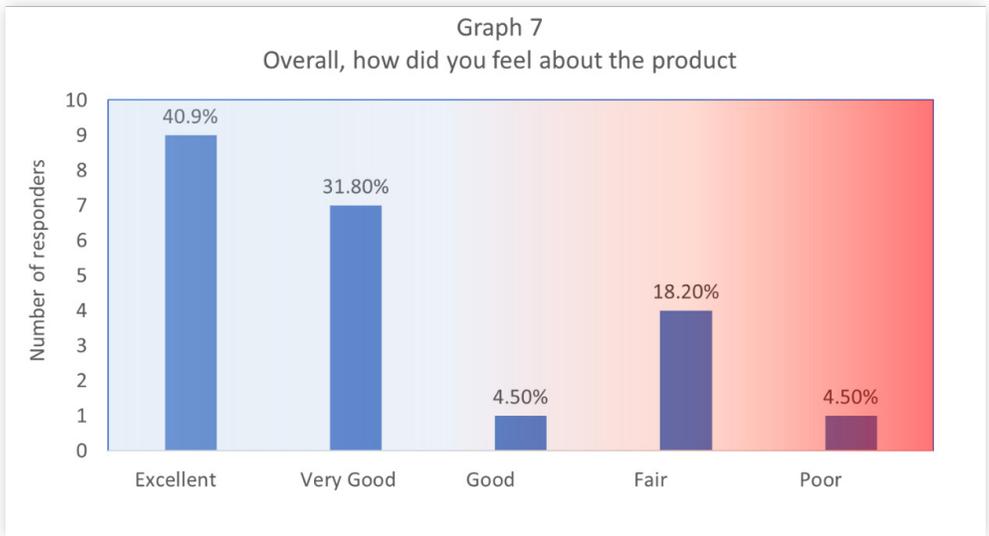
The subjects were instructed to use the product three or more times a day for the course of the study. Graph 5 shows that 90.9% of the subjects followed instructions and used the product 3 or more time a day, one subject went beyond the minimal use requirement and one subject used the product slightly less frequently.



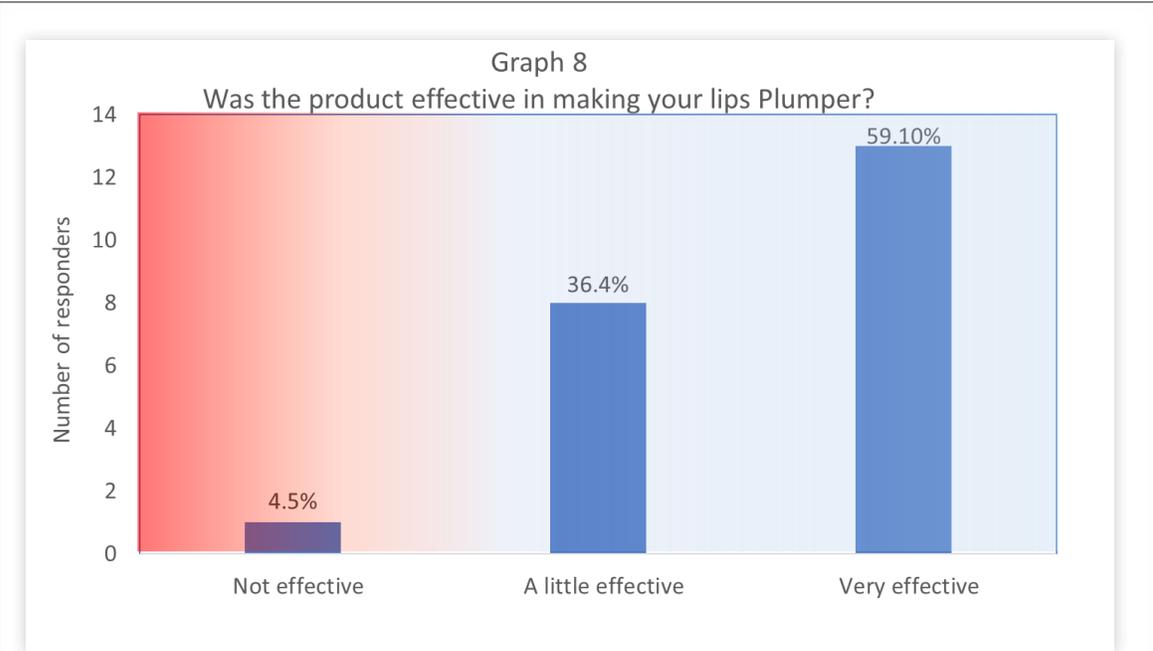
When asked if they would purchase the product if it was available at a convenient store at a reasonable price, 40.9% of the subjects definitely wanted the product while 31.8% of the subjects professed that they would probably purchase it (Graph 6). Four subjects were uncertain while two subjects did not appear to like the product.



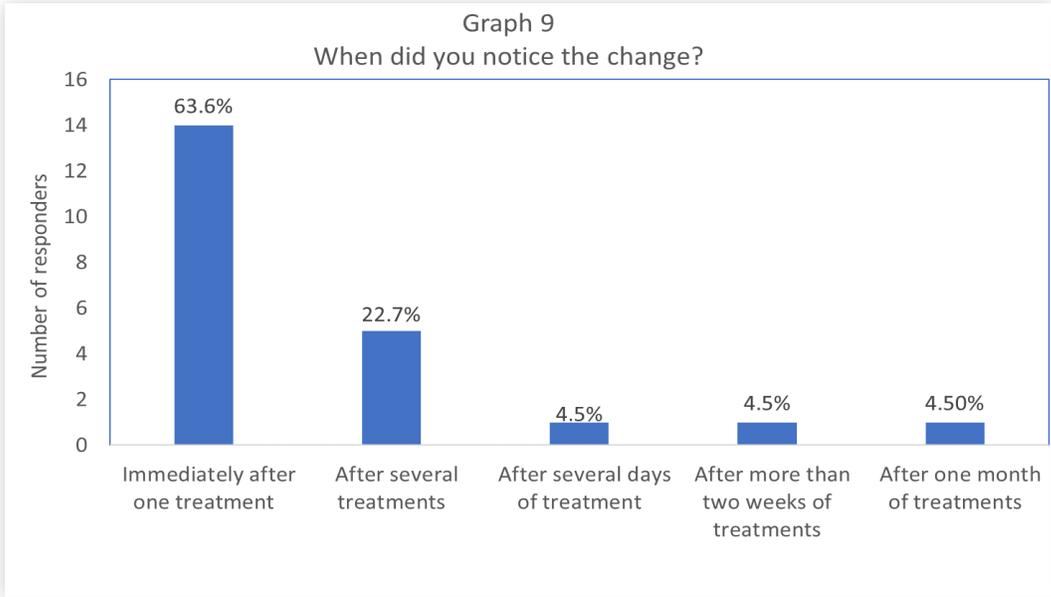
Graph 7 shows the overall approval of the product. 40.9% of the subjects declared it was excellent and 31.8% said it was “very good”. One subject said it was “good” while five subjects did not appear to like it very much.



As observed in graph 8, 59.8% of the subjects professed the product to be very effective as a lip plumper; 36.4% found it a little effective. One subject did not find it effective at all.

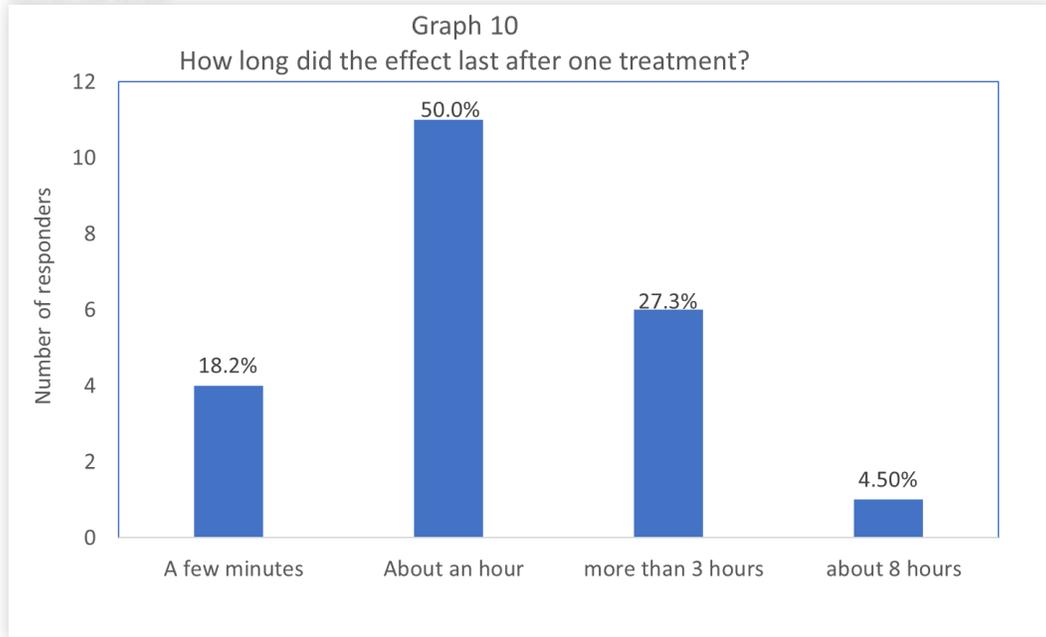


Graph 9 displays the number of treatments before the product appeared to take effect. Most (63.6%) of the subjects found it effective immediately after one treatment. The remaining panel found it effective after multiple treatments.

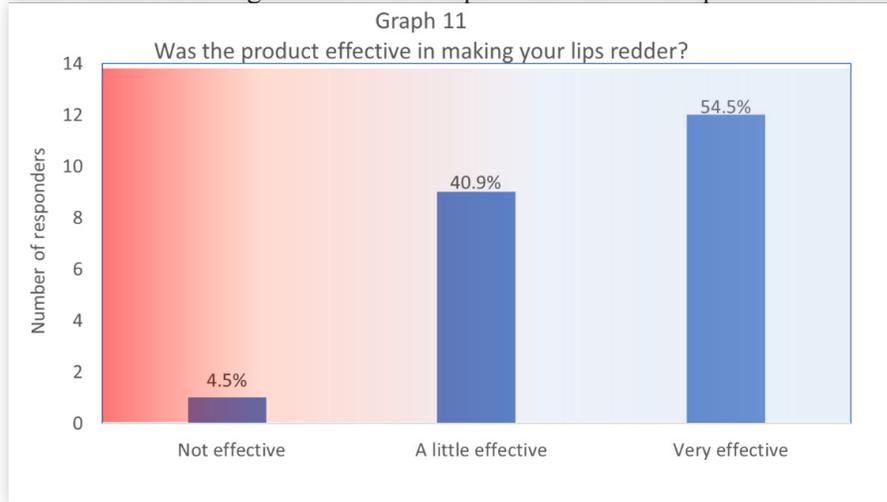


When asked how long the effect of lip plumping lasted, 4 subjects (18.2%) declared it lasted only a few minutes. The majority of the panel (50%) said it lasted about an hour; 27.3% of the panel found it lasted more than 3 hours. One subject declared the lip

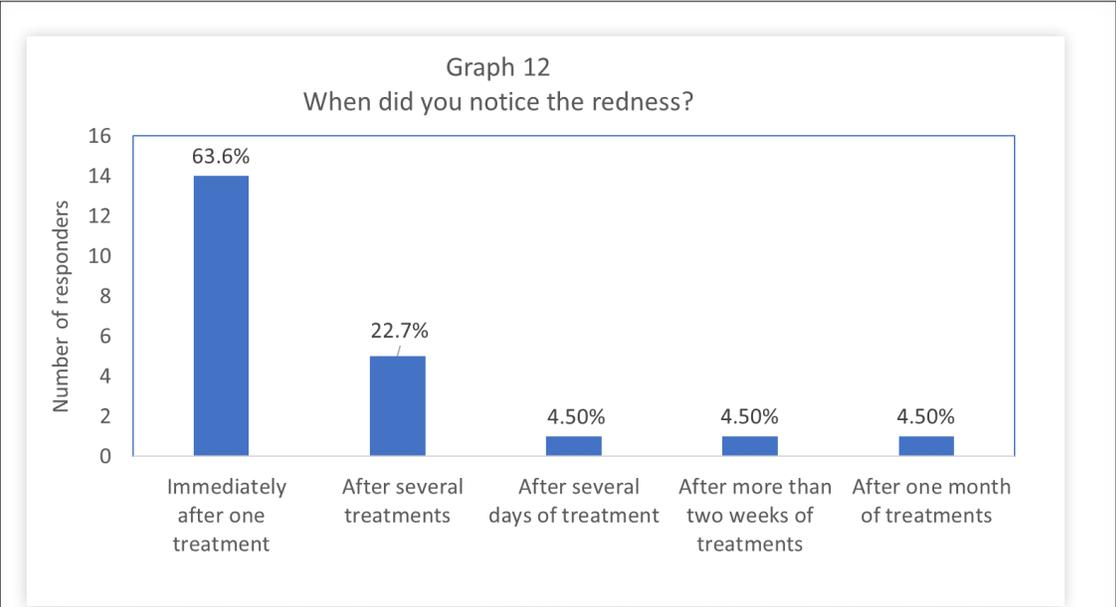
plumping lasted more than 8 hours. These data are in agreement with the volume data (Graphs 1- 3). Clearly the product is effective when the blood flow is initiated immediately after treatment and the effect recedes when the inflammation is resolved in about an hour.



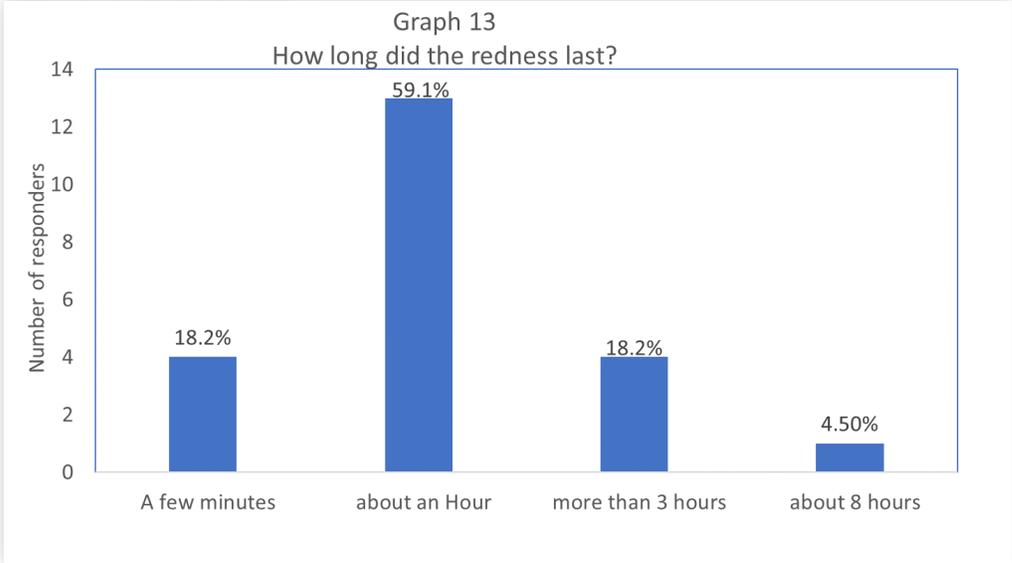
Graph 11 addresses the question about lip redness. Most subjects found it to be very effective in reddening lips (54.5%) while 40.9% found it to be a little effective. One subject did not find the product to be effective in reddening her lips. These subject observations are in agreement with Graph 4 that shows the quantitated red values.



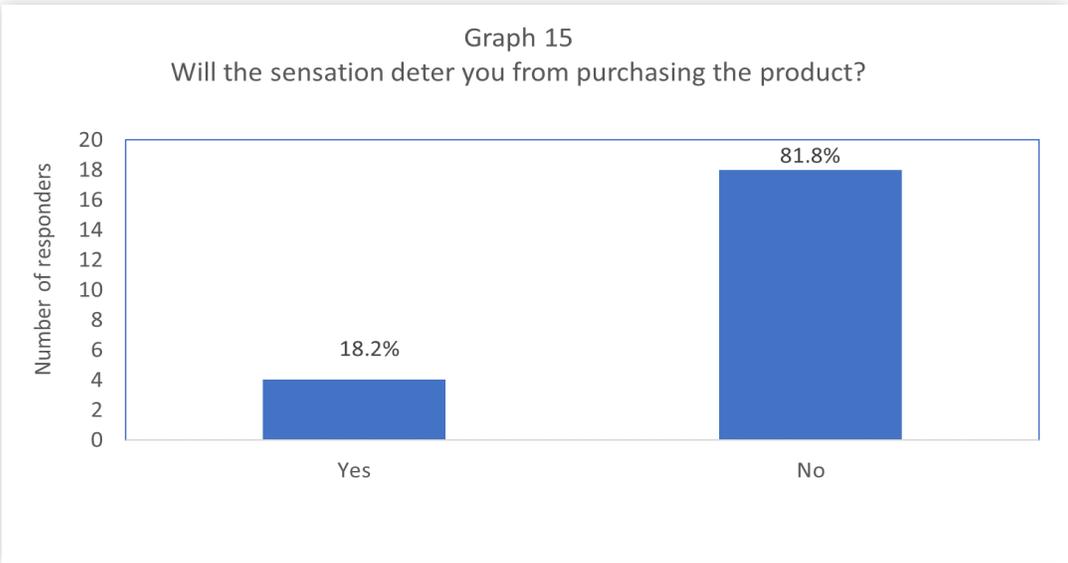
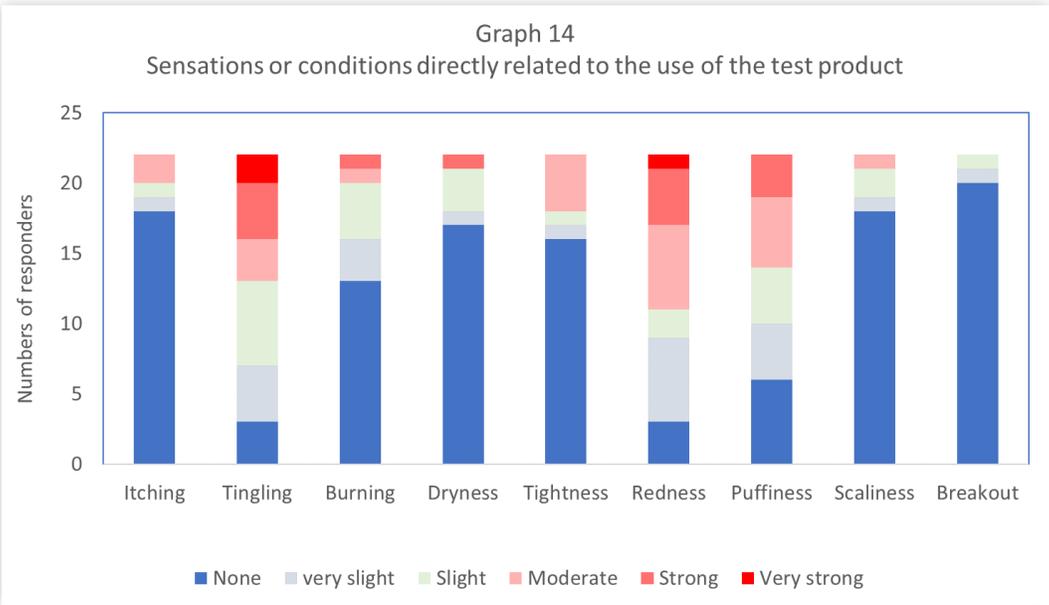
Graph 12 shows that most subjects (63.6%) noticed the redness immediately after treatment. 22.7% (5 subjects) noticed redness after several treatments and three subjects did not notice redness until after multiple treatments.



When asked how long the redness lasted, 59.1% of the panel declared it lasted for about an hour. Four subjects (18.2%) found the redness to last more than three hours and even up to eight hours for one subject. Four subjects (18.2%) declared the redness only lasted a few minutes. Clearly the product is effective in reddening the lips when the blood flow is initiated immediately after treatment and the effect recedes when the inflammation is resolved in about an hour.



As expected from an inflammatory effect of rubefacients the subjects experiences some sensations after using Topix. Most subjects reported of tingling, puffiness and redness. A few subjects even reported of burning, dryness and tightness (Graph 14). Nevertheless, 81.8% of the subjects declared these sensations will not deter them from purchasing the product (Graph 15). Four subjects did not like the sensations and did not want to purchase the product.



**Conclusion**

Based on the confines and conditions of this study:

- Topix Plumping Lip Treatment #1020 was significantly effective in reddening and plumping of lips immediately after treatment
- The increase in lip volume was visually observable and was noticed and approved by most subjects
- The plumping effect lasted for an hour or so.
- Multiple treatments did not have an additive effect as expected from a Rubefacient.