Instituto de Fotomedicina
plataformalaser

In Use efficacy Efficacy Y.en Effect Serum and Cream Containing HA-Conjugated Gold Nanocomplexes to Increase the Synthesis of the Epidermal Extracellular Matrix and Improve the Skin Condition.

INDEX

INTRODUCTION

The use of gold in medicine has been put in practice for centuries. Its use as a material for implants (e.g. dental implants) are widespread and its application as a drug for the treatment of rheumatoid arthritis has been well documented since 1935[1]. It is without a doubt a remarkable material both for its high bio and inmunocompatibility as well as for its chemistry, which allows binding it to almost any kind of molecule in a wide array of ways[2]. Recently, as a result of the nanotechnology developments, the applications of gold nanoparticles are blossoming in all fields as a paradigm shift. Its aforementioned virtues (biocompatibility, versatile chemistry) and the inherent physical and mechanical advantages of operating at a nanometrical scale allow envisioning all kind of strategies to use them as a vehicle in medicine and aesthetics[3][4][5].

This study is centered in one of these possibilities. In this case, the gold nanoparticles are bonded to several Hyaluronic Acid (HA) glucosaccharides, thus creating gold nanocomplexes (AuNCs) acting as HA antagonists for the CD44 receptor in the keratinocyte. The effects of these nanocomplexes have been tested in vitro, showing a significant increase of HA and collagen synthesis by epidermal keratinocytes[6][7] and fibroblasts[8][9] as well as an increased antioxidant activity[10]. In parallel, its use on human skin has been tested and proven as safe[11] and skin penetration tests[12] indicate that the AuNCs remain in the epidermis, consequently dissipating the risk of a systemic distribution through the human body. These AuNCs can be applied in many different forms such as the Y.en Effect serum and cream; this study aims to assess the antiaging efficacy of the combination of both products.

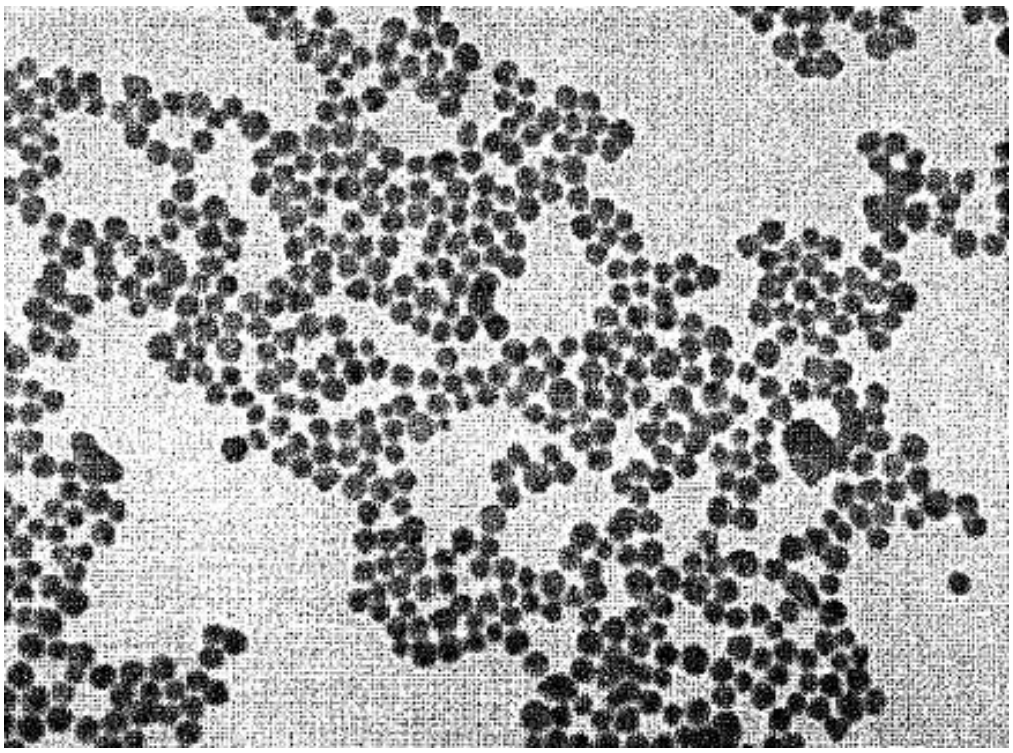


Figure 1. Transmission electron microscopy (TEM) images of the conjugate compound.

The study was entirely carried out by Instituto de Fotomedicina. Insituto de Fotomedicina is, since 1997, the Photomedicine and Laser Service of Hospital Quirón Teknon (Know before as Centro Médico Teknon) deploying all kind of cutting-edge techniques for the analysis, diagnosis and treatment of the skin. Hospital Quirón Teknon is renown nationally and internationally for their medical service quality and high standard of care as is proven by the continuous renewal of the Joint Comission International Accreditation and the Generalitat of Catalonia's Acute Hospital Care Accreditation (base don the excellency model of the *European Foundation for Quality Management*). This study was supervised by Instituto de Fotomedicina's Medical Director, Dr. Joan Ramón Garcés (Dermatologist) and its Cutaneous Laser Director, Dra. Eva Ciscar (Aesthetics Physician). The investigator was Gabriel Buendía Bordera (Scientific Director).

MATERIALS AND METHODS

23 healthy women aged between 35 and 50 years old were recruited for this study and the average age of the group was 39,61 years. Following the inclusion criteria, none of them were smokers or pregnant neither were they menopausal or under any kind of hormonal treatment. They presented a certain degree of visible aging signals (wrinkles, spots, etc.) as well as a facial melasma condition. The volunteers were forbidden to use any cosmetic product or perform any kind of scrubbing or aesthetic procedure in their face for the duration of the study.

The study design required that these volunteers applied twice a day (morning and night), as part of their daily hygiene procedures, both the serum and the cream all over the face for a total period of 28 days for the texture, wrinkles and epidermal/dermal ultrasound analysis, and 84 days for the skin moisture analysis. In this last case, a new batch of serum and cream was delivered on a monthly basis to all volunteers in order to ensure that they wouldn't run out of it.

The assessment of the efficacy for the texture, wrinkles and epidermal/dermal ultrasound analysis was made through the quantitative data gathered during two visits: the baseline and the 28 days follow-up. Additionally skin moisture measurements were made at the baseline, visit, the 28 days follow-up and a final 84 days follow-up. On the base-line visit a physician would examine the volunteer in order to ensure that her skin condition enabled her to pursue the study Skin texture and wrinkles assessment were performed through 3D topometry, epidermal and dermal conditions were evaluated through 50MHz High Frequency Ultrasounds and skin moisture was measured through a dielectric capacitance probe. The details of the machinery, information capture and processing of the data is as follows:

Photography: Photographs of the face were taken at 0^{o} and $\pm$ 45^{o} with a Nikon D300 on a specifically designed structure on a capturing bench, the Visio 4D (Eotech, France), in order to ensure that camera height, angle and distance to the volunteer remained constant over the study.. The volunteer positioning was also performed on the Visio 4D bench, thanks to a head structure that repositions the

volunteer based on their ears and chin position. Homogenous diffuse and cross-polarized lighting was obtained through two Elinchrom StyleRX 600 flashes and linear-polarization gel filters when required. Another linear-polarization filter was added to the camera lens on these occasions.

Skin Moisture assessment was performed with a MY-808S dielectric capacitance probe (Scalar, Japan) by taking 3 measures on both cheeks, crowfeet and the forehead and averaging them in order to obtain a global representation of the skin moisturing. The manufacturer establishes 38% as a reference for a skin normally moisture. However, as skin condition, season, age, time of the day, etc. can have an impact we established a new internal reference. For this we measured the skin of a two-year long Y.en effect user assuming that her condition is the maximum effect reachable. Then, we normalized by dividing them using the new internal reference. The results of the internal reference were 43% at the bas-line, 41% after 28 days and 38% after 84 days. The results are displayed as a moisture percentage.

Figure 2. Scalar Moisturemeter.

3D Topometry: 3D captures of the skin texture and topometry were captured using the FOITS (Fast Optical In vivo Topometry of human Skin) with a dermaTOP Blue fringe projection system (Breuckmann, Germany) and a Visio4D bench (Eotech, France) allowing to reposition both the volunteers and the fringe projection system at the same place, height and angles. An area of 60x80mm of both crowfeet was captured using the 50mm objective, intended for skin texture (roughness) and crowfeet wrinkles assessment[13][14][15][16][17] The metrical variable considered are defined below:

Figure 3. Visio 4D Positionning bench.

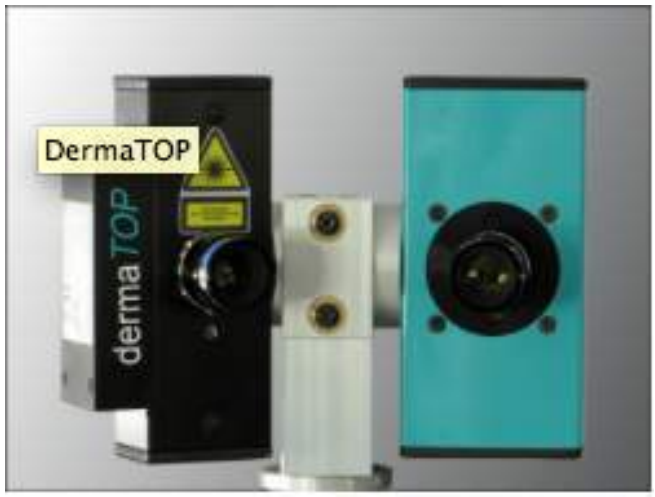


Figure 4. Fringe Projection System.

Texture:

Sa (Average Roughness Height): It is the average of the roughness profile ordinates. It has practically become one of the standard roughness variables used to control very fine surfaces in scientific measurements and statistical evaluations. It is given in mm.

St (Maximum Roughness Depth): It is the vertical distance between the highest peak and the lowest valley of the surface. It is given in mm.

Wrinkles measurement:

Volume (mm^3): Represents the sum of the negative volumes created by the wrinkles present in the 3D capture.

Circumference (mm): Represents the sum of the wrinkle perimeters.

Area (mm^2): Represents the sum of the skin surface constituting the wrinkles present in the capture.

Max Depth Average (mm): Represents the average of the vertical distance between the lowest and the highest parts of the wrinkle.

Mean Depth Average (mm): Represents the average of all the vertical distances present in all the wrinkles.

The processing of these captures was performed with the software AEVA 14.0 (Eotech, France). An area of at least 50x50 mm was analyzed in every case. Cutoff filters were applied for noise removal.

High Frequency Ultrasounds (HFUS): A DUB 75 HFUS system (TPM, Germany) with a 50 MHz open probe was used to measure the epidermal and dermal thickness as well as the epidermal and dermal echogenic density. Both variables are defined below:

Epidermal/Dermal Thickness (µm): It is the average of the 300 vertical distances going from the upper to lower limit of the epidermis/dermis measured by the probe during its 12mm sampling movement[18][19].

Epidermal/Dermal Echogenic Density (arbitrary unit): Represents the amount of sound the tissues echoes back in function of its quantity and structure[20]. Highly structured molecules such as collagen and HA and other components of the extracellular matrix are among the most echogenic structures present in the skin and thus, an echogenic density increase is directly related a to an increased amount of extracellular matrix and consequently, an increased amount of collagen and HA.

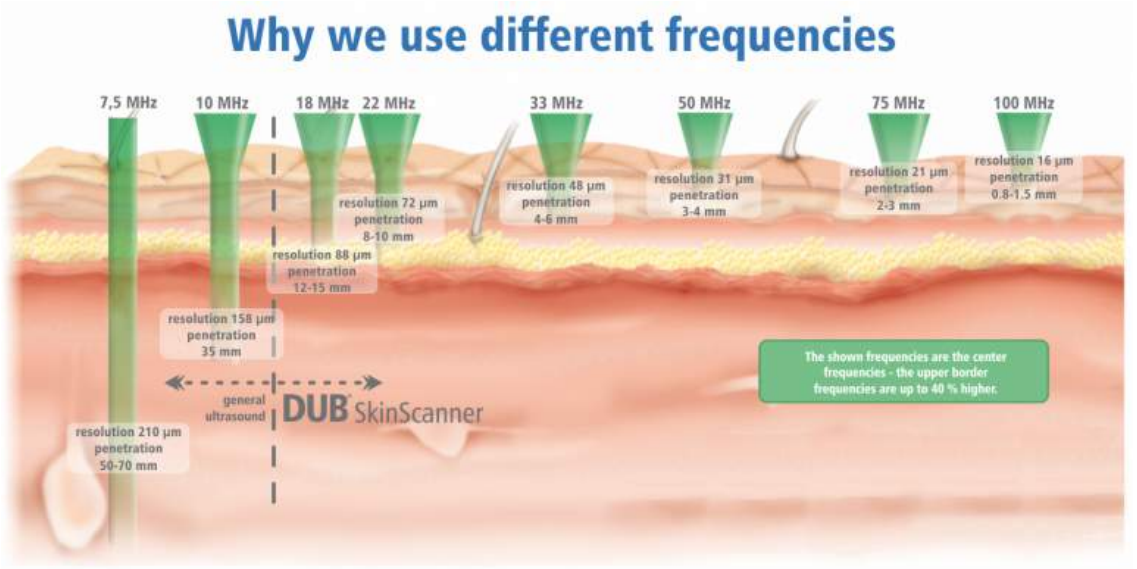


Figure 5. High Frequency Ultrasounds skin penetration vs. resolution chart.

At least 40 samples were taken for every thigh at every visit on the external side of the thigh in order to have a pool of data that would be representative of the cheek skin of both sides. Out of the total amount of samples present for every cheek and visit 3 with good signal were chosen at regular intervals and analyzed with SkinScanner 5.0 software (TPM, Germany) in order to obtain the data. The thickness and density of these 3 samples was averaged in order to obtain the final data used in the statistic analysis.

Finally, the statistical methods used to process the data were the Smirnov-Kolmogorov Goodness-of-fit for a Normal Distribution (ND) test, the Student t-test for paired samples and, in the few cases were Normality could not be proven the

Wilcoxon sign rank test for paired samples was used. Statistical significance was considered in those tests when $p<0,05$. In a very few cases a $p<0,1$ was considered significant in order to assess some apparent data trends.

RESULTS

Out of the 23 initial volunteers, 22 attended to the 28 days follow-up visit while only 18 attended the final 84 days visit.

Skin Moisture Analysis

Skin moisture was measured with a MY-808S dielectric capacitance probe on left and right cheeks, left and right crowfeet and forehead. 3 samples were taken for each region and then the whole was averaged. Out of the 23 initial volunteers, 22 remained 28 days after, and only 18 reached the 84th day of the study. No noticeable differences between face regions, except maybe the forehead, that was always slightly more moisted. The whole results can be seen in the Annex I. The averages are as follow:

	Right Cheek		**Left Cheek**		**Right Crowfeet**		**Left Crowfeet**		**Forehead**	
	Average	Std. Dev	Average	Std. Dev	Average	Std. Dev	Average	Std. Dev	Average	Std. Dev
D0	36,5	1,613	36,9	1,221	37,0	1,645	37,6	1,039	37,8	1,150
D28	35,9	1,046	36,1	1,269	35,8	0,728	36,6	1,455	37,3	0,943
D84	38,0	0,747	37,8	0,675	37,7	0,578	38,4	1,338	38,6	0,810

Table 1. Moisture Average for each face region and evaluation time.

	D0 (N=23)	**D28 (N=22)**	**D84 (N=18)**	**% ΔD28-D0**	**% ΔD84-D0**
Average	37,18	36,32	38,13	-2,31	2,19
Std. Dev.	2,05	1,99	0,70	6,02	6,24

Table 2. Moisture Average for the whole face for each evaluation time and percentage of difference compared to the baseline.

Once these results were obtained we proceeded to normalize them using our pre-established internal reference. Then, they turned into this:

	D0 (N=23)	**D28 (N=22)**	**D84 (N=18)**	**% ΔD28-D0**	**% ΔD84-D0**
Average	0,87	0,89	1,00	2,21	15,64
Std. Dev.	0,05	0,05	0,02	6,34	7,06

Table 3. Moisture after normalization.

Once these numerical data was obtained its statistical analysis began (the full statistical report can be found in the Annex II). First of all, The Normal Distribution (ND) of the data was tested with the Smirnov-Kolmogorov Goodness-of-fit test. As it followed a Normal distribution, we performed a two-tailed paired t-test to compared day 28 to day 0 and day 84 to day 0. We obtained the following:

	D28 - D0	D84 –D0
Moisture	$p > 0,1$	$p < 0,0001$

Table 4. Statistical results for the two-tailed paired t-test

Texture Analysis

3D Texture was measured by means of a fringe projection device on the left and right crowfeet. Then the data from one of the sides was chosen for each volunteer according to a randomized pattern. Two variables where quantified and analyzed out of these captures: the Average Roughness Height of the surface Sa and the Maximum Roughness Depth ST. Cutoff filtering was implemented in several layers in order to reduce as much as possible the noise signals, generally attributed to small face movements. The whole results can be seen in the Annex I. Three volunteers data was considered as outlier, and thus all the following data is from the 19 volunteers considered as valid. The Sa and ST averaged results for those 19 volunteers that reached Day 28 are summarized here:

	Sa	ST
Day 0	0,00722 ± 0,00380	0,10675 ± 0,05629
Day 28	0,00670 ± 0,00228	0,09074 ± 0,03116

Table 5. Sa and St averages and standard deviations.

The averaged differences (in percentage) between the Day 0 and Day 28 results as well as its corresponding Standard Deviations can be seen below:

	Sa	ST
D28 – D0	-5,25 ± 7,39	-21,89 ± 11,19

Table 6. Averaged texture differences between D0 and D28

Once these numerical data was obtained its statistical analysis began (the full statistical report can be found in the Annex II). First of all, The Normal Distribution (ND) of the data was tested with the Smirnov-Kolmogorov Goodness-of-fit test. All the data turned out to be Normal, therefore the paired Student t-test was applied. Table 7 summarizes the result of the tests:

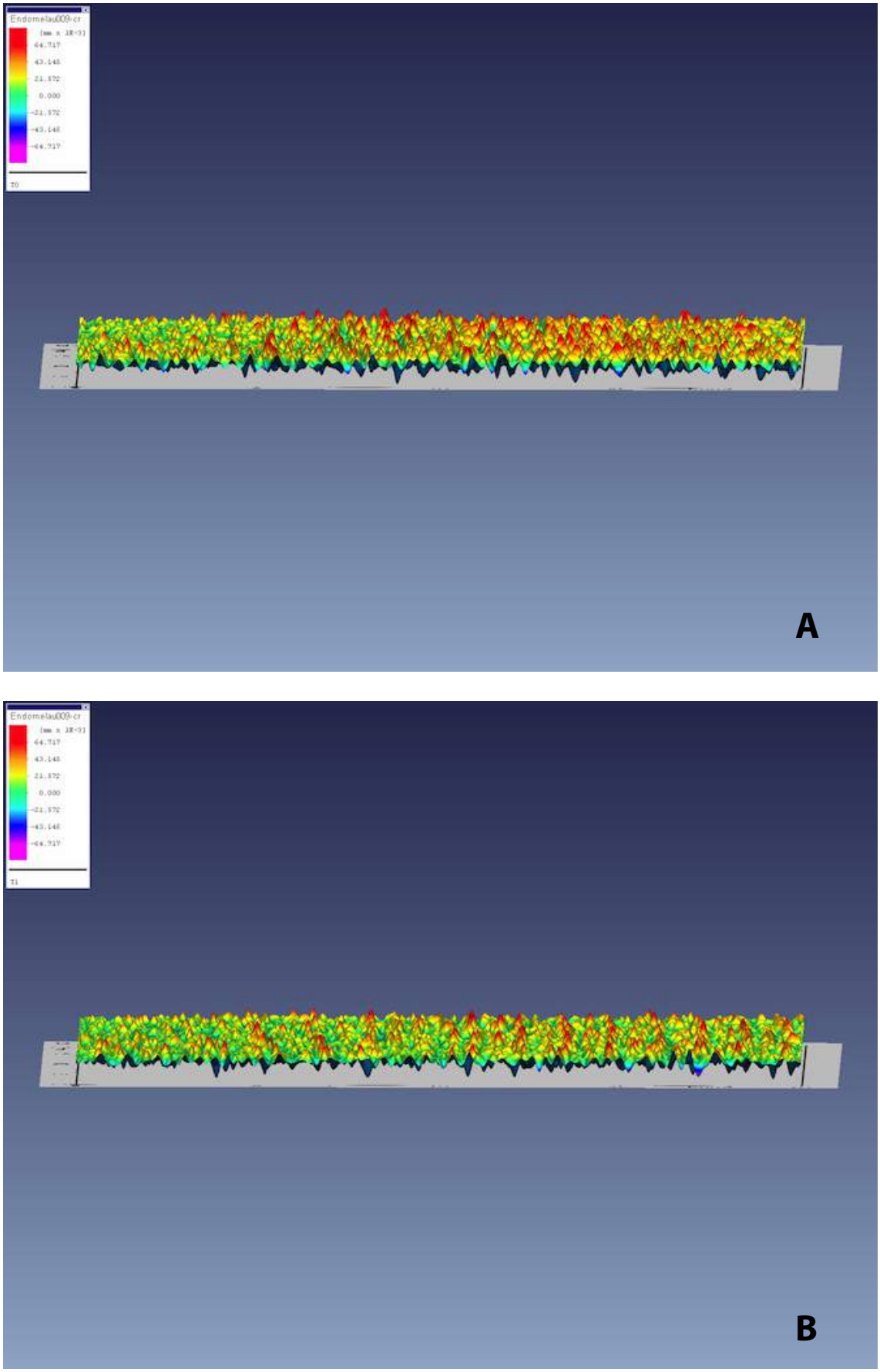


Figure 6. A. Roughness Profile of volunteer's ILA09 left crowfeet analyzed area at T0. **B.** Roughness Profile of volunteer's ILA09 left crowfeet at T1.

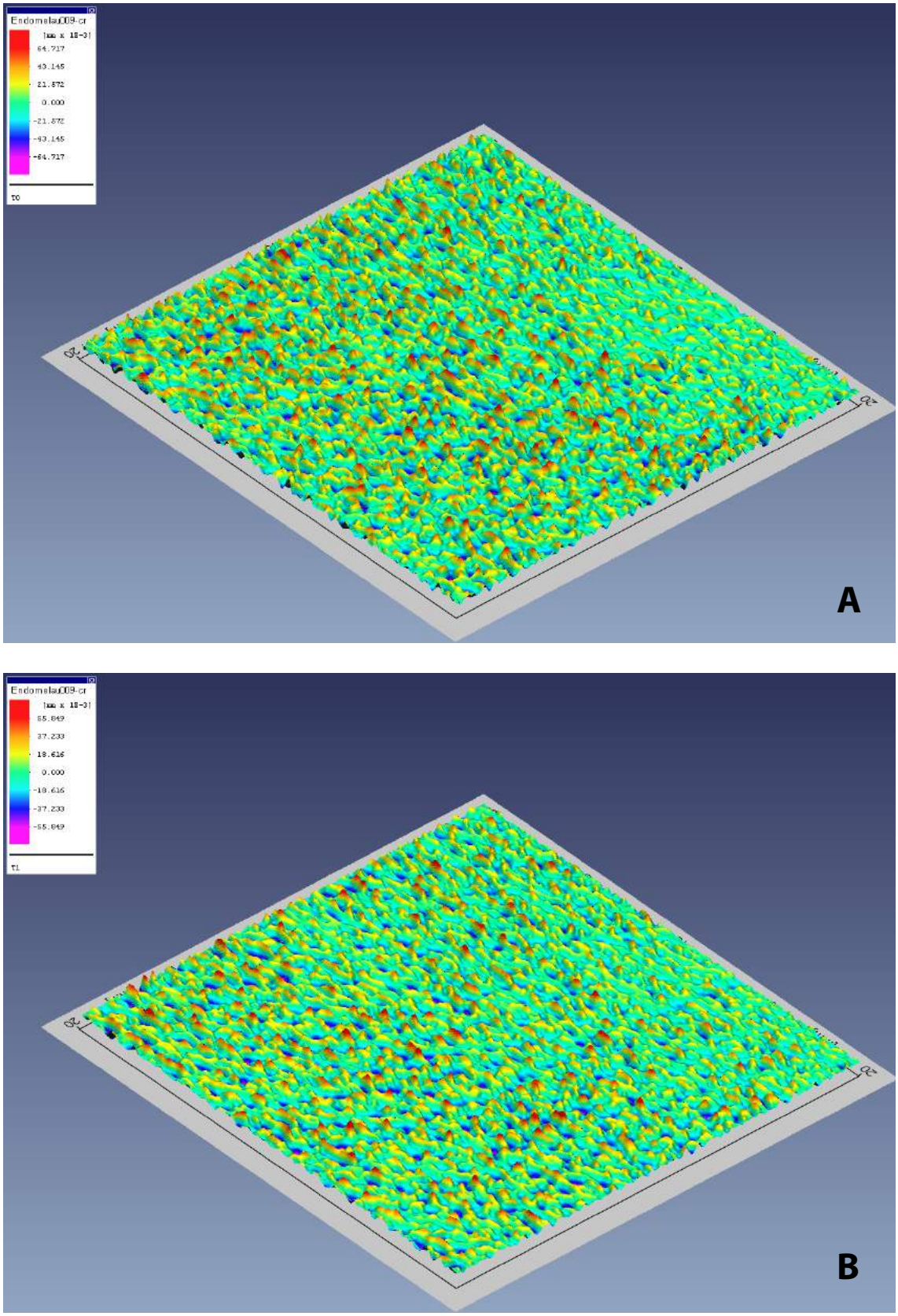


Figure 7. A. Roughness oblique view of volunteer's ILA09 left crowfeet analyzed area at T0. **B.** Roughness oblique view of volunteer's ILA09 left crowfeet at T1.

	D28 - D0
Sa	p < 0,01
ST	p < 0,005

Table 7. Statistical significances for the texture tests.

Wrinkles Analysis

3D topometric measures were carried out along with the texture measurements on both crowfeet in order to measure the averaged wrinkles volume (Vol), circumference (Circ), Area, maximum depth (MaxD) and mean depth (MeanD). They were evaluated on an area of 50x50mm and the whole data can be seen in the Annex I. Then the data from one of the sides was chosen for each volunteer according to a randomized pattern. Three volunteers data was considered as outlier, and thus all the following data is from the 19 volunteers considered as valid. The Vol, Circ, Area, MaxD and MeanD averaged results for these 19 volunteers at Day 0 and Day 28 are recapitulated here:

	Vol (mm^3)	Circ (mm)	Area(mm^2)	MaxD (mm)	MeanD (mm)
Day 0	0,864 ± 0,547	138,57 ± 42,35	28,02 ± 11,87	0,042 ± 0,021	0,015 ± 0,006
Day 28	0,651 ± 0,472	130,89 ± 51,67	24,47 ± 10,31	0,036 ± 0,016	0,014 ± 0,005

Table 8. Vol, Circ, Area, MaxD and MeanD of the wrinkles measured on the crowfeet.

The averaged differences (in percentage) between the Day 0 and Day 28 results as well as its corresponding Standard Deviations (Std. Dev.) of the 16 final volunteers can be seen below:

	Vol (mm^3)	Circ (mm)	Area(mm^2)	MaxD (mm)	MeanD (mm)
Average (%)	-24,69	-6,91	-12,11	-9,36	-7,03
Std. Dev.	*16,79*	*11,74*	*16,25*	*16,27*	*12,90*

Table 9. Vol, Circ, Area, MaxD and MeanD averaged D28 to D0 differences (in %).

When all the numerical data was gathered its statistical analysis began (the full statistical report can be found in the Annex II). As a first step, The ND of the data was tested with the Smirnov-Kolmogorov Goodness-of-fit test. All the data turned out to be Normal both on Day 0 and Day 28. Therefore, the Student t-test was applied to all the data. Table 12 recapitulates the result of the tests:

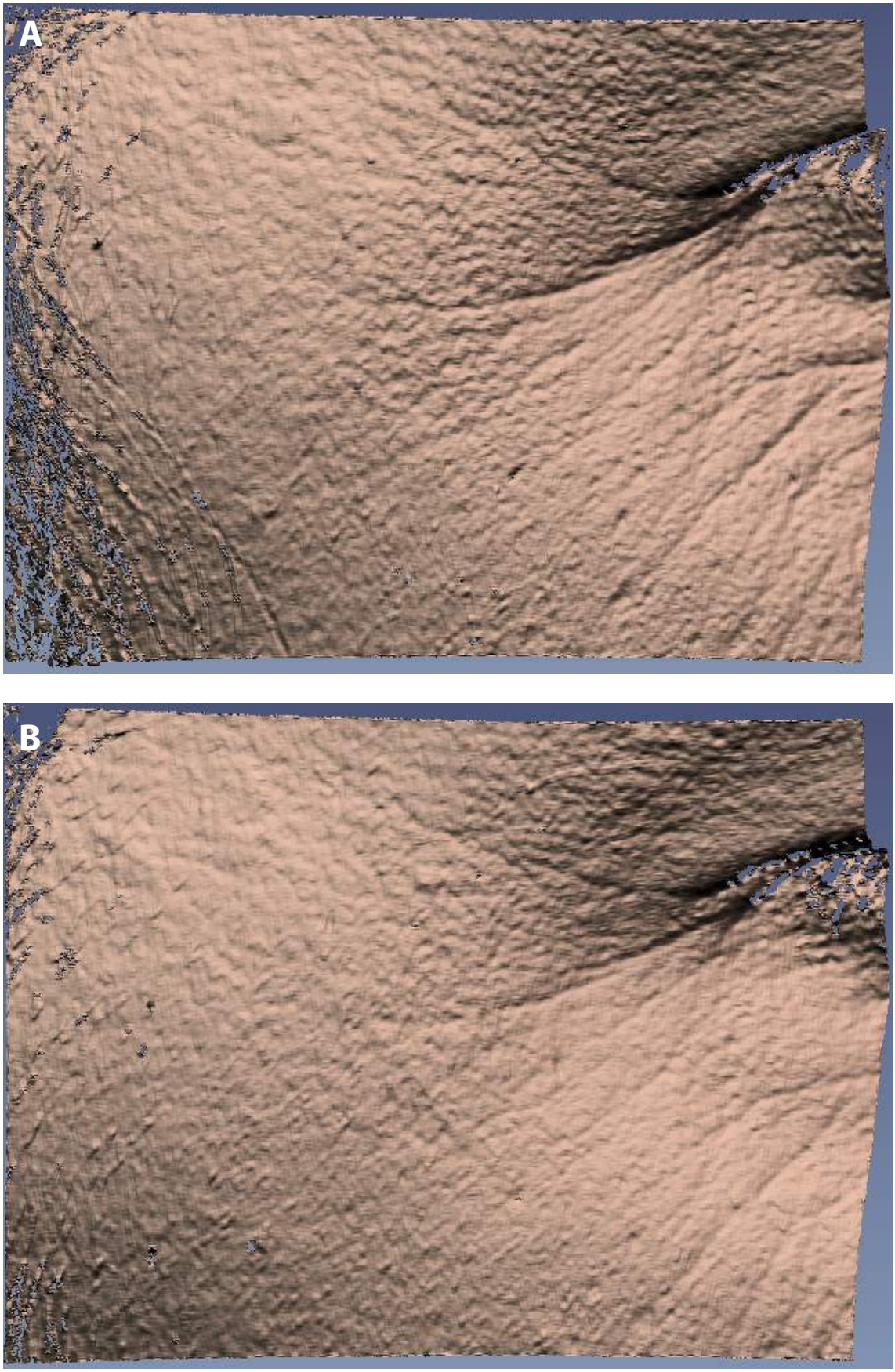


Figure 8. A. Volunteer's MSE10 right crowfeet 3D capture at T0. **B.** Volunteer's MSE10 right crowfeet 3D capture at T1.

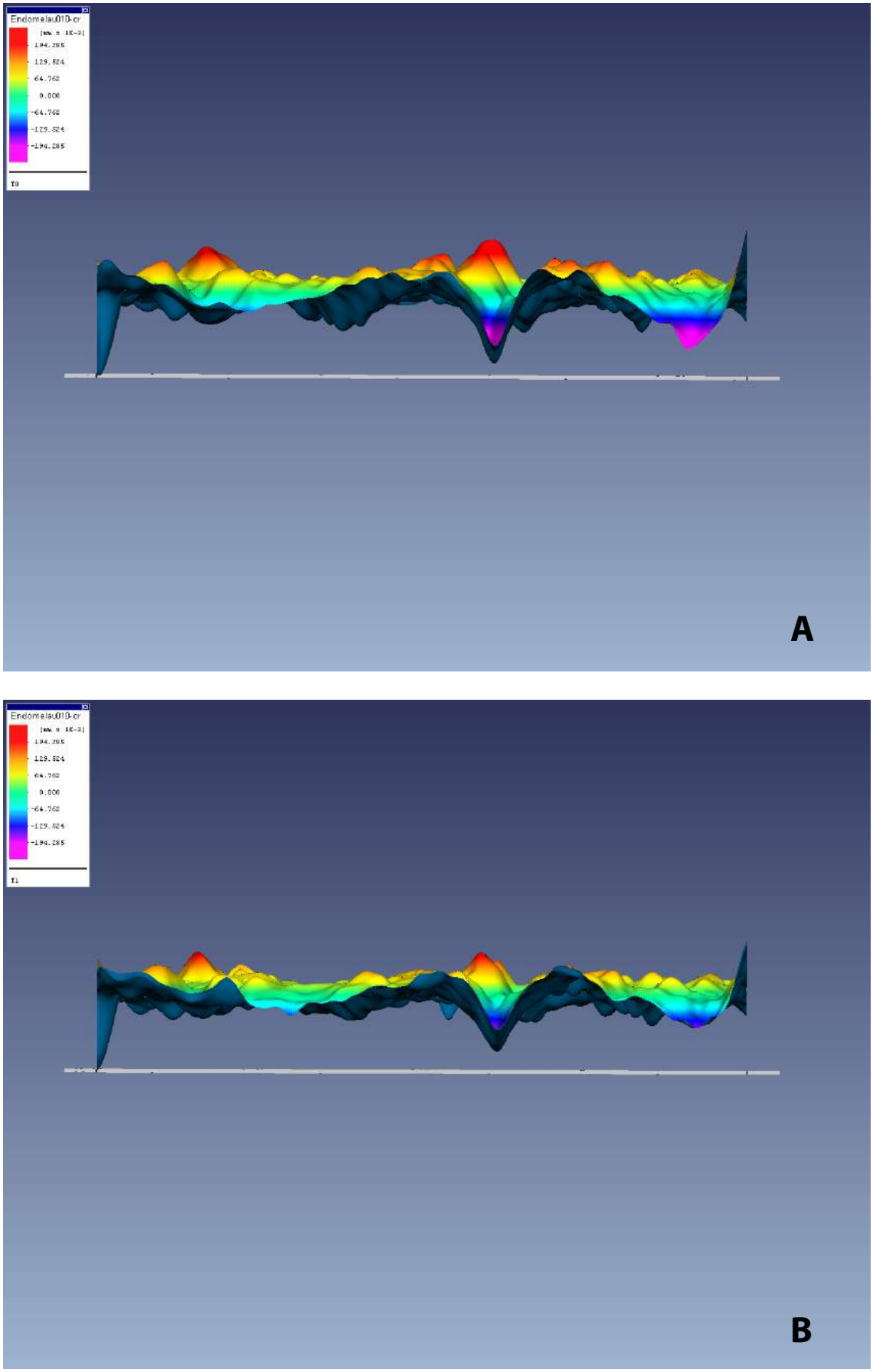


Figure 9. A. Wrinkles Profile of volunteer's MSE10 right crowfeet analyzed area at T0. **B.** Wrinkles Profile of volunteer's ILA09 right crowfeet at T1.

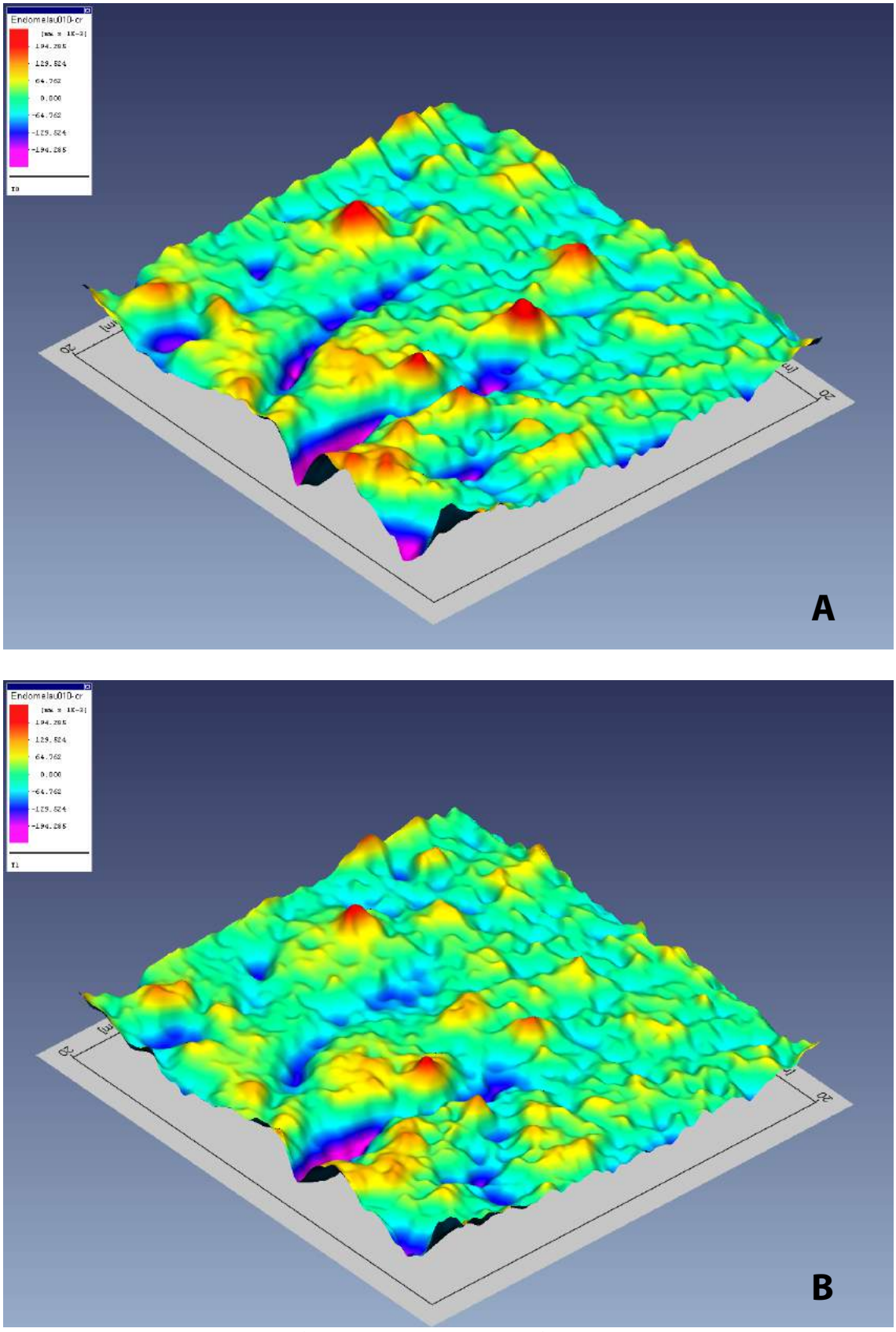


Figure 10. A. Wrinkles oblique view of volunteer's MSE10 right crowfeet analyzed area at T0. **B.** Wrinkles oblique view of volunteer's ILA09 right crowfeet at T1.

	C- D28 - D0
Vol	p < 0,0001
Circ	p < 0,1
Area	p < 0,01
MaxD	p < 0,05
MeanD	p < 0,05

Table 10. Statistical significances for the wrinkles measurements tests.

Epidermal/Dermal Ultrasound Analysis

The epidermal and dermal thickness and echogenic density were quantified by means of 50MHz HFUS. They were averaged from the measurements of 3 samples for each cheek and the data from one of the sides was chosen for each volunteer according to a randomized pattern. The whole results can be seen in the Annex I. The data obtained is reviewed in the tables 11 and 12 as follows:

	Density	Thickness
Day 0	93,04 ± 14,78	100,89 ± 36,18
Day 28	118,04 ± 13,45	96,64 ± 8,21

Table 11. HFUS measurements of the epidermis at Day 0 and Day 28.

	Density	Thickness
Day 0	22,07 ± 5,58	826,80 ± 177,11
Day 28	28,50 ± 5,35	766,80 ± 150,24

Table 12. HFUS measurements of the dermis at Day 0 and Day 28 .

The averaged differences (in percentage) between the Day 0 and Day 28 results of the 22 final volunteers can be seen below:

	Density	Thickness
Average (%)	30,04	2,13
Std. Dev.	*26,17*	*21,09*

Table 13. HFUS epidermis averaged differences (in %) between D0 and D28.

	Density	Thickness
Average (%)	37,40	-4,95
Std. Dev.	*21,98*	*18,64*

Table 14. HFUS dermis averaged differences (in %) between D0 and D28.

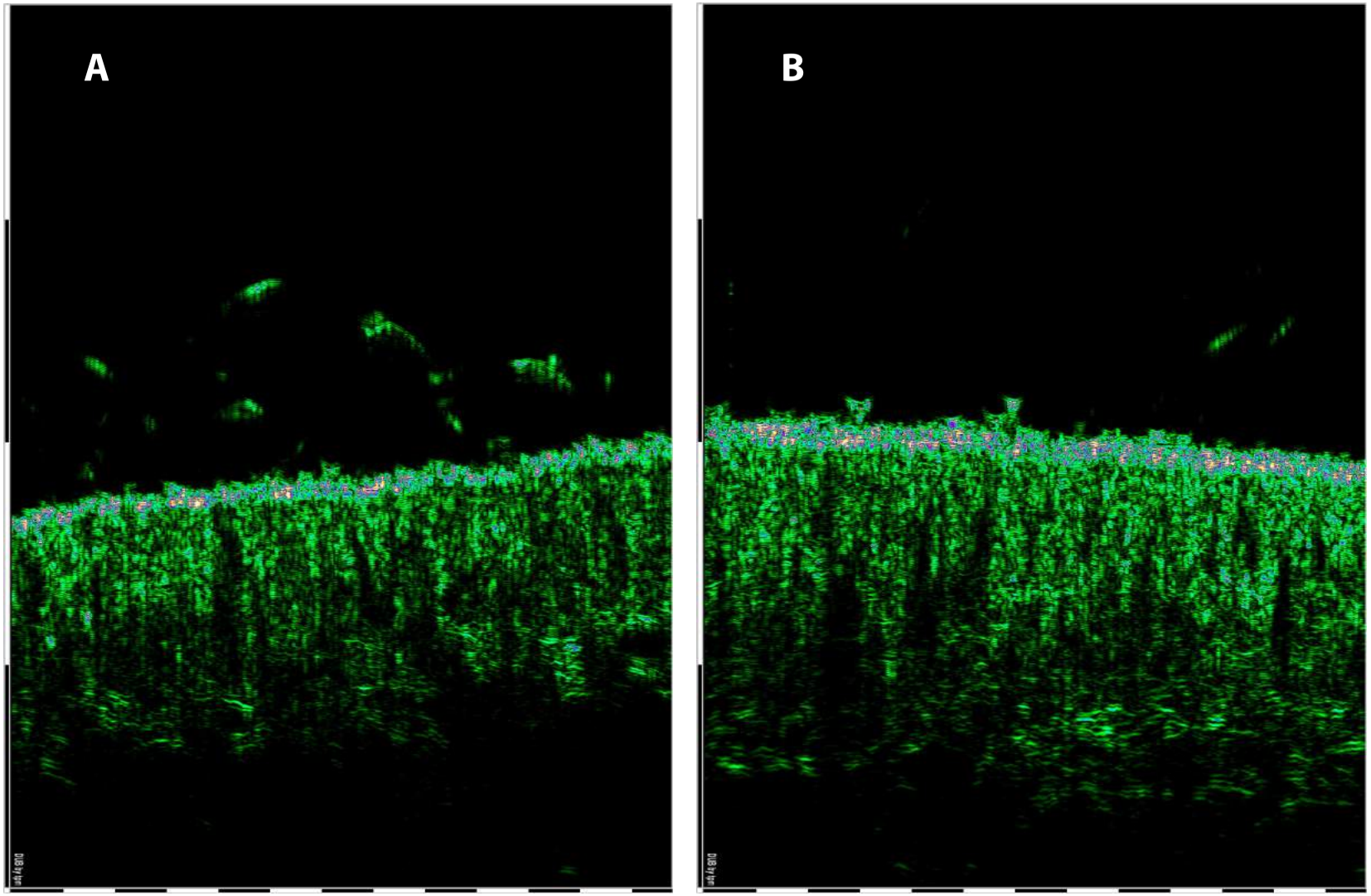


Figure 11. A. Volunteer's ZFO17 face's left side High Frequency Ultrasound captured area at T0. **B.** Volunteer's ZFO17 face's left side High Frequency Ultrasound captured area at T0.

Then the statistical analysis was carried out. All the data sets followed a ND except for the epidermal thickness at D0; thus we proceeded to perform the Wilcoxon Signed-Rank test for the epidermal thickness and the paired t-test for the rest of the data sets. The results are available on Table 15 while the full statistical processing is available in the Annex II.

	Epidermis D28 - D0	**Dermis D28 - D0**
Density	p < 0,0001	p < 0,0005
Thickness	w > 0,1	p > 0,1

Table 15. Statistical significances for the epidermis HFUS data tests.

DISCUSSION

The skin moisture results are somehow surprising. Despite a clearly visible improvement of the volunteers skin condition and their own testimonial on this subject, the numerical data at D28 suggests no gain was obtained. This seem to be in direct contradiction with the results obtained with the HFUS and may be related to a slightly too high standard deviation observed and the relatively small size of the sample. Another possibility is that, as HA has a highly negative charge, its sudden increased synthesis may be affecting a measuring technique based on electric principles. During its initial steps, hence all the skin tissue is reorganizing. Nevertheless, on the bright side, it only took 84 days to the volunteers to reach the hydration levels of a two-years-long regular user considered as a success story and a reference. Not only that but the more the 15% moisture increase was clearly considered as significant. To top it all, the standard deviation was drastically reduced, suggesting that the skin moisture condition is becoming not only better but also more homogenous.

This relates well with the 3D data. Both the texture and wrinkles results were striking to say the least. A 5% Average Roughness decrease with a statistical significance is considered a good result for a rejuvenation product, but an almost 22% decrease of the ST is frankly uncommon and reveals that a profound restructuring of the skin is taking place. This is confirmed by the outstanding wrinkles results. A 25% wrinkle reduction is clearly exceptional. Accompanied with the wrinkle area and depth reduction, al of them with a robust statistical significance, they make for strong candidate to a new cosmetic gold standard.

The explanation to these wrinkles results, however, lies in the breathtaking ultrasound results. Obviously, given the observed improvements, some extracellular matrix increase was expected, especially in the epidermis, as the AuNCs can't reach the dermis. However a 30% increase in echogenic density is, again, a very remarkable

and rare result. Still the real surprise was yet to come as the 37,5% increase of dermal echogenic density was far from expected but is, in hindsight, logical, as the observed wrinkle improvements couldn't come from an epidermis strengthening alone. This dermal extracellular matrix synthesis, mainly HA and collagen, has to be triggered by a signaling pathway triggered on the epidermis and has apparently the potential to overtake its epidermal counterpart. Obviously a 30% increase of the echogenic density doesn't mean a 30% increase of HA and collagen as HFUS are a semiquantitative technique, but still gains three to five times smaller than this one are already considered a success for a cosmetic product, which puts on perspective how huge this gains are. Moreover they are taking place in a sheer restructuring process as almost no skin thickness increase took place.

CONCLUSIONS

This study was extremely successful as it managed to prove the in vivo efficacy of the product for all its end points. Skin hydration was maintained and even improved throughout the study despite the explicit lack of use of any moisturizing product. This skin hydration is caused by an increased synthesis of extracellular matrix in the epidermis, involving HA and collagen, and correlating with the in vitro findings. In vivo, they are noticed by both the volunteers and the physicians, but also deducible from the density increase observed with High Frequency Ultrasounds. Furthermore, evidence of a dermis remodeling is already taking place as the ultrasonograms suggest. From all this, an improved skin condition is obtained, with a smoother texture and reduced wrinkles that occurs thanks to a tightening effect and some firmness gains that could be assessed through the 3D surface analysis of the skin. In addition, the excellent statistical results obtained as well as the incredibly high percentages of improvement observed are proof that the effects of the serum and cream combination not only surpassed any expectation but are outstanding antiaging products on its own right.

SIGNATURES AND DATES

Investigator: Gabriel Buendía Bordera

REFERECENCES

[1]. Fraser TN. Gold Treatment in Rheumatoid Arthritis. Ann Rheum Dis. 1945;4(4):71-5.

[2]. Rudolf R, Anžel M, Marković E. Gold in the past, today and future. Metal …. 2012;51(2):261-264.

[3]. Jelveh S, Chithrani DB. Gold Nanocomplexes as a Platform for Combinational Therapy in Future Cancer Therapeutics. Cancers (Basel). 2011;3:1081-1110. doi:10.3390/cancers3011081

[4]. Lohani A, Verma A, Joshi H, Yadav N, Karki N. Nanotechnology-based cosmeceuticals. ISRN Dermatol. 2014;2014:843687. doi:10.1155/2014/843687.

[5]. Kemp MM, Kumar A, Mousa S, et al. Synthesis of gold and silver nanoparticles stabilized with glycosaminoglycans having distinctive biological activities. Biomacromolecules. 2009;10(3):589-95. doi:10.1021/bm801266t.

[6]. Querol Sastre J. ENDOR Nanotechnologies Report- Hyaluronic Acid In Vitro Expression in Skin Keratynocites.; 2012:1

[7]. Kage M, Tokudome Y, Matsunaga Y, Hariya T, Hashimoto F. Effect of hyaluronan tetrasaccharides on epidermal differentiation in normal human epidermal keratinocytes. Int J Cosmet Sci. 2013:109-115. doi:10.1111/ics.12105.

[8]. Kaya G, Tran C, Sorg O, et al. Hyaluronate fragments reverse skin atrophy by a CD44-dependent mechanism. PLoS Med. 2006;3(12):e493. doi:10.1371/journal.pmed.0030493.

[9]. Tolg C, Telmer P, Turley E. Specific sizes of hyaluronan oligosaccharides stimulate fibroblast migration and excisional wound repair. PLoS One. 2014;9(2):e88479. doi:10.1371/journal.pone.0088479.

[10]. Leitat Technological Center. In Vitro Antioxidant Efficacy in Dermal Fibroblasts of Article GEN-NYG2-001.; 2012:1.

[11]. Bodet D, Reynoso I, Carcamo A. Checking In Human Of The Skin Compatibility Of A Test Product.; 2008:9.

[12]. Querol Sastre J. ENDOR Nanotechnologies Report- Transdermal Penetration of Gold Nanoparticles Conjugated to HA.; 2012:1

[13]. Abella ML. Evaluation of anti-wrinkle efficacy of adenosine-containing products using the FOITS technique. Int J Cosmet Sci. 2006;28(6):447-51. doi:10.1111/j.1467-2494.2006.00349.x.

[14]. Lagarde JM, Rouvrais C, Black D. Topography and anisotropy of the skin surface with ageing. Skin Res Technol. 2005;11(2):110-9. doi:10.1111/j.1600-0846.2005.00096.x.

[15]. Lagarde JM, Rouvrais C, Black D, Diridollou S, Gall Y. Skin topography measurement by interference fringe projection: a technical validation. Skin Res Technol. 2001;7(2):112-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11393203.

[16]. Vogelgesang B, Bonnet I, Godard N, Sohm B, Perrier E. In vitro and in vivo efficacy of sulfo-carrabiose, a sugar-based cosmetic ingredient with anti-cellulite properties. Int J Cosmet Sci. 2011;33(2):120-5. doi:10.1111/j.1468-2494.2010.00593.x.

[17]. Sainthillier J-M, Mac-Mary S, Monnier D, et al. Exploratory study of the typology of various grades of mature skin. Skin Res Technol. 2013;19(1):e507-14. doi:10.1111/srt.12002.

[18]. Crisan D, Lupsor M, Boca A, Crisan M, Badea R. Ultrasonographic assessment of skin structure according to age. Indian J Dermatol Venereol Leprol. 2012;78(4):519. doi:10.4103/0378-6323.98096.

[19]. Kong L, Caspall J, Duckworth M, Sprigle S. Assessment of an ultrasonic dermal scanner for skin thickness measurements. Medical Engineering & Physics. 2008;30(6):804-7. doi:10.1016/j.medengphy.2007.10.002.

[20]. Milner S, Memar O. The histological interpretation of high frequency cutaneous ultrasound imaging. Dermatologic …. 1997. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1524-4725.1997.tb00006.x/abstract. Accessed July 22, 2014.

[21]. Mofid Y, Ossant F, Imberdis C, Josse G, Patat F. In-vivo imaging of skin under stress: potential of high-frequency (20 MHz) static 2-D elastography. IEEE Trans Ultrason Ferroelectr Freq Control. 2006;53(5):925-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16764447.

[22]. Mofid Y, Josse G, Gahagnon S, Delalleau A, Ossant F. Mechanical skin thinning-to-thickening transition observed in vivo through 2D high frequency elastography. J Biomech. 2010;43(15):2954-62. doi:10.1016/j.jbiomech.2010.07.014.
[23]. Turlier V, Delalleau A, Casas C, et al. Association between collagen production and mechanical stretching in dermal extracellular matrix: in vivo effect of cross-linked hyaluronic acid filler. A randomised, placebo-controlled study. J Dermatol Sci. 2013;69(3):187-94. doi:10.1016/j.jdermsci.2012.12.006.

ANNEX I

DATA

Skin Moisture Measurements (%) of the Facial Skin of the Volunteers Attending the D0, D28 and D84 Visits

Volunteer	Time	Right Cheek			Average	Std. Dev.	Left Cheek			Average	Std. Dev.	Right Temple			Average	Std. Dev.	Left temple			Average	Std. Dev.	Front			Average	Std. Dev.
1	1	34,4	30,9	36,9	34,1	3,0	33,5	33,6	38,4	35,2	2,8	35,8	37,7	34,7	36,1	1,5	39,3	34,7	37,4	37,1	2,3	38,7	38,3	37,4	38,1	0,7
2	1	37,4	37,2	34,4	36,3	1,7	37,1	35,1	37,5	36,6	1,3	37,5	37,1	37,5	37,4	0,2	39,6	37,9	37,9	38,5	1,0	38	38,9	38,7	38,5	0,5
3	1	35,3	33,4	31,6	33,4	1,9	35,3	30,7	31,5	32,5	2,5	35,2	34,9	33	34,4	1,2	33	34,7	33,1	33,6	1,0	36,9	39,3	37,8	38,0	1,2
4	1	35,1	35,8	36	35,6	0,5	38,4	37,3	36,2	37,3	1,1	36,6	36,8	32,9	35,4	2,2	37,3	36,4	38,4	37,4	1,0	36,6	37,3	34,9	36,3	1,2
5	1	35,5	37,1	36,5	36,4	0,8	33,3	36,3	37,1	35,6	2,0	36,8	37	35,3	36,4	0,9	34,8	38,7	34,7	36,1	2,3	38,4	35,8	36,1	36,8	1,4
6	1	37,6	32,7	35,4	35,2	2,5	35,2	36	37,2	36,1	1,0	37,4	34,6	36,5	36,2	1,4	33,9	36,2	39,5	36,5	2,8	35,1	39,2	33,2	35,8	3,1
7	1	37,7	34,8	31,9	34,8	2,9	36,9	31,8	37,2	35,3	3,0	36,2	36,2	25,1	32,5	6,4	35,9	38,5	37	37,1	1,3	34,6	36,5	35	35,4	1,0
8	1	36,9	37,7	37,1	37,2	0,4	33,4	35,7	41	36,7	3,9	40,9	39,2	39,7	39,9	0,9	38,5	40	36,2	38,2	1,9	39,2	36,2	33,3	36,2	3,0
9	1	35	36,3	43,1	38,1	4,4	38,8	36,4	38,5	37,9	1,3	38,4	43,4	36,8	39,5	3,4	39,8	39,1	37,9	38,9	1,0	37	38,7	35,1	36,9	1,8
10	1	47,1	38,2	41,9	42,4	4,5	37,8	37,2	41,9	39,0	2,6	39,4	38,2	31,5	36,4	4,3	41,4	33,6	38,4	37,8	3,9	37,8	38,2	36,5	37,5	0,9
11	1	34,4	29,7	33,7	32,6	2,5	32,3	31,2	33,7	32,4	1,3	33,4	36,6	34,9	35,0	1,6	38,6	36,3	34,5	36,5	2,1	34,6	37,5	37,1	36,4	1,6
12	1	32,9	32,6	37,5	34,3	2,7	37,9	29,4	37,6	35,0	4,8	34,8	36,4	32,9	34,7	1,8	35,6	33,8	35,9	35,1	1,1	37,5	40,9	39,4	39,3	1,7
13	1	38,4	27,7	37,8	34,6	6,0	37,9	33,8	34	35,2	2,3	37,7	38,1	39,3	38,4	0,8	37,2	37,6	39,8	38,2	1,4	36,7	41,9	42,7	40,4	3,3
14	1	40,1	34,2	44,4	39,6	5,1	43,5	46,8	48,5	46,3	2,5	43,5	41,5	34	39,7	5,0	37,5	42,8	40,1	40,1	2,7	45,6	35,3	39,3	40,1	5,2
15	1	43,1	34,3	43,2	40,2	5,1	39,1	37,7	38,3	38,4	0,7	40	39,8	34	37,9	3,4	38,5	37,6	37,3	37,8	0,6	38,4	40,7	42,2	40,4	1,9
16	1	34,5	32,3	36,2	34,3	2,0	32,8	34,5	38,3	35,2	2,8	36,6	35,9	36,5	36,3	0,4	36,5	37,7	33,4	35,9	2,2	31,5	35	32,1	32,9	1,9
17	1	39,7	36,2	43,1	39,7	3,5	37,6	37,1	39,8	38,2	1,4	44	39,3	39,6	41,0	2,6	41,7	44	40,7	42,1	1,7	41,6	41,5	46	43,0	2,6
18	1	31,4	30,8	37,3	33,2	3,6	34,9	33,4	39,6	36,0	3,2	35,2	36,3	39,4	37,0	2,2	37,5	38,2	35,3	37,0	1,5	37,2	37,2	37,8	37,4	0,3
19	1	43,8	44,8	35,6	41,4	5,0	44,5	37,8	46,8	43,0	4,7	40,5	42,4	34,4	39,1	4,2	43,6	45,3	37,1	42,0	4,3	41,4	46	40,4	42,6	3,0
20	1	40,8	35,1	33,8	36,6	3,7	39	40,7	33,5	37,7	3,8	40,7	37,5	37,2	38,5	1,9	40,8	39,9	37,8	39,5	1,5	42,8	40	38,7	40,5	2,1
21	1	38,3	38,1	40,2	38,9	1,2	37,3	34,1	41,9	37,8	3,9	39	37,6	38,3	38,3	0,7	37,6	38	38,2	37,9	0,3	35,7	35,5	34	35,1	0,9
22	1	35,2	34,6	37	35,6	1,2	37	33,9	36,8	35,9	1,7	36	36	34,9	35,6	0,6	36,6	35,4	35,6	35,9	0,6	38	36	34,9	36,3	1,6
23	1	35,9	30,1	37,7	34,6	4,0	35,6	34,9	36,8	35,8	1,0	35,9	36,5	35,6	36,0	0,5	37	36,3	36,2	36,5	0,4	36,8	36,2	36,8	36,6	0,3
Average					**36,5**	**1,613**				**36,9**	**1,221**				**37,0**	**1,645**				**37,6**	**1,039**				**37,8**	**1,150**
1	2	35	36	34,7	35,2	0,7	35,8	35,7	36,8	36,1	0,6	35,4	34,5	35,9	35,3	0,7	34,3	37	36,3	35,9	1,4	38,9	37,8	34,8	37,2	2,1
2	2	30,2	35,6	39,3	35,0	4,6	35,4	32,3	38,4	35,4	3,1	36,3	36,8	37,2	36,8	0,5	38,1	35,2	36,4	36,6	1,5	37,2	36,6	39,5	37,8	1,5
3	2	36,5	33,8	37,5	35,9	1,9	38,3	32,1	37,1	35,8	3,3	37,1	34,9	36,2	36,1	1,1	35,9	36,3	38,3	36,8	1,3	39,7	39,6	38,3	39,2	0,8
4	2	32,8	30,6	28,9	30,8	2,0	28,7	31,9	32,4	31,0	2,0	30,2	31,6	33,1	31,6	1,5	35	33,8	31,3	33,4	1,9	34,8	32,5	29,4	32,2	2,7
5	2	36,8	30,8	36,2	34,6	3,3	39,4	34,1	31,8	35,1	3,9	36	32,4	36,3	34,9	2,2	36,1	35,1	35,1	35,4	0,6	38,7	38,5	38,4	38,5	0,2
6	2	35,5	33,3	36,1	35,0	1,5	30,6	27,9	36,8	31,8	4,6	36,9	34,7	37,2	36,3	1,4	38	35,2	35,8	36,3	1,5	37,9	37	36,1	37,0	0,9
7	2	34,4	32,3	35	33,9	1,4	34,1	33,7	34,6	34,1	0,5	36,9	35,8	34,8	35,8	1,1	36,3	35,3	34,6	35,4	0,9	37,2	36,8	36	36,7	0,6
8	2	35,6	34,8	38,5	36,3	1,9	33,3	35,2	36,9	35,1	1,8	36,6	36,7	35,1	36,1	0,9	36,5	36,5	35,9	36,3	0,3	36,9	35,4	33,6	35,3	1,7
9	2	32,6	32,8	34,3	33,2	0,9	36,1	29,4	34,7	33,4	3,5	35,6	35,1	33	34,6	1,4	36,8	34,4	29,4	33,5	3,8	35,3	37	35,1	35,8	1,0
10	2	38,2	32,6	41,3	37,4	4,4	37,1	37,6	41,4	38,7	2,4	38,7	37,7	37	37,8	0,9	38,1	35	37,2	36,8	1,6	36,5	37,9	39	37,8	1,3
11	2	37	32,8	35,2	35,0	2,1	34,4	31,8	34,7	33,6	1,6	36	32,1	34,4	34,2	2,0	32	32,7	35,3	33,3	1,7	36,7	37	33,2	35,6	2,1
13	2	39,2	37,6	39,6	38,8	1,1	37,4	34	38,3	36,6	2,3	36,4	38,8	37,8	37,7	1,2	37,5	37,7	39	38,1	0,8	40,3	38,6	39,6	39,5	0,9
14	2	39	39,9	41,4	40,1	1,2	41,9	38,8	43,6	41,4	2,4	39,8	35,2	39,3	38,1	2,5	39,7	37	38,1	38,3	1,4	38,2	43,2	40,3	40,6	2,5
15	2	34,2	33,3	30,8	32,8	1,8	34,6	33,5	32,1	33,4	1,3	35,3	33,1	33,4	33,9	1,2	34,1	35,3	35,5	35,0	0,8	36,2	36,2	37	36,5	0,5
16	2	37	35,6	36,8	36,5	0,8	35,2	33,9	37,4	35,5	1,8	36,7	37	35,7	36,5	0,7	38,7	39,2	38,4	38,8	0,4	36,7	35,9	38,4	37,0	1,3
17	2	34,6	34,3	37,9	35,6	2,0	36,8	40,5	46,8	41,4	5,1	36,4	37,2	35,4	36,3	0,9	40,1	36,6	36,1	37,6	2,2	37,2	37,9	37,4	37,5	0,4
18	2	39,5	37,7	41,6	39,6	2,0	42,2	38,3	35,5	38,7	3,4	40,4	37	37,8	38,4	1,8	54,1	43,3	40,8	46,1	7,1	38,8	38,5	37,7	38,3	0,6
19	2	38,1	37,1	40,5	38,6	1,7	40,1	35,6	41,5	39,1	3,1	40,1	35,6	41,5	39,1	3,1	39,5	34,8	37,6	37,3	2,4	45,7	38	39,1	40,9	4,2
20	2	34,7	35,6	38,5	36,3	2,0	36,2	33	37,8	35,7	2,4	36,5	33,2	35,2	35,0	1,7	34,1	35,8	34,9	34,9	0,9	36,3	38,3	36,1	36,9	1,2
21	2	38,7	36,5	37,5	37,6	1,1	36,9	39,7	36,4	37,7	1,8	35,4	35,4	36,1	35,6	0,4	37	37,2	37,6	37,3	0,3	35	37,8	38,8	37,2	2,0
22	2	38,8	33,7	39,4	37,3	3,1	37,8	37,8	38,6	38,1	0,5	36,5	35,6	34,8	35,6	0,9	37	35,7	37,7	36,8	1,0	38,8	37,7	38	38,2	0,6
23	2	33,5	31,1	35,6	33,4	2,3	34,8	35,1	36,7	35,5	1,0	35,8	30,7	31,8	32,8	2,7	36,2	33,9	33,9	34,7	1,3	36,5	35,1	33,8	35,1	1,4
Average					**35,9**	**1,046**				**36,1**	**1,269**				**35,8**	**0,728**				**36,6**	**1,455**				**37,3**	**0,943**
2	4	38,5	38,7	38,8	38,7	0,2	41,2	36,9	39,7	39,3	2,2	37,1	36,8	38,6	37,5	1,0	36,6	37,5	41,5	38,5	2,6	37,5	37	37,1	37,2	0,3
3	4	37	37,4	37,3	37,2	0,2	39,9	37,8	37,4	38,4	1,3	37,1	37,2	38,1	37,5	0,6	37,2	37,8	46,4	40,5	5,1	38	39,6	38,5	38,7	0,8
5	4	37,8	38,8	37,4	38,0	0,7	38,4	38,3	38,6	38,4	0,2	36,9	36,7	36,9	36,8	0,1	36,4	37,6	41,5	38,5	2,7	37,9	37,4	39,6	38,3	1,2
6	4	38	36,4	37,3	37,2	0,8	38,4	36,6	37,8	37,6	0,9	38,1	36,5	37,4	37,3	0,8	37,2	38	36,8	37,3	0,6	37,2	37,5	38,1	37,6	0,5
7	4	35,7	37,1	38,6	37,1	1,5	35,9	36,3	38,5	36,9	1,4	36,3	37,1	36,5	36,6	0,4	35,9	38,4	37,6	37,3	1,3	38,7	38,6	38,9	38,7	0,2
8	4	38,6	36,4	38,1	37,7	1,2	37,6	36,7	38,1	37,5	0,7	40,3	38,7	41,5	40,2	1,4	40,1	39,4	40,3	39,9	0,5	37,7	37,8	41,3	38,9	2,1
9	4	37,2	37,8	37,9	37,6	0,4	36,9	35,8	38,6	37,1	1,4	36,4	36,2	35,9	36,2	0,3	37,1	36,9	36,9	37,0	0,1	39,9	37,8	39,7	39,1	1,2
10	4	36,8	38,9	41,8	39,2	2,5	36,9	39,3	40,6	38,9	1,9	39,3	36,6	39,4	38,4	1,6	36,7	40,1	38,6	38,5	1,7	37,5	40	40,3	39,3	1,5
11	4	37,2	36,3	38,6	37,4	1,2	37,9	37,2	36,5	37,2	0,7	37,4	36,4	38	37,3	0,8	37,5	37,4	36,5	37,1	0,6	40,6	38,3	41,9	40,3	1,8
14	4	36	37,7	39	37,6	1,5	37,8	38,1	39,5	38,5	0,9	38,2	37	39,7	38,3	1,4	38,2	38,3	38,9	38,5	0,4	38	38,4	37,7	38,0	0,4
15	4	37,7	37,4	36,3	37,1	0,7	39,5	37,3	37,6	38,1	1,2	36,9	37,5	40,3	38,2	1,8	36,3	36,2	41	37,8	2,7	37	37,6	38	37,5	0,5
16	4	37,3	38,7	40,7	38,9	1,7	38,4	37,5	37,3	37,7	0,6	39	37,8	37,8	38,2	0,7	40,6	38,1	39,6	39,4	1,3	38	36,8	37,1	37,3	0,6
17	4	36,6	38,1	40,1	38,3	1,8	35,6	36,7	37,5	36,6	1,0	37,9	38,4	37,9	38,1	0,3	44,7	38,5	38,9	40,7	3,5	36,5	38,3	41,2	38,7	2,4
18	4	35,6	38,9	39,7	38,1	2,2	34,6	36,9	39,9	37,1	2,7	39	37,5	37,6	38,0	0,8	44	38,6	41	41,2	2,7	41,5	47,1	42,5	43,7	3,0
19	4	38,3	39,4	38,6	38,8	0,6	38,6	38,9	38,7	38,7	0,2	38,4	36,2	39,1	37,9	1,5	37,4	37	37,5	37,3	0,3	39,8	39	38,7	39,2	0,6
20	4	38,4	37,4	37,4	37,7	0,6	38,7	38,1	38,1	38,3	0,3	40,7	37,1	37	38,3	2,1	37,5	36,5	39,5	37,8	1,5	38,7	36,1	38,6	37,8	1,5
21	4	38,1	36,8	36,5	37,1	0,9	37,5	35,3	36,1	36,3	1,1	37,6	35,5	35,2	36,1	1,3	35,8	35,6	38,2	36,5	1,4	35,7	35,6	38,2	36,5	1,5
23	4	36,9	39,8	42	39,6	2,6	39,1	38	38,3	38,5	0,6	37,3	38	40,1	38,5	1,5	38,9	37,7	37,4	38,0	0,8	38,4	38,7	39,1	38,7	0,4
Average					**38,0**	**0,747**				**37,8**	**0,675**				**37,7**	**0,578**				**38,4**	**1,338**				**38,6**	**0,810**

Normalized Skin Moisture Measurements of the Facial Skin of the Volunteers Attending the D0, D28 and D84 Visits

Volunteer	Time	Right Cheek			Average	Std. Dev.	Left Cheek			Average	Std. Dev.	Right Temple			Average	Std. Dev.	Left temple			Average	Std. Dev.	Front			Average	Std. Dev.
1	1	0,800	0,719	0,858	0,792	0,070	0,779	0,781	0,893	0,818	0,065	0,833	0,877	0,807	0,839	0,035	0,914	0,807	0,870	0,864	0,054	0,900	0,891	0,870	0,887	0,015
2	1	0,870	0,865	0,800	0,845	0,039	0,863	0,816	0,872	0,850	0,030	0,872	0,863	0,872	0,869	0,005	0,921	0,881	0,881	0,895	0,023	0,884	0,905	0,900	0,896	0,011
3	1	0,821	0,777	0,735	0,778	0,043	0,821	0,714	0,733	0,756	0,057	0,819	0,812	0,767	0,799	0,028	0,767	0,807	0,770	0,781	0,022	0,858	0,914	0,879	0,884	0,028
4	1	0,816	0,833	0,837	0,829	0,011	0,893	0,867	0,842	0,867	0,026	0,851	0,856	0,765	0,824	0,051	0,867	0,847	0,893	0,869	0,023	0,851	0,867	0,812	0,843	0,029
5	1	0,826	0,863	0,849	0,846	0,019	0,774	0,844	0,863	0,827	0,047	0,856	0,860	0,821	0,846	0,022	0,809	0,900	0,807	0,839	0,053	0,893	0,833	0,840	0,855	0,033
6	1	0,874	0,760	0,823	0,819	0,057	0,819	0,837	0,865	0,840	0,023	0,870	0,805	0,849	0,841	0,033	0,788	0,842	0,919	0,850	0,065	0,816	0,912	0,772	0,833	0,071
7	1	0,877	0,809	0,742	0,809	0,067	0,858	0,740	0,865	0,821	0,071	0,842	0,842	0,584	0,756	0,149	0,835	0,895	0,860	0,864	0,030	0,805	0,849	0,814	0,822	0,023
8	1	0,858	0,877	0,863	0,866	0,010	0,777	0,830	0,953	0,853	0,091	0,951	0,912	0,923	0,929	0,020	0,895	0,930	0,842	0,889	0,045	0,912	0,842	0,774	0,843	0,069
9	1	0,814	0,844	1,002	0,887	0,101	0,902	0,847	0,895	0,881	0,030	0,893	1,009	0,856	0,919	0,080	0,926	0,909	0,881	0,905	0,022	0,860	0,900	0,816	0,859	0,042
10	1	1,095	0,888	0,974	0,986	0,104	0,879	0,865	0,974	0,906	0,059	0,916	0,888	0,733	0,846	0,099	0,963	0,781	0,893	0,879	0,091	0,879	0,888	0,849	0,872	0,021
11	1	0,800	0,691	0,784	0,758	0,059	0,751	0,726	0,784	0,753	0,029	0,777	0,851	0,812	0,813	0,037	0,898	0,844	0,802	0,848	0,048	0,805	0,872	0,863	0,847	0,037
12	1	0,765	0,758	0,872	0,798	0,064	0,881	0,684	0,874	0,813	0,112	0,809	0,847	0,765	0,807	0,041	0,828	0,786	0,835	0,816	0,026	0,872	0,951	0,916	0,913	0,040
13	1	0,893	0,644	0,879	0,805	0,140	0,881	0,786	0,791	0,819	0,054	0,877	0,886	0,914	0,892	0,019	0,865	0,874	0,926	0,888	0,033	0,853	0,974	0,993	0,940	0,076
14	1	0,933	0,795	1,033	0,920	0,119	1,012	1,088	1,128	1,076	0,059	1,012	0,965	0,791	0,922	0,116	0,872	0,995	0,933	0,933	0,062	1,060	0,821	0,914	0,932	0,121
15	1	1,002	0,798	1,005	0,935	0,119	0,909	0,877	0,891	0,892	0,016	0,930	0,926	0,791	0,882	0,079	0,895	0,874	0,867	0,879	0,015	0,893	0,947	0,981	0,940	0,045
16	1	0,802	0,751	0,842	0,798	0,045	0,763	0,802	0,891	0,819	0,065	0,851	0,835	0,849	0,845	0,009	0,849	0,877	0,777	0,834	0,052	0,733	0,814	0,747	0,764	0,044
17	1	0,923	0,842	1,002	0,922	0,080	0,874	0,863	0,926	0,888	0,033	1,023	0,914	0,921	0,953	0,061	0,970	1,023	0,947	0,980	0,039	0,967	0,965	1,070	1,001	0,060
18	1	0,730	0,716	0,867	0,771	0,084	0,812	0,777	0,921	0,836	0,075	0,819	0,844	0,916	0,860	0,051	0,872	0,888	0,821	0,860	0,035	0,865	0,865	0,879	0,870	0,008
19	1	1,019	1,042	0,828	0,963	0,117	1,035	0,879	1,088	1,001	0,109	0,942	0,986	0,800	0,909	0,097	1,014	1,053	0,863	0,977	0,101	0,963	1,070	0,940	0,991	0,069
20	1	0,949	0,816	0,786	0,850	0,087	0,907	0,947	0,779	0,878	0,088	0,947	0,872	0,865	0,895	0,045	0,949	0,928	0,879	0,919	0,036	0,995	0,930	0,900	0,942	0,049
21	1	0,891	0,886	0,935	0,904	0,027	0,867	0,793	0,974	0,878	0,091	0,907	0,874	0,891	0,891	0,016	0,874	0,884	0,888	0,882	0,007	0,830	0,826	0,791	0,816	0,022
22	1	0,819	0,805	0,860	0,828	0,029	0,860	0,788	0,856	0,835	0,040	0,837	0,837	0,812	0,829	0,015	0,851	0,823	0,828	0,834	0,015	0,884	0,837	0,812	0,844	0,037
23	1	0,835	0,700	0,877	0,804	0,092	0,828	0,812	0,856	0,832	0,022	0,835	0,849	0,828	0,837	0,011	0,860	0,844	0,842	0,849	0,010	0,856	0,842	0,856	0,851	0,008
Average					**0,8**	**0,038**				**0,9**	**0,028**				**0,9**	**0,038**				**0,9**	**0,024**				**0,9**	**0,027**
1	2	0,854	0,878	0,846	0,859	0,017	0,873	0,871	0,898	0,880	0,015	0,863	0,841	0,876	0,860	0,017	0,837	0,902	0,885	0,875	0,034	0,949	0,922	0,849	0,907	0,052
2	2	0,737	0,868	0,959	0,854	0,112	0,863	0,788	0,937	0,863	0,074	0,885	0,898	0,907	0,897	0,011	0,929	0,859	0,888	0,892	0,036	0,907	0,893	0,963	0,921	0,037
3	2	0,890	0,824	0,915	0,876	0,047	0,934	0,783	0,905	0,874	0,080	0,905	0,851	0,883	0,880	0,027	0,876	0,885	0,934	0,898	0,031	0,968	0,966	0,934	0,956	0,019
4	2	0,800	0,746	0,705	0,750	0,048	0,700	0,778	0,790	0,756	0,049	0,737	0,771	0,807	0,772	0,035	0,854	0,824	0,763	0,814	0,046	0,849	0,793	0,717	0,786	0,066
5	2	0,898	0,751	0,883	0,844	0,081	0,961	0,832	0,776	0,856	0,095	0,878	0,790	0,885	0,851	0,053	0,880	0,856	0,856	0,864	0,014	0,944	0,939	0,937	0,940	0,004
6	2	0,866	0,812	0,880	0,853	0,036	0,746	0,680	0,898	0,775	0,111	0,900	0,846	0,907	0,885	0,033	0,927	0,859	0,873	0,886	0,036	0,924	0,902	0,880	0,902	0,022
7	2	0,839	0,788	0,854	0,827	0,035	0,832	0,822	0,844	0,833	0,011	0,900	0,873	0,849	0,874	0,026	0,885	0,861	0,844	0,863	0,021	0,907	0,898	0,878	0,894	0,015
8	2	0,868	0,849	0,939	0,885	0,047	0,812	0,859	0,900	0,857	0,044	0,893	0,895	0,856	0,881	0,022	0,890	0,890	0,876	0,885	0,008	0,900	0,863	0,820	0,861	0,040
9	2	0,795	0,800	0,837	0,811	0,023	0,880	0,717	0,846	0,815	0,086	0,868	0,856	0,805	0,843	0,034	0,898	0,839	0,717	0,818	0,092	0,861	0,902	0,856	0,873	0,025
10	2	0,932	0,795	1,007	0,911	0,108	0,905	0,917	1,010	0,944	0,057	0,944	0,920	0,902	0,922	0,021	0,929	0,854	0,907	0,897	0,039	0,890	0,924	0,951	0,922	0,031
11	2	0,902	0,800	0,859	0,854	0,051	0,839	0,776	0,846	0,820	0,039	0,878	0,783	0,839	0,833	0,048	0,780	0,798	0,861	0,813	0,042	0,895	0,902	0,810	0,869	0,052
13	2	0,956	0,917	0,966	0,946	0,026	0,912	0,829	0,934	0,892	0,055	0,888	0,946	0,922	0,919	0,029	0,915	0,920	0,951	0,928	0,020	0,983	0,941	0,966	0,963	0,021
14	2	0,951	0,973	1,010	0,978	0,030	1,022	0,946	1,063	1,011	0,059	0,971	0,859	0,959	0,929	0,062	0,968	0,902	0,929	0,933	0,033	0,932	1,054	0,983	0,989	0,061
15	2	0,834	0,812	0,751	0,799	0,043	0,844	0,817	0,783	0,815	0,031	0,861	0,807	0,815	0,828	0,029	0,832	0,861	0,866	0,853	0,018	0,883	0,883	0,902	0,889	0,011
16	2	0,902	0,868	0,898	0,889	0,018	0,859	0,827	0,912	0,866	0,043	0,895	0,902	0,871	0,889	0,017	0,944	0,956	0,937	0,946	0,010	0,895	0,876	0,937	0,902	0,031
17	2	0,844	0,837	0,924	0,868	0,049	0,898	0,988	1,141	1,009	0,123	0,888	0,907	0,863	0,886	0,022	0,978	0,893	0,880	0,917	0,053	0,907	0,924	0,912	0,915	0,009
18	2	0,963	0,920	1,015	0,966	0,048	1,029	0,934	0,866	0,943	0,082	0,985	0,902	0,922	0,937	0,043	1,320	1,056	0,995	1,124	0,172	0,946	0,939	0,920	0,935	0,014
19	2	0,929	0,905	0,988	0,941	0,043	0,978	0,868	1,012	0,953	0,075	0,978	0,868	1,012	0,953	0,075	0,963	0,849	0,917	0,910	0,058	1,115	0,927	0,954	0,998	0,102
20	2	0,846	0,868	0,939	0,885	0,048	0,883	0,805	0,922	0,870	0,060	0,890	0,810	0,859	0,853	0,041	0,832	0,873	0,851	0,852	0,021	0,885	0,934	0,880	0,900	0,030
21	2	0,944	0,890	0,915	0,916	0,027	0,900	0,968	0,888	0,919	0,043	0,863	0,863	0,880	0,869	0,010	0,902	0,907	0,917	0,909	0,007	0,854	0,922	0,946	0,907	0,048
22	2	0,946	0,822	0,961	0,910	0,076	0,922	0,922	0,941	0,928	0,011	0,890	0,868	0,849	0,869	0,021	0,902	0,871	0,920	0,898	0,025	0,946	0,920	0,927	0,931	0,014
23	2	0,817	0,759	0,868	0,815	0,055	0,849	0,856	0,895	0,867	0,025	0,873	0,749	0,776	0,799	0,065	0,883	0,827	0,827	0,846	0,032	0,890	0,856	0,824	0,857	0,033
Average					**0,9**	**0,026**				**0,9**	**0,031**				**0,9**	**0,018**				**0,9**	**0,035**				**0,9**	**0,023**
2	4	1,013	1,018	1,021	1,018	0,004	1,084	0,971	1,045	1,033	0,057	0,976	0,968	1,016	0,987	0,025	0,963	0,987	1,092	1,014	0,069	0,987	0,974	0,976	0,979	0,007
3	4	0,974	0,984	0,982	0,980	0,005	1,050	0,995	0,984	1,010	0,035	0,976	0,979	1,003	0,986	0,014	0,979	0,995	1,221	1,065	0,135	1,000	1,042	1,013	1,018	0,022
5	4	0,995	1,021	0,984	1,000	0,019	1,011	1,008	1,016	1,011	0,004	0,971	0,966	0,971	0,969	0,003	0,958	0,989	1,092	1,013	0,070	0,997	0,984	1,042	1,008	0,030
6	4	1,000	0,958	0,982	0,980	0,021	1,011	0,963	0,995	0,989	0,024	1,003	0,961	0,984	0,982	0,021	0,979	1,000	0,968	0,982	0,016	0,979	0,987	1,003	0,989	0,012
7	4	0,939	0,976	1,016	0,977	0,038	0,945	0,955	1,013	0,971	0,037	0,955	0,976	0,961	0,964	0,011	0,945	1,011	0,989	0,982	0,034	1,018	1,016	1,024	1,019	0,004
8	4	1,016	0,958	1,003	0,992	0,030	0,989	0,966	1,003	0,986	0,019	1,061	1,018	1,092	1,057	0,037	1,055	1,037	1,061	1,051	0,012	0,992	0,995	1,087	1,025	0,054
9	4	0,979	0,995	0,997	0,990	0,010	0,971	0,942	1,016	0,976	0,037	0,958	0,953	0,945	0,952	0,007	0,976	0,971	0,971	0,973	0,003	1,050	0,995	1,045	1,030	0,031
10	4	0,968	1,024	1,100	1,031	0,066	0,971	1,034	1,068	1,025	0,049	1,034	0,963	1,037	1,011	0,042	0,966	1,055	1,016	1,012	0,045	0,987	1,053	1,061	1,033	0,040
11	4	0,979	0,955	1,016	0,983	0,031	0,997	0,979	0,961	0,979	0,018	0,984	0,958	1,000	0,981	0,021	0,987	0,984	0,961	0,977	0,014	1,068	1,008	1,103	1,060	0,048
14	4	0,947	0,992	1,026	0,989	0,040	0,995	1,003	1,039	1,012	0,024	1,005	0,974	1,045	1,008	0,036	1,005	1,008	1,024	1,012	0,010	1,000	1,011	0,992	1,001	0,009
15	4	0,992	0,984	0,955	0,977	0,019	1,039	0,982	0,989	1,004	0,031	0,971	0,987	1,061	1,006	0,048	0,955	0,953	1,079	0,996	0,072	0,974	0,989	1,000	0,988	0,013
16	4	0,982	1,018	1,071	1,024	0,045	1,011	0,987	0,982	0,993	0,015	1,026	0,995	0,995	1,005	0,018	1,068	1,003	1,042	1,038	0,033	1,000	0,968	0,976	0,982	0,016
17	4	0,963	1,003	1,055	1,007	0,046	0,937	0,966	0,987	0,963	0,025	0,997	1,011	0,997	1,002	0,008	1,176	1,013	1,024	1,071	0,091	0,961	1,008	1,084	1,018	0,062
18	4	0,937	1,024	1,045	1,002	0,057	0,911	0,971	1,050	0,977	0,070	1,026	0,987	0,989	1,001	0,022	1,158	1,016	1,079	1,084	0,071	1,092	1,239	1,118	1,150	0,079
19	4	1,008	1,037	1,016	1,020	0,015	1,016	1,024	1,018	1,019	0,004	1,011	0,953	1,029	0,997	0,040	0,984	0,974	0,987	0,982	0,007	1,047	1,026	1,018	1,031	0,015
20	4	1,011	0,984	0,984	0,993	0,015	1,018	1,003	1,003	1,008	0,009	1,071	0,976	0,974	1,007	0,055	0,987	0,961	1,039	0,996	0,040	1,018	0,950	1,016	0,995	0,039
21	4	1,003	0,968	0,961	0,977	0,022	0,987	0,929	0,950	0,955	0,029	0,989	0,934	0,926	0,950	0,034	0,942	0,937	1,005	0,961	0,038	0,939	0,937	1,005	0,961	0,039
23	4	0,971	1,047	1,105	1,041	0,067	1,029	1,000	1,008	1,012	0,015	0,982	1,000	1,055	1,012	0,038	1,024	0,992	0,984	1,000	0,021	1,011	1,018	1,029	1,019	0,009
Average					**1,0**	**0,021**				**1,0**	**0,017**				**1,0**	**0,017**				**1,0**	**0,033**				**1,0**	**0,020**

Normalized Moisture Measurents Average of the Right Cheek at D0, D28 and D84

	D0	D28	D84	%ΔD28-D0	%ΔD84-D0
1	0,792	0,859		8,47	
2	0,845	0,854	1,018	1,13	20,42
3	0,778	0,876	0,980	12,72	26,02
4	0,829	0,750		-9,45	
5	0,846	0,844	1,000	-0,22	18,24
6	0,819	0,853	0,980	4,08	19,58
7	0,809	0,827	0,977	2,17	20,75
8	0,866	0,885	0,992	2,25	14,58
9	0,887	0,811	0,990	-8,60	11,67
10	0,986	0,911	1,031	-7,57	4,53
11	0,758	0,854	0,983	12,60	29,70
12	0,798				
13	0,805	0,946		17,50	
14	0,920	0,978	0,989	6,29	7,44
15	0,935	0,799	0,977	-14,51	4,53
16	0,798	0,889	1,024	11,39	28,21
17	0,922	0,868	1,007	-5,87	9,16
18	0,771	0,966	1,002	25,22	29,88
19	0,963	0,941	1,020	-2,30	5,96
20	0,850	0,885	0,993	4,02	16,77
21	0,904	0,916	0,977	1,37	8,11
22	0,828	0,910		9,89	
23	0,804	0,815	1,041	1,34	29,53

Average	0,85	0,87	1,00	3,27	16,95
Std. Dev.	0,06	0,06	0,02	9,47	9,15
Median	0,83	0,87	0,99	2,21	17,50
Min.	0,76	0,75	0,98	-14,51	4,53
Max.	0,99	0,98	1,04	25,22	29,88

Normalized Moisture Measurents Average of the Left Cheek at D0, D28 and D84

	D0	D28	D84	%ΔD28-D0	%ΔD84-D0
1	0,818	0,880		7,66	
2	0,850	0,863	1,033	1,44	21,51
3	0,756	0,874	1,010	15,63	33,58
4	0,867	0,756		-12,84	
5	0,827	0,856	1,011	3,50	22,28
6	0,840	0,775	0,989	-7,80	17,75
7	0,821	0,833	0,971	1,41	18,29
8	0,853	0,857	0,986	0,40	15,52
9	0,881	0,815	0,976	-7,57	10,77
10	0,906	0,944	1,025	4,16	13,06
11	0,753	0,820	0,979	8,87	29,92
12	0,813				
13	0,819	0,892		8,85	
14	1,076	1,011	1,012	-6,08	-5,92
15	0,892	0,815	1,004	-8,70	12,47
16	0,819	0,866	0,993	5,77	21,30
17	0,888	1,009	0,963	13,67	8,51
18	0,836	0,943	0,977	12,75	16,83
19	1,001	0,953	1,019	-4,79	1,85
20	0,878	0,870	1,008	-0,87	14,86
21	0,878	0,919	0,955	4,60	8,76
22	0,835	0,928		11,21	
23	0,832	0,867	1,012	4,19	21,70

Average	0,86	0,88	1,00	2,52	15,73
Std. Dev.	0,07	0,07	0,02	7,93	9,33
Median	0,84	0,87	1,00	3,83	16,18
Min.	0,75	0,76	0,96	-12,84	-5,92
Max.	1,08	1,01	1,03	15,63	33,58

Normalized Moisture Measurents Average of the Right Temple at D0, D28 and D84

	D0	D28	D84	%ΔD28-D0	%ΔD84-D0
1	0,839	0,860		2,55	
2	0,869	0,897	0,987	3,19	13,56
3	0,799	0,880	0,986	10,07	23,37
4	0,824	0,772		-6,37	
5	0,846	0,851	0,969	0,65	14,61
6	0,841	0,885	0,982	5,17	16,81
7	0,756	0,874	0,964	15,63	27,55
8	0,929	0,881	1,057	-5,10	13,82
9	0,919	0,843	0,952	-8,30	3,52
10	0,846	0,922	1,011	9,01	19,59
11	0,813	0,833	0,981	2,48	20,60
12	0,807				
13	0,892	0,919		2,96	
14	0,922	0,929	1,008	0,74	9,26
15	0,882	0,828	1,006	-6,18	14,05
16	0,845	0,889	1,005	5,26	18,97
17	0,953	0,886	1,002	-6,98	5,15
18	0,860	0,937	1,001	8,94	16,42
19	0,909	0,953	0,997	4,79	9,69
20	0,895	0,853	1,007	-4,66	12,57
21	0,891	0,869	0,950	-2,42	6,66
22	0,829	0,869		4,88	
23	0,837	0,799	1,012	-4,54	20,91

Average	0,86	0,87	0,99	1,44	14,84
Std. Dev.	0,05	0,04	0,03	6,42	6,44
Median	0,85	0,88	1,00	2,52	14,33
Min.	0,76	0,77	0,95	-8,30	3,52
Max.	0,95	0,95	1,06	15,63	27,55

Normalized Moisture Measurents Average of the Left Temple at D0, D28 and D84

	D0	D28	D84	%ΔD28-D0	%ΔD84-D0
1	0,864	0,875		1,30	
2	0,895	0,892	1,014	-0,30	13,35
3	0,781	0,898	1,065	14,97	36,28
4	0,869	0,814		-6,35	
5	0,839	0,864	1,013	3,04	20,79
6	0,850	0,886	0,982	4,30	15,64
7	0,864	0,863	0,982	-0,02	13,67
8	0,889	0,885	1,051	-0,43	18,19
9	0,905	0,818	0,973	-9,67	7,44
10	0,879	0,897	1,012	2,01	15,15
11	0,848	0,813	0,977	-4,13	15,23
12	0,816				
13	0,888	0,928		4,51	
14	0,933	0,933	1,012	0,00	8,46
15	0,879	0,853	0,996	-2,98	13,26
16	0,834	0,946	1,038	13,36	24,41
17	0,980	0,917	1,071	-6,41	9,31
18	0,860	1,124	1,084	30,58	26,00
19	0,977	0,910	0,982	-6,86	0,49
20	0,919	0,852	0,996	-7,25	8,38
21	0,882	0,909	0,961	3,03	8,98
22	0,834	0,898		7,61	
23	0,849	0,846	1,000	-0,39	17,81

Average	0,88	0,89	1,01	1,82	15,16
Std. Dev.	0,05	0,06	0,04	8,96	8,21
Median	0,87	0,89	1,01	-0,01	14,41
Min.	0,78	0,81	0,96	-9,67	0,49
Max.	0,98	1,12	1,08	30,58	36,28

Normalized Moisture Measurents Average of the Front at D0, D28 and D84

	D0	D28	D84	%ΔD28-D0	%ΔD84-D0
1	0,887	0,880		-0,71	
2	0,896	0,863	0,979	-3,74	9,24
3	0,884	0,874	1,018	-1,10	15,24
4	0,843	0,756		-10,35	
5	0,855	0,856	1,011	0,12	18,29
6	0,833	0,775	0,989	-7,02	18,74
7	0,822	0,833	0,971	1,22	18,06
8	0,843	0,857	0,986	1,69	17,01
9	0,859	0,815	0,976	-5,16	13,67
10	0,872	0,944	1,025	8,23	17,48
11	0,847	0,820	0,979	-3,09	15,64
12	0,913				
13	0,940	0,892		-5,15	
14	0,932	1,011	1,001	8,46	7,42
15	0,940	0,815	0,988	-13,37	5,04
16	0,764	0,866	0,982	13,28	28,42
17	1,001	1,009	1,018	0,82	1,68
18	0,870	0,943	1,150	8,43	32,22
19	0,991	0,953	1,031	-3,82	4,04
20	0,942	0,870	0,995	-7,64	5,61
21	0,816	0,919	0,961	12,65	17,78
22	0,844	0,928		9,98	
23	0,851	0,867	1,019	1,82	19,75

Average	0,88	0,88	1,00	0,25	14,74
Std. Dev.	0,06	0,07	0,04	7,37	8,15
Median	0,87	0,87	0,99	-0,30	16,33
Min.	0,76	0,76	0,96	-13,37	1,68
Max.	1,00	1,01	1,15	13,28	32,22

Normalized Moisture Measurents Average of theFive Areas Average at D0, D28 and D84

	D0	D28	D84	%ΔD28-D0	%ΔD84-D0
1	0,886	0,876		-1,06	
2	0,871	0,885	1,006	1,65	15,51
3	0,800	0,897	1,012	12,18	26,54
4	0,847	0,776		-8,38	
5	0,842	0,871	1,000	3,39	18,74
6	0,837	0,860	0,985	2,80	17,69
7	0,814	0,858	0,983	5,38	20,65
8	0,876	0,874	1,022	-0,23	16,68
9	0,890	0,832	0,984	-6,57	10,54
10	0,898	0,919	1,022	2,38	13,88
11	0,804	0,838	0,996	4,23	23,90
12	0,830				
13	0,869	0,930		6,97	
14	0,957	0,968	1,004	1,19	4,98
15	0,906	0,837	0,994	-7,62	9,75
16	0,812	0,899	1,008	10,64	24,15
17	0,949	0,919	1,012	-3,13	6,69
18	0,840	0,981	1,043	16,83	24,21
19	0,968	0,951	1,010	-1,77	4,31
20	0,897	0,872	1,000	-2,76	11,49
21	0,874	0,904	0,961	3,43	9,93
22	0,834	0,907		8,78	
23	0,835	0,837	1,017	0,24	21,86

Average	0,87	0,89	1,00	2,21	15,64
Std. Dev.	0,05	0,05	0,02	6,34	7,06
Median	0,87	0,88	1,01	2,01	16,10
Min.	0,80	0,78	0,96	-8,38	4,31
Max.	0,97	0,98	1,04	16,83	26,54

Subjects Roughness Analysis Side-Randomization

Subject	Analyzed Side
Volunteer 01	Left
Volunteer 03	Right
Volunteer 04	Left
Volunteer 05	Right
Volunteer 06	Right
Volunteer 07	Left
Volunteer 08	Right
Volunteer 09	Right
Volunteer 10	Right
Volunteer 11	Left
Volunteer 13	Left
Volunteer 14	Left
Volunteer 15	Left
Volunteer 16	Right
Volunteer 17	Left
Volunteer 18	Right
Volunteer 19	Right
Volunteer 20	Left
Volunteer 21	Right
Volunteer 23	Right

ST Roughness Data of the Final 19 Considered Subjects

	D0	D28	%ΔD28-D0
1	0,439	0,339	-22,83
2	0,523	0,439	-16,16
3	0,409	0,347	-15,20
4	0,972	0,838	-13,82
5	0,326	0,305	-6,30
6	0,344	0,308	-10,66
7	0,411	0,264	-35,79
9	0,615	0,415	-32,47
10	0,825	0,660	-20,03
11	1,240	0,607	-51,07
13	0,362	0,299	-17,34
14	0,657	0,527	-19,79
15	0,776	0,457	-41,16
17	1,132	1,003	-11,39
18	0,652	0,539	-17,33
19	3,616	2,771	-23,36
20	0,349	0,296	-15,18
21	0,377	0,294	-22,06
23	0,452	0,344	-23,98

Averge	0,762	0,582	-21,89
Std. Dev.	0,744	0,567	11,19
Median	0,523452	0,415252	-19,79
MIN	0,325571	0,263583	-51,07
MAX	3,6164	2,77148	-6,30

SA Roughness Data of the Final 19 Considered Subjects

	D0	D28	%ΔD28-D0
1	0,023	0,018	-21,42
3	0,026	0,024	-5,33
4	0,062	0,065	4,79
5	0,021	0,021	-0,74
6	0,027	0,027	0,00
7	0,017	0,019	10,22
8	0,031	0,030	-1,74
9	0,044	0,037	-15,76
10	0,060	0,051	-14,58
11	0,032	0,031	-2,81
13	0,027	0,024	-7,96
14	0,032	0,030	-6,41
15	0,036	0,032	-9,36
16	0,024	0,023	-4,59
17	0,051	0,049	-5,34
18	0,047	0,044	-5,97
19	0,033	0,033	-2,01
20	0,031	0,027	-11,77
23	0,026	0,027	1,02

MEDIA	0,034	0,032	-5,25
SD	0,013	0,012	7,39
MEDIANA	0,031147	0,029605	-5,33
MIN	0,0173756	0,0182044	-21,42
MAX	0,0618941	0,0648593	10,22

Subjects Wrinkles Analysis Side-Randomization

Subject	Analyzed Side
Volunteer 01	Left
Volunteer 03	Right
Volunteer 04	Left
Volunteer 05	Right
Volunteer 06	Right
Volunteer 07	Left
Volunteer 08	Right
Volunteer 09	Right
Volunteer 10	Right
Volunteer 11	Left
Volunteer 13	Left
Volunteer 14	Left
Volunteer 15	Left
Volunteer 16	Right
Volunteer 17	Left
Volunteer 18	Right
Volunteer 19	Right
Volunteer 20	Left
Volunteer 21	Right
Volunteer 23	Right

Crowfeet Wrinkles Volume (mm^3) of the Final 19 Considered Subjects

	D0	D28	%ΔD28-D0
1	0,188	0,148	-21,28
3	0,261	0,163	-37,55
5	0,344	0,337	-2,03
6	0,403	0,319	-20,84
7	0,391	0,38	-2,81
8	0,692	0,551	-20,37
9	1,159	0,528	-54,44
10	1,552	0,877	-43,49
11	1,75	1,574	-10,06
13	0,824	0,631	-23,42
14	0,5	0,483	-3,40
15	0,524	0,271	-48,28
16	0,56	0,41	-26,79
17	2,145	1,868	-12,91
18	1,398	1,13	-19,17
19	0,645	0,321	-50,23
20	1,007	0,596	-40,81
21	1,247	1,162	-6,82
23	0,819	0,619	-24,42

Average	0,864	0,651	-24,69
Std. Dev.	0,547	0,472	16,79
Median	0,692	0,528	-21,28
Min.	0,188	0,148	-54,44
Max.	2,145	1,868	-2,03

Crowfeet Wrinkles Circumference (mm) of the Final 19 Considered Subjects

	D0	D28	%ΔD28-D0
1	122,46	104,85	-14,38
3	114,72	96,9	-15,53
5	127,47	138,6	8,73
6	134,04	137,31	2,44
7	250,98	279,87	11,51
8	103,65	106,56	2,81
9	129,27	102,93	-20,38
10	108,66	87,48	-19,49
11	218,25	229,65	5,22
13	134,28	118,65	-11,64
14	87,87	76,05	-13,45
15	118,89	86,55	-27,20
16	214,08	191,22	-10,68
17	146,1	148,44	1,60
18	123,15	123,03	-0,10
19	114,75	99,24	-13,52
20	136,89	105,6	-22,86
21	115,14	119,28	3,60
23	132,21	134,79	1,95

Average	138,572	130,895	-6,91
Std. Dev.	42,354	51,675	11,74
Median	127,47	118,65	-10,68
Min.	87,87	76,05	-27,20
Max.	250,98	279,87	11,51

Crowfeet Wrinkles Area (mm^2) of the Final 19 Considered Subjects

	D0	D28	%ΔD28-D0
1	16,107	13,966	-13,29
3	17,487	12,54	-28,29
5	19,368	19,17	-1,02
6	21,837	21,849	0,05
7	29,576	38,839	31,32
8	20,317	20,156	-0,79
9	25,335	24,713	-2,46
10	27,336	19,307	-29,37
11	65,903	50,141	-23,92
13	25,245	20,17	-20,10
14	17,318	16,613	-4,07
15	22,382	14,083	-37,08
16	33,015	26,6	-19,43
17	49,008	44,185	-9,84
18	32,106	27,933	-13,00
19	22,958	15,632	-31,91
20	29,704	22,022	-25,86
21	29,215	29,832	2,11
23	28,162	27,292	-3,09

Average	28,020	24,476	-12,11
Std. Dev.	11,871	10,308	16,25
Median	25,335	21,849	-13,00
Min.	16,107	12,54	-37,08
Max.	65,903	50,141	31,32

Crowfeet Wrinkles Maximum Depth (mm) of the Final 19 Considered Subjects

	D0	D28	%ΔD28-D0
1	-0,021	-0,022	7,21
3	-0,027	-0,020	-23,79
5	-0,027	-0,034	28,29
6	-0,027	-0,026	-4,11
7	-0,023	-0,019	-17,94
8	-0,037	-0,031	-16,01
9	-0,048	-0,040	-16,49
10	-0,074	-0,060	-19,55
11	-0,052	-0,034	-35,07
13	-0,028	-0,032	12,42
14	-0,048	-0,053	9,38
15	-0,039	-0,032	-17,78
16	-0,031	-0,027	-12,12
17	-0,109	-0,083	-23,60
18	-0,050	-0,042	-16,29
19	-0,038	-0,027	-29,00
20	-0,034	-0,036	5,11
21	-0,049	-0,050	2,98
23	-0,028	-0,024	-11,49

Average	-0,042	-0,036	-9,36
Std. Dev.	0,021	0,016	16,27
Median	-0,03709375	-0,03202439	-16,01
Min.	-0,1085714	-0,08295	-35,07
Max.	-0,020975	-0,01898969	28,29

Crowfeet Wrinkles Average Depth (mm) of the Final 19 Considered Subjects

	D0	D28	%ΔD28-D0
1	-0,008	-0,009	14,51
3	-0,010	-0,009	-12,45
5	-0,010	-0,012	10,93
6	-0,011	-0,010	-6,34
7	-0,009	-0,008	-18,36
8	-0,014	-0,012	-9,66
9	-0,019	-0,016	-14,94
10	-0,029	-0,026	-11,59
11	-0,015	-0,013	-13,04
13	-0,012	-0,014	14,31
14	-0,019	-0,020	5,37
15	-0,015	-0,012	-18,90
16	-0,013	-0,011	-12,98
17	-0,026	-0,020	-25,84
18	-0,020	-0,016	-20,22
19	-0,014	-0,011	-21,20
20	-0,013	-0,015	11,80
21	-0,018	-0,018	0,23
23	-0,010	-0,010	-5,14

Average	-0,015	-0,014	-7,03
Std. Dev.	0,006	0,005	12,90
Median	-0,01359375	-0,01243478	-11,59
Min.	-0,02940909	-0,026	-25,84
Max.	-0,008025	-0,007649485	14,51

Raw Ultrasound Data of the 22 Final Volunteers

Subject	Time	Side	Epidermis Thickness 1	Dermis Thickness 1	Epidermis Density 1	Dermis Density 1	Epidermis Thickness 2	Dermis Thickness 2	Epidermis Density 2	Dermis Density 2	Epidermis Thickness 3	Dermis Thickness 3	Epidermis Density 3	Dermis Density 3	Average Epidermis Thickness	Average Dermis Thickness	Average Epidermis Density	Average Dermis Density
1	0	L	71	570	94,51	25,17	71	562	109,93	25,6	78	613	106,45	23,42	73,33	581,67	103,63	24,73
1	0	R	145	656	97,03	28,95	137	625	102,91	32,02	129	652	99,4	25,9	137,00	644,33	99,78	28,96
2	0	L	71	613	94,39	15,85	82	617	90,93	14,08	82	660	85,98	13,44	78,33	630,00	90,43	14,46
2	0	R	71	1191	81,27	16,61	86	1238	68,91	15,95	86	1098	74,79	19,38	81,00	1175,67	74,99	17,31
3	0	L	105	793	114,88	21,79	106	656	113,04	22,1	118	691	106,5	21,61	109,67	713,33	111,47	21,83
3	0	R	113	770	133,69	29,47	106	699	112,2	22,26	94	781	102,03	22,5	104,33	750,00	115,97	24,74
4	0	L	102	750	106,98	22,52	97	684	113,97	23,08	97	645	109,12	23,83	98,67	693,00	110,02	23,14
4	0	R	101	676	93,9	17,65	97	723	97,87	16,95	94	742	114,29	15,68	97,33	713,67	102,02	16,76
5	0	R	109	707	77,23	18,62	117	684	81,32	17,83	106	652	80,58	18,58	110,67	681,00	79,71	18,34
5	0	L	82	625	80,56	13,05	79	691	91,07	11,73	75	691	86,13	11,74	78,67	669,00	85,92	12,17
6	0	L	113	727	137,89	32,54	98	707	106,5	21,29	106	785	105,08	18,68	105,67	739,67	116,49	24,17
6	0	R	152	664	87,53	20,21	128	688	97,36	21,81	121	625	100,28	23,21	133,67	659,00	95,06	21,74
7	0	L	70	832	71,01	13,73	71	824	66,12	12,43	74	719	66,61	15,35	71,67	791,67	67,91	13,84
7	0	R	86	883	85,14	17,89	94	867	81,8	16,05	90	859	77,96	17,55	90,00	869,67	81,63	17,16
8	0	R	94	812	80,63	15,66	105	727	79,56	16,24	113	770	77,81	16,58	104,00	769,67	79,33	16,16
8	0	L	97	684	119,37	25,99	106	699	117,32	21,83	98	652	115,44	23,49	100,33	678,33	117,38	23,77
9	0	R	239	1073	105,79	19,93	250	885	106,87	20,2	260	1042	92,99	18,11	249,67	1000,00	101,88	19,41
9	0	L	56	734	79,85	13,99	86	754	87,19	14,51	82	758	102,53	11,28	74,67	748,67	89,86	13,26
10	0	R	66	645	76,66	14,82	70	711	76,35	14,6	62	797	81,5	13,95	66,00	717,67	78,17	14,46
10	0	L	110	734	62,77	16,61	106	738	68,17	17,22	105	727	70,84	17,65	107,00	733,00	67,26	17,16
11	0	L	86	789	75,38	21,04	98	746	88,72	22,22	94	781	92,03	23,9	92,67	772,00	85,38	22,39
11	0	R	109	727	85,36	19,1	109	680	100,75	21,89	121	695	91,8	19,53	113,00	700,67	92,64	20,17
13	0	R	105	895	104,2	32,63	102	953	107,08	29,96	105	938	95,84	27,59	104,00	928,67	102,37	30,06
13	0	L	89	973	82,28	19,65	89	895	82,6	19,52	90	1023	77,7	17,58	89,33	963,67	80,86	18,92
14	0	R	98	1297	78,9	15,86	78	1090	93,48	19,46	102	949	84,56	19,98	92,67	1112,00	85,65	18,43
14	0	L	74	1188	79,56	14,85	79	1066	68,39	15,33	67	980	81,55	16,46	73,33	1078,00	76,50	15,55
15	0	R	105	1055	83,23	23,12	98	1062	90,14	25,5	97	1094	89,08	22,29	100,00	1070,33	87,48	23,64
15	0	L	68	605	99,82	19,03	69	625	98,92	17,09	56	630	95,14	17,8	64,33	620,00	97,96	17,97
16	0	R	97	805	113,86	28,03	98	773	115,33	27,72	97	723	118,35	28,88	97,33	767,00	115,85	28,21
16	0	L	94	750	95,83	21,31	98	812	101,65	20,86	105	672	100,07	25,99	99,00	744,67	99,18	22,72
17	0	L	79	816	82,37	16,93	89	645	111,29	15,26	91	625	113,7	22,95	86,33	695,33	102,45	18,38
17	0	R	125	723	95,63	22,89	110	691	109,39	25,01	97	645	108,7	26,13	110,67	686,33	104,57	24,68
18	0	R	101	711	85,94	22,64	117	699	90,84	23,06	122	648	101,7	26,2	113,33	686,00	92,83	23,97
18	0	L	102	613	88,22	29,66	94	629	93,23	27,97	98	668	93,36	25,31	98,00	636,67	91,60	27,65
19	0	R	106	1066	94,21	22,77	90	1117	72,59	19,18	98	1090	77,79	20,12	98,00	1091,00	81,53	20,69
19	0	L	74	1082	80,24	19,94	90	941	80,82	21,88	90	945	86,37	23,02	84,67	989,33	82,48	21,61
20	0	L	102	1148	74,52	22,17	101	969	89,01	26,34	117	1039	84,16	25,95	106,67	1052,00	82,56	24,82
20	0	R	90	652	96,09	19,36	105	676	105,79	23,39	101	629	109,97	27,93	98,67	652,33	103,95	23,56
21	0	L	9	1219	60,09	16,54	82	1176	68,57	22,71	109	1129	69,98	19,83	66,67	1174,67	66,21	19,69
21	0	R	106	730	98,85	25,33	121	707	91,07	24,09	125	711	86,87	25,48	117,33	716,00	92,26	24,97
22	0	L	102	738	94,09	25,49	102	707	98,94	25,55	101	637	111,32	32,25	101,67	694,00	101,45	27,76
22	0	R	137	711	100,92	21,81	137	789	90,15	23,42	140	758	103,18	26,06	138,00	752,67	98,08	23,76
23	0	L	98	902	103,25	35,99	90	812	104,4	36,52	90	773	104,59	38,1	92,67	829,00	104,08	36,87
23	0	R	90	844	113,84	26,58	86	734	112,36	29,88	85	895	115,13	24,71	87,00	824,33	113,78	27,06

Subject	Time	Side	Epidermis Thickness 1	Dermis Thickness 1	Epidermis Density 1	Dermis Density 1	Epidermis Thickness 2	Dermis Thickness 2	Epidermis Density 2	Dermis Density 2	Epidermis Thickness 3	Dermis Thickness 3	Epidermis Density 3	Dermis Density 3	Average Epidermis Thickness	Average Dermis Thickness	Average Epidermis Density	Average Dermis Density
1	1	L	90	668	131,17	29,23	90	648	129,53	20,04	94	691	132,8	27,51	91,33	669,00	131,17	25,59
1	1	R	90	695	128,6	33,76	90	629	123,05	32,44	90	785	127,71	28,57	90,00	703,00	126,45	31,59
2	1	L	94	629	121,12	41,27	90	680	115,21	36,12	105	598	121,27	40,25	96,33	635,67	119,20	39,21
2	1	R	125	832	94,61	23,8	109	754	97,85	25,64	105	707	96,15	26,76	113,00	764,33	96,20	25,40
3	1	L	109	746	125,41	32,03	105	641	122,06	32,87	114	734	122,23	32,06	109,33	707,00	123,23	32,32
3	1	R	132	688	97,8	29,8	133	746	92,14	25,53	121	676	94,86	28,96	128,67	703,33	94,93	28,10
4	1	L	86	680	130,56	21,94	90	617	130,28	27,49	93	766	133,17	27,5	89,67	687,67	131,34	25,64
4	1	R	90	652	121,17	23,28	89	602	122,51	26,61	90	676	117,28	23,18	89,67	643,33	120,32	24,36
5	1	R	98	1004	89,39	27,62	86	879	86,25	25,38	86	1004	88,47	23,4	90,00	962,33	88,04	25,47
5	1	L	129	930	83,31	31,09	129	875	83,35	28,82	136	84,32	84,32	31,12	131,33	629,77	83,66	30,34
6	1	L	94	633	120,73	23,84	94	742	121,91	21,25	101	719	120,67	22,06	96,33	698,00	121,10	22,38
6	1	R	125	801	73,77	16,99	102	816	76,93	18,25	106	785	75,59	16,22	111,00	800,67	75,43	17,15
7	1	L	90	980	143,44	39,07	94	863	120,9	29,86	86	941	120,68	29,21	90,00	928,00	128,34	32,71
7	1	R	102	656	122,08	33,28	109	762	120,27	29,15	105	707	118,94	34,8	105,33	708,33	120,43	32,41
8	1	R	98	754	95,77	23,27	98	754	101,78	23,98	110	691	103,11	25,62	102,00	733,00	100,22	24,29
8	1	L	97	715	118,42	23,48	101	719	119,75	25,04	90	656	124,77	28,1	96,00	696,67	120,98	25,54
9	1	R	94	773	98,84	19,48	94	672	103,3	21,93	94	711	99,62	16,98	94,00	718,67	100,59	19,46
9	1	L	118	773	81,21	17,62	90	840	87,67	18,94	90	844	80,14	17,37	99,33	819,00	83,01	17,98
10	1	R	89	641	120,13	34,15	86	715	120,14	33,94	85	645	125,15	42,52	86,67	667,00	121,81	36,87
10	1	L	98	734	115,15	28,36	113	645	102,93	32,81	117	664	102,58	33,21	109,33	681,00	106,89	31,46
11	1	L	105	680	135,95	27,53	101	676	107,91	31,39	102	648	113,11	26,11	102,67	668,00	118,99	28,34
11	1	R	75	1066	82,27	21,13	78	1074	73,9	20,7	113	1203	87,23	21,06	88,67	1114,33	81,13	20,96
13	1	R	117	797	118,88	37,37	102	859	121,23	29,56	97	684	119,9	31,02	105,33	780,00	120,00	32,65
13	1	L	106	984	115,8	31,7	94	664	122,46	33,6	102	617	112,28	36,36	100,67	755,00	116,85	33,89
14	1	R	86	1195	82,51	21,34	70	1250	91	16,99	101	1180	91,2	21,57	85,67	1208,33	88,24	19,97
14	1	L	137	992	123,28	35,47	125	910	90,42	24	129	980	82,55	24,94	130,33	960,67	98,75	28,14
15	1	R	109	668	121,41	26,63	102	707	128,4	27,58	102	605	134,28	28,71	104,33	660,00	128,03	27,64
15	1	L	102	664	118,47	20,79	105	641	121,25	28,23	114	691	115,17	24,06	107,00	665,33	118,30	24,36
16	1	R	94	879	118,24	29,68	97	809	118,18	30,7	98	695	117,33	29,95	96,33	794,33	117,92	30,11
16	1	L	71	945	103,87	19,54	125	914	99,67	16,97	90	918	112,52	30,8	95,33	925,67	105,35	22,44
17	1	L	109	676	111,01	26,41	129	719	101,06	26,39	106	730	103,43	25,01	114,67	708,33	105,17	25,94
17	1	R	94	1258	118,44	26,64	90	820	98,31	21,26	90	867	98,15	21,71	91,33	981,67	104,97	23,20
18	1	R	109	621	118,62	27,46	98	629	117,32	31,49	97	637	120,57	31,97	101,33	629,00	118,84	30,31
18	1	L	117	633	111,63	29,34	105	680	112,35	27,08	114	648	104,1	30,1	112,00	653,67	109,36	28,84
19	1	R	98	1172	131,67	19	102	1027	128,93	23,63	105	1055	139,54	31,74	101,67	1084,67	133,38	24,79
19	1	L	102	953	108,9	28,16	98	828	106,24	28,49	106	824	133,35	41,03	102,00	868,33	116,16	32,56
20	1	L	113	699	137,23	36,6	106	699	131,01	27,68	93	680	132,5	28,16	104,00	692,67	133,58	30,81
20	1	R	98	625	122,17	35,08	98	656	124	35,08	102	652	118,13	31	99,33	644,33	121,43	33,72
21	1	L	82	684	126,37	25,16	86	793	122,14	26,57	86	695	123,45	25,14	84,67	724,00	123,99	25,62
21	1	R	98	707	118,03	25,93	89	723	116,13	24,57	94	746	115,96	26,33	93,67	725,33	116,71	25,61
22	1	L	90	773	129,62	26,58	90	660	132,58	32,59	90	660	121,29	27,07	90,00	697,67	127,83	28,75
22	1	R	70	1332	78,25	15,08	94	871	85,96	18,89	62	969	87,99	17,33	75,33	1057,33	84,07	17,10
23	1	L	86	820	116,68	32,07	86	785	113,97	32,81	97	844	116,8	49,45	89,67	816,33	115,82	38,11
23	1	R	121	848	102,15	29,98	125	863	102,66	29,08	121	809	104,06	30,9	122,33	840,00	102,96	29,99

Subjects Ultrasound Analysis Side-Randomization

Subject	Analyzed Side
Volunteer 01	Left
Volunteer 03	Left
Volunteer 02	Left
Volunteer 04	Left
Volunteer 05	Right
Volunteer 06	Left
Volunteer 07	Left
Volunteer 08	Right
Volunteer 09	Right
Volunteer 10	Right
Volunteer 11	Left
Volunteer 13	Right
Volunteer 14	Right
Volunteer 15	Right
Volunteer 16	Right
Volunteer 17	Left
Volunteer 18	Right
Volunteer 19	Right
Volunteer 20	Left
Volunteer 21	Left
Volunteer 22	Left
Volunteer 23	Left

Ultrasound Epidermis thickness (µm) of the Final 22 Considered Subjects

	D0	D28	%ΔD28-D0
1	73,33	91,33	24,55
2	78,33	96,33	22,98
3	109,67	109,33	-0,30
4	98,67	89,67	-9,12
5	110,67	90,00	-18,67
6	105,67	96,33	-8,83
7	71,67	90,00	25,58
8	104,00	102,00	-1,92
9	249,67	94,00	-62,35
10	66,00	86,67	31,31
11	92,67	102,67	10,79
13	104,00	105,33	1,28
14	92,67	85,67	-7,55
15	100,00	104,33	4,33
16	97,33	96,33	-1,03
17	86,33	114,67	32,82
18	113,33	101,33	-10,59
19	98,00	101,67	3,74
20	106,67	104,00	-2,50
21	66,67	84,67	27,00
22	101,67	90,00	-11,48
23	92,67	89,67	-3,24

Average	100,89	96,64	2,13
Std. Dev.	98,33	96,33	-0,67
Median	66,00	84,67	-62,35
Min.	249,67	114,67	32,82
Max.	249,67	114,67	32,82

Ultrasound Dermis thickness (µm) of the Final 22 Considered Subjects

	D0	D28	%ΔD28-D0
1	581,67	669,00	15,01
2	630,00	635,67	0,90
3	713,33	707,00	-0,89
4	693,00	687,67	-0,77
5	681,00	962,33	41,31
6	739,67	698,00	-5,63
7	791,67	928,00	17,22
8	769,67	733,00	-4,76
9	1000,00	718,67	-28,13
10	717,67	667,00	-7,06
11	772,00	668,00	-13,47
13	928,67	780,00	-16,01
14	1112,00	1208,33	8,66
15	1070,33	660,00	-38,34
16	767,00	794,33	3,56
17	695,33	708,33	1,87
18	686,00	629,00	-8,31
19	1091,00	1084,67	-0,58
20	1052,00	692,67	-34,16
21	1174,67	724,00	-38,37
22	694,00	697,67	0,53
23	829,00	816,33	-1,53

Average	826,80	766,80	-4,95
Std. Dev.	177,11	150,24	18,64
Median	768,33	707,67	-1,21
Min.	581,67	629,00	-38,37
Max.	1174,67	1208,33	41,31

Ultrasound Epidermis Echogenic Density (arbitrary Unit) of the Final 22 Considered Subjects

	D0	D28	%ΔD28-D0
1	103,63	131,17	26,57
2	90,43	119,20	31,81
3	111,47	123,23	10,55
4	110,02	131,34	19,37
5	79,71	88,04	10,45
6	116,49	121,10	3,96
7	67,91	128,34	88,98
8	79,33	100,22	26,33
9	101,88	100,59	-1,27
10	78,17	121,81	55,82
11	85,38	118,99	39,37
13	102,37	120,00	17,22
14	85,65	88,24	3,02
15	87,48	128,03	46,35
16	115,85	117,92	1,79
17	102,45	105,17	2,65
18	92,83	118,84	28,02
19	81,53	133,38	63,60
20	82,56	133,58	61,79
21	66,21	123,99	87,25
22	101,45	127,83	26,00
23	104,08	115,82	11,28

Average	93,04	118,04	30,04
Std. Dev.	14,78	13,45	26,98
Median	91,63	120,55	26,17
Min.	66,21	88,04	-1,27
Max.	116,49	133,58	88,98

Ultrasound Dermis Echogenic Density (arbitrary Unit) of the Final 22 Considered Subjects

	D0	D28	%ΔD28-D0
1	24,73	25,59	3,49
2	14,46	39,21	171,25
3	21,83	32,32	48,03
4	23,14	25,64	10,80
5	18,34	25,47	38,83
6	24,17	22,38	-7,39
7	13,84	32,71	136,42
8	16,16	24,29	50,31
9	19,41	19,46	0,26
10	14,46	36,87	155,04
11	22,39	28,34	26,61
13	30,06	32,65	8,62
14	18,43	19,97	8,32
15	23,64	27,64	16,94
16	28,21	30,11	6,74
17	18,38	25,94	41,11
18	23,97	30,31	26,45
19	20,69	24,79	19,82
20	24,82	30,81	24,15
21	19,69	25,62	30,11
22	27,76	28,75	3,54
23	36,87	38,11	3,36

Average	22,07	28,50	37,40
Std. Dev.	5,58	5,36	50,34
Median	22,11	27,99	21,98
Min.	13,84	19,46	-7,39
Max.	36,87	39,21	171,25

ANNEX II

STATISTICAL ANALYSIS

Goodness-of-Fit Tests for Moist_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,126973
DMINUS	0,0895655
DN	0,126973
P-Value	0,870112

The StatAdvisor

This pane shows the results of tests run to determine whether Moist_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Moist_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Moist_D28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,0813183
DMINUS	0,0874989
DN	0,0874989
P-Value	0,995974

The StatAdvisor

This pane shows the results of tests run to determine whether Moist_D28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Moist_D28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for MoistD0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,152064
DMINUS	0,100004
DN	0,152064
P-Value	0,79948

The StatAdvisor

This pane shows the results of tests run to determine whether MoistD0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that MoistD0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Moist_D84

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,0989847
DMINUS	0,0959956
DN	0,0989847
P-Value	0,994531

The StatAdvisor

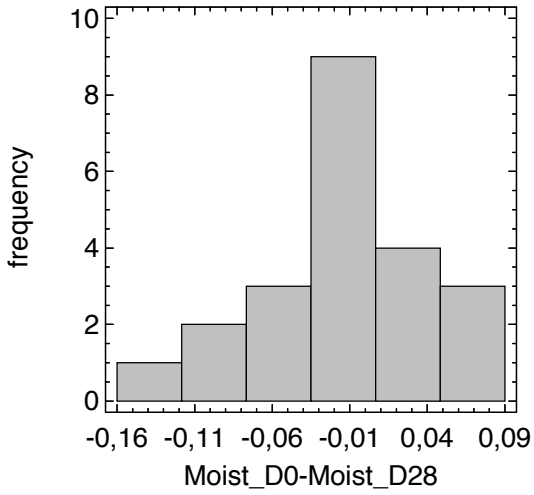
This pane shows the results of tests run to determine whether Moist_D84 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Moist_D84 comes from a normal distribution with 95% confidence.

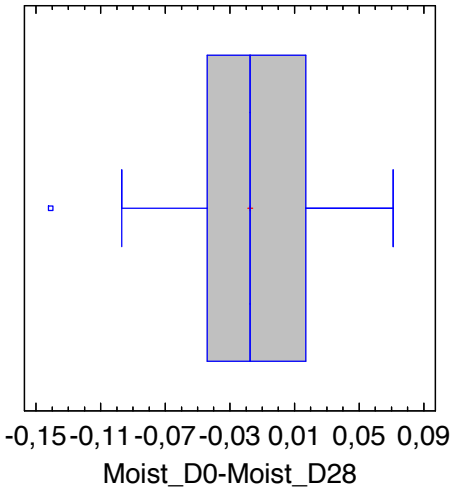
SnapStat: Paired Sample Comparison

Data variable: Moist_D0-Moist_D28
Count = 22
Average = -0,0175
Standard deviation = 0,053621
Coeff. of variation = -306,406%
Minimum = -0,141
Maximum = 0,071
Range = 0,212
Stnd. skewness = -0,633588
Stnd. kurtosis = 0,117826

Histogram



Box-and-Whisker Plot

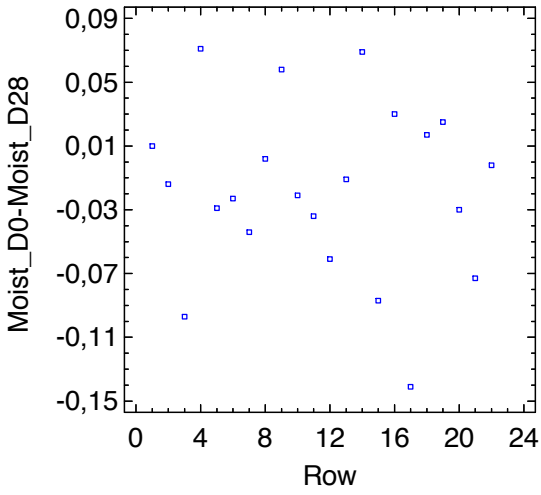


95% confidence intervals
Mean difference: -0,0175 +/- 0,0237743 [-0,0412743; 0,0062742
Sigma: [0,0412534; 0,0766279]

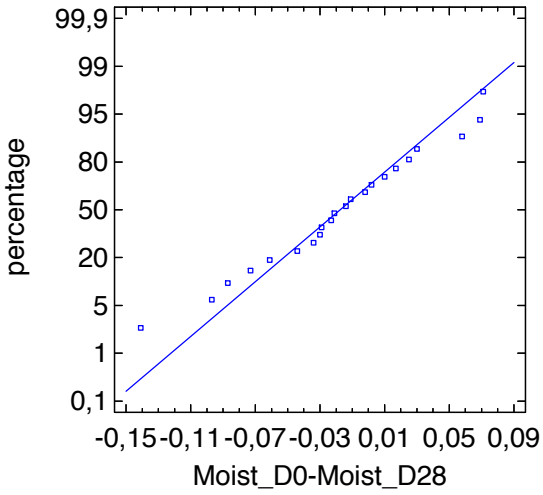
Comparison of Means
Null hypothesis: difference = 0
t statistic = -1,53079
Two-sided P-value = 0,1407

Diagnostics
Shapiro-Wilks P-value = 0,8611
Lag 1 autocorrelation = -0,413249 +/- 0,417867

Time Sequence Plot



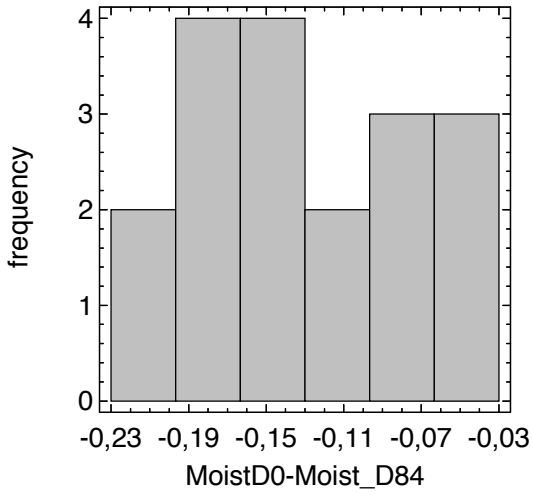
Normal Probability Plot



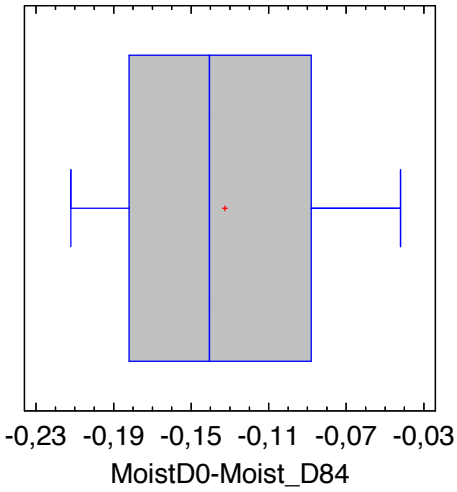
SnapStat: Paired Sample Comparison

Data variable: MoistD0-Moist_D84
Count = 18
Average = -0,132722
Standard deviation = 0,0545191
Coeff. of variation = -41,0776%
Minimum = -0,212
Maximum = -0,042
Range = 0,17
Stnd. skewness = 0,345919
Stnd. kurtosis = -1,01539

Histogram



Box-and-Whisker Plot

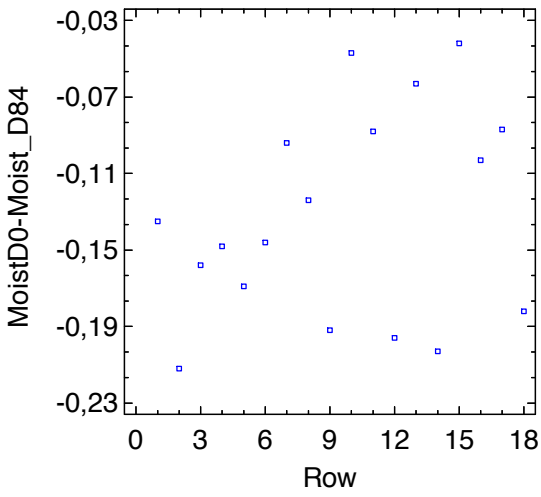


95% confidence intervals
Mean difference: -0,132722 +/- 0,0271118 [-0,159834; -0,10561]
Sigma: [0,0409104; 0,081732]

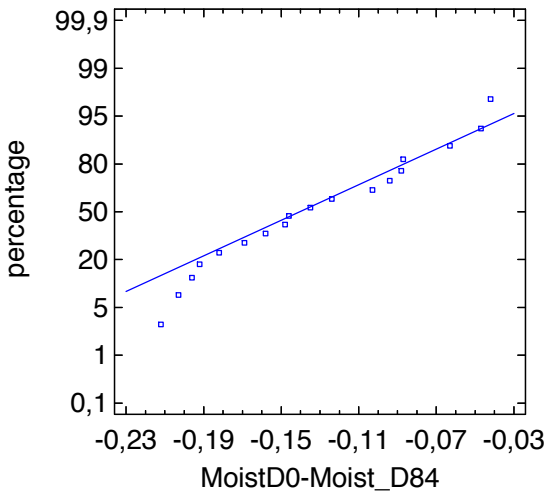
Comparison of Means
Null hypothesis: difference = 0
t statistic = -10,3284
Two-sided P-value = 0,0000

Diagnostics
Shapiro-Wilks P-value = 0,4028
Lag 1 autocorrelation = -0,297838 +/- 0,461969

Time Sequence Plot



Normal Probability Plot



Goodness-of-Fit Tests for SA_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,22186
DMINUS	0,0985523
DN	0,22186
P-Value	0,308676

The StatAdvisor

This pane shows the results of tests run to determine whether SA_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that SA_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for SA_D28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,21108
DMINUS	0,122403
DN	0,21108
P-Value	0,369049

The StatAdvisor

This pane shows the results of tests run to determine whether SA_D28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that SA_D28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for ST_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,255683
DMINUS	0,278844
DN	0,278844
P-Value	0,1042

The StatAdvisor

This pane shows the results of tests run to determine whether ST_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that ST_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for ST_D28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,287136
DMINUS	0,287506
DN	0,287506
P-Value	0,0864768

The StatAdvisor

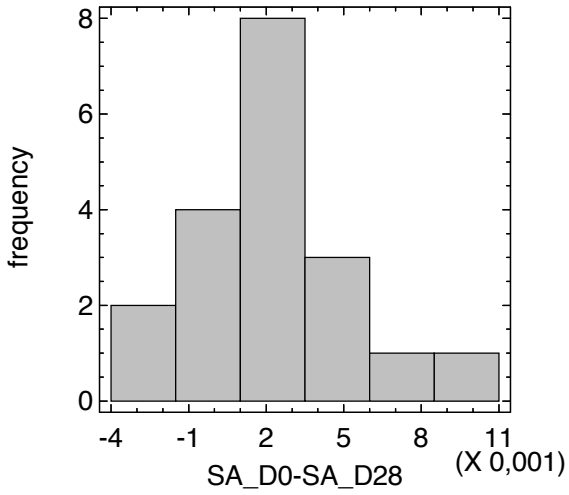
This pane shows the results of tests run to determine whether ST_D28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that ST_D28 comes from a normal distribution with 95% confidence.

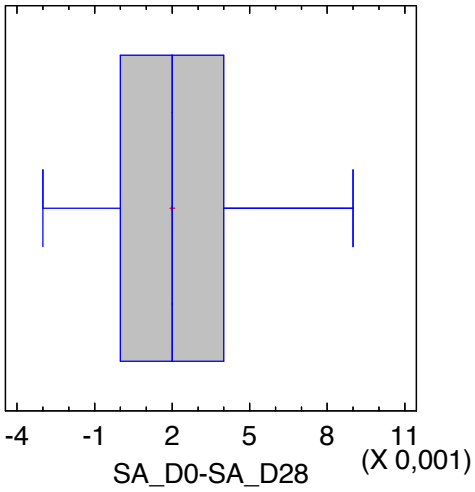
SnapStat: Paired Sample Comparison

Data variable: SA_D0-SA_D28
Count = 19
Average = 0,002
Standard deviation = 0,00296273
Coeff. of variation = 148,137%
Minimum = -0,003
Maximum = 0,009
Range = 0,012
Stnd. skewness = 1,14715
Stnd. kurtosis = 0,54358

Histogram



Box-and-Whisker Plot

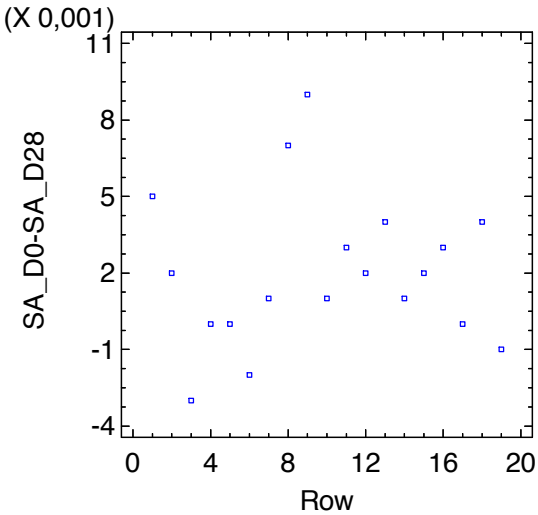


95% confidence intervals
Mean difference: 0,002 +/- 0,00142799 [0,000572006; 0,0034279
Sigma: [0,00223868; 0,00438136]

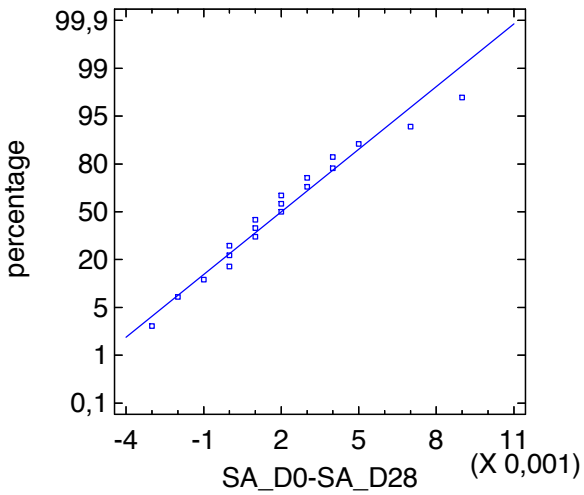
Comparison of Means
Null hypothesis: difference = 0
t statistic = 2,94249
Two-sided P-value = 0,0087

Diagnostics
Shapiro-Wilks P-value = 0,6776
Lag 1 autocorrelation = 0,21519 +/- 0,449647

Time Sequence Plot



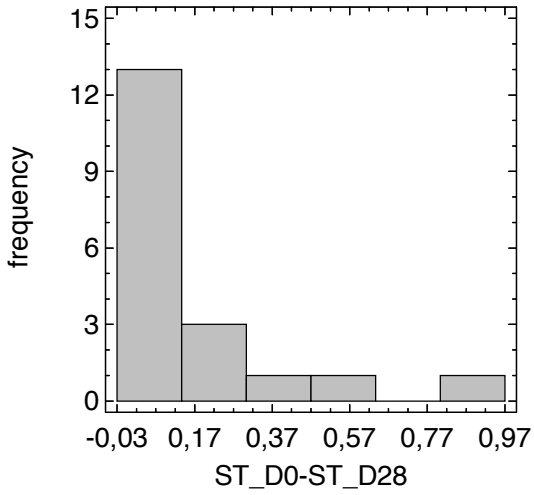
Normal Probability Plot



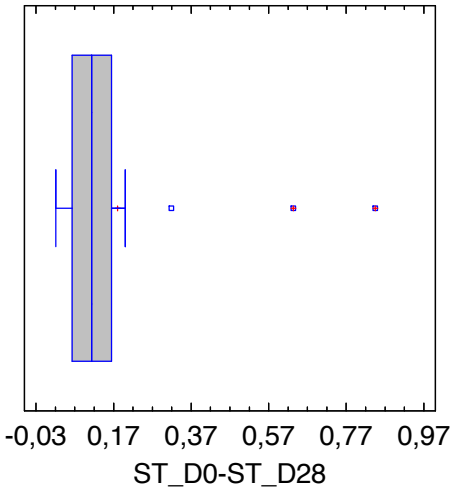
SnapStat: Paired Sample Comparison

Data variable: ST_D0-ST_D28
Count = 19
Average = 0,180263
Standard deviation = 0,210837
Coeff. of variation = 116,961%
Minimum = 0,021
Maximum = 0,845
Range = 0,824
Stnd. skewness = 4,40246
Stnd. kurtosis = 5,19557

Histogram



Box-and-Whisker Plot

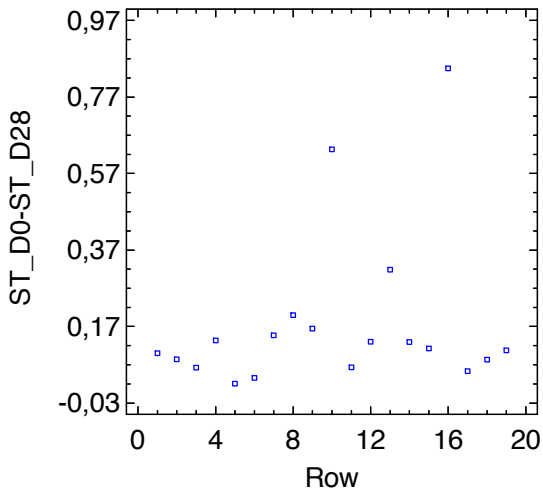


95% confidence intervals
Mean difference: 0,180263 +/- 0,10162 [0,0786427; 0,281884]
Sigma: [0,159311; 0,311791]

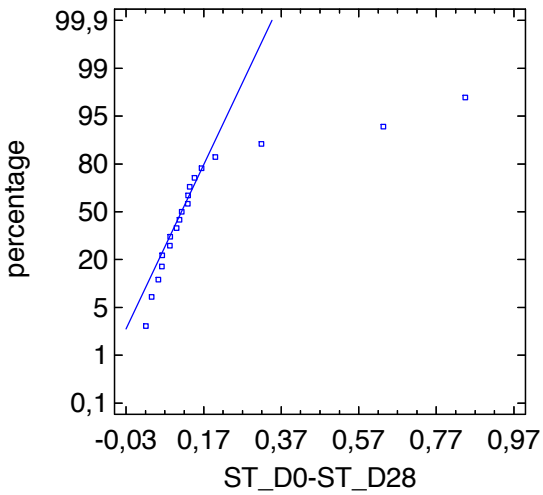
Comparison of Means
Null hypothesis: difference = 0
t statistic = 3,7268
Two-sided P-value = 0,0015

Diagnostics
Shapiro-Wilks P-value = 0,0000
Lag 1 autocorrelation = -0,144822 +/- 0,449647

Time Sequence Plot



Normal Probability Plot



Goodness-of-Fit Tests for Vol_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,160456
DMINUS	0,108423
DN	0,160456
P-Value	0,712214

The StatAdvisor

This pane shows the results of tests run to determine whether Vol_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Vol_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Vol_D28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,253685
DMINUS	0,143524
DN	0,253685
P-Value	0,173417

The StatAdvisor

This pane shows the results of tests run to determine whether Vol_D28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Vol_D28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Circ_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,305312
DMINUS	0,152191
DN	0,305312
P-Value	0,0579013

The StatAdvisor

This pane shows the results of tests run to determine whether Circ_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Circ_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Circ_D28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,230204
DMINUS	0,144266
DN	0,230204
P-Value	0,267286

The StatAdvisor

This pane shows the results of tests run to determine whether Circ_D28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Circ_D28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Area_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,233065
DMINUS	0,157801
DN	0,233065
P-Value	0,254114

The StatAdvisor

This pane shows the results of tests run to determine whether Area_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Area_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Area_D28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,173034
DMINUS	0,123444
DN	0,173034
P-Value	0,620037

The StatAdvisor

This pane shows the results of tests run to determine whether Area_D28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Area_D28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for ProfMed_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,162953
DMINUS	0,204162
DN	0,204162
P-Value	0,412109

The StatAdvisor

This pane shows the results of tests run to determine whether ProfMed_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that ProfMed_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for ProfMed_D28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,136086
DMINUS	0,1948
DN	0,1948
P-Value	0,476039

The StatAdvisor

This pane shows the results of tests run to determine whether ProfMed_D28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that ProfMed_D28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for ProfMax_D0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,10836
DMINUS	0,184213
DN	0,184213
P-Value	0,556553

The StatAdvisor

This pane shows the results of tests run to determine whether ProfMax_D0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that ProfMax_D0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for ProfMaxD28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,106543
DMINUS	0,176146
DN	0,176146
P-Value	0,5973

The StatAdvisor

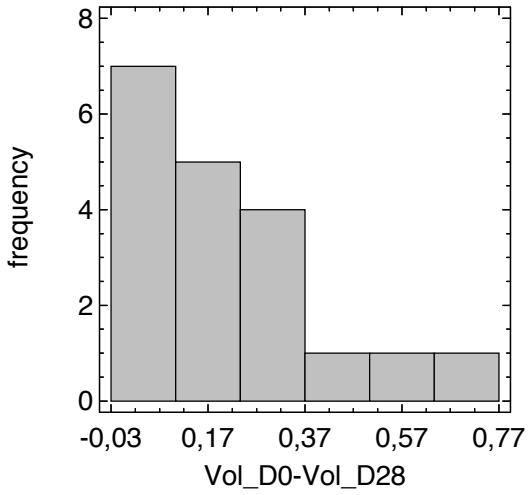
This pane shows the results of tests run to determine whether ProfMaxD28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that ProfMaxD28 comes from a normal distribution with 95% confidence.

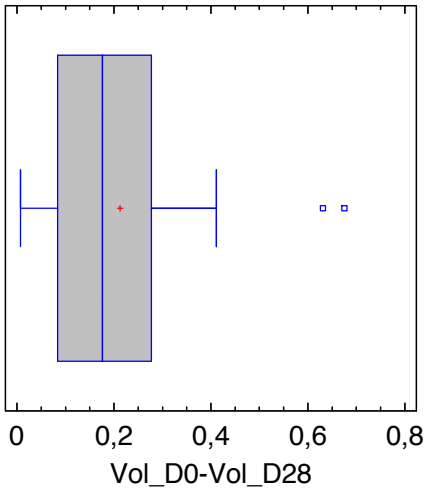
SnapStat: Paired Sample Comparison

Data variable: Vol_D0-Vol_D28
Count = 19
Average = 0,212684
Standard deviation = 0,191099
Coeff. of variation = 89,851%
Minimum = 0,007
Maximum = 0,675
Range = 0,668
Stnd. skewness = 2,30765
Stnd. kurtosis = 1,20069

Histogram



Box-and-Whisker Plot

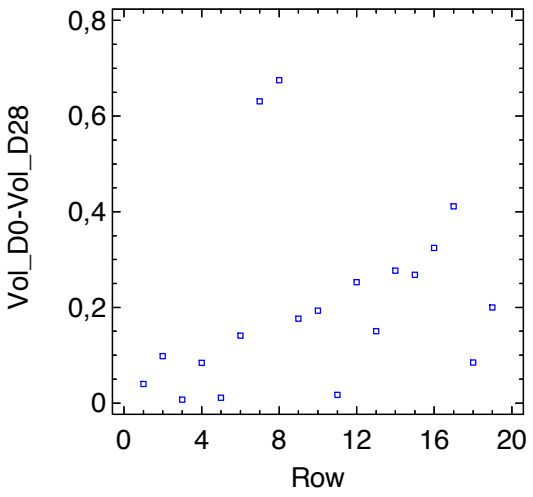


95% confidence intervals
Mean difference: 0,212684 +/- 0,0921069 [0,120577; 0,304791]
Sigma: [0,144397; 0,282602]

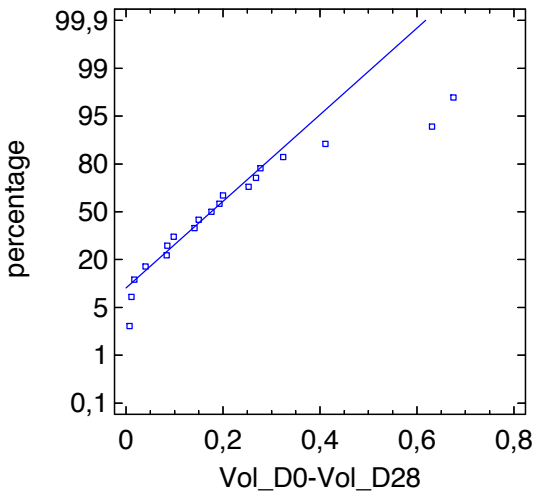
Comparison of Means
Null hypothesis: difference = 0
t statistic = 4,85125
Two-sided P-value = 0,0001

Diagnostics
Shapiro-Wilks P-value = 0,0116
Lag 1 autocorrelation = 0,387829 +/- 0,449647

Time Sequence Plot



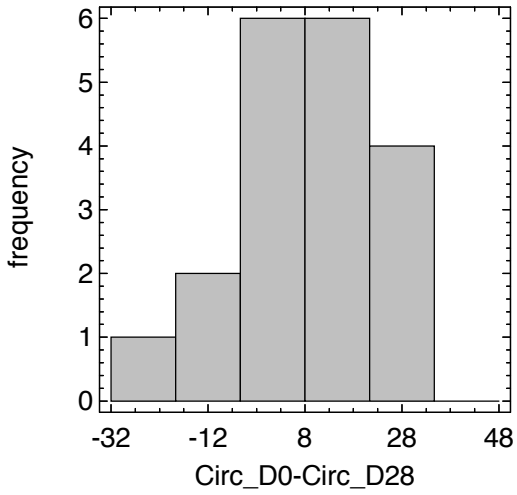
Normal Probability Plot



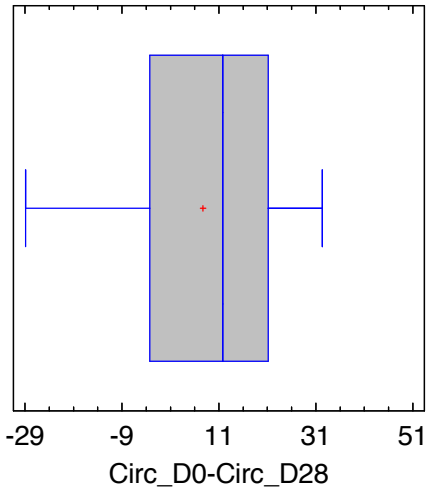
SnapStat: Paired Sample Comparison

Data variable: Circ_D0-Circ_D28
Count = 19
Average = 7,67684
Standard deviation = 16,5987
Coeff. of variation = 216,218%
Minimum = -28,89
Maximum = 32,34
Range = 61,23
Stnd. skewness = -0,614742
Stnd. kurtosis = -0,420095

Histogram



Box-and-Whisker Plot

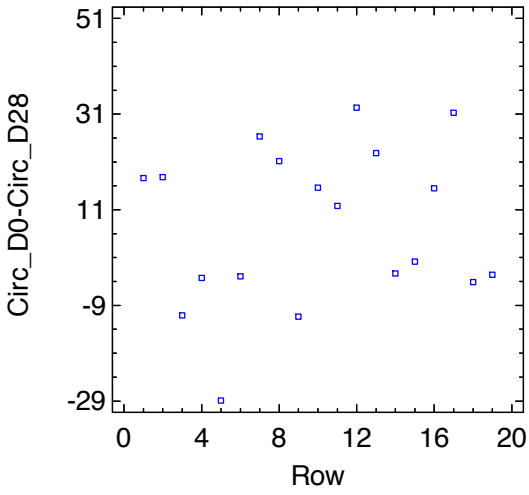


95% confidence intervals
Mean difference: 7,67684 +/- 8,00034 [-0,3235; 15,6772]
Sigma: [12,5422; 24,5466]

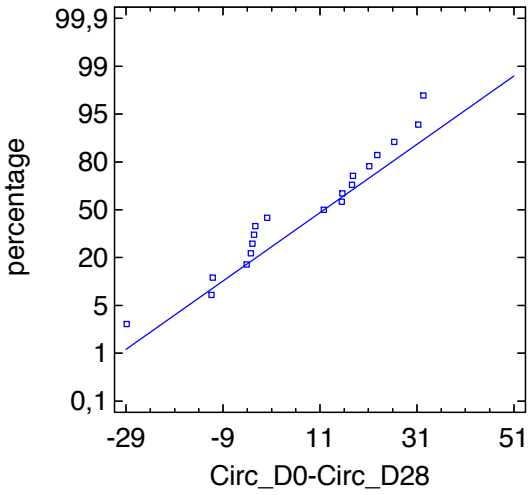
Comparison of Means
Null hypothesis: difference = 0
t statistic = 2,01597
Two-sided P-value = 0,0590

Diagnostics
Shapiro-Wilks P-value = 0,3411
Lag 1 autocorrelation = 0,191467 +/- 0,449647

Time Sequence Plot



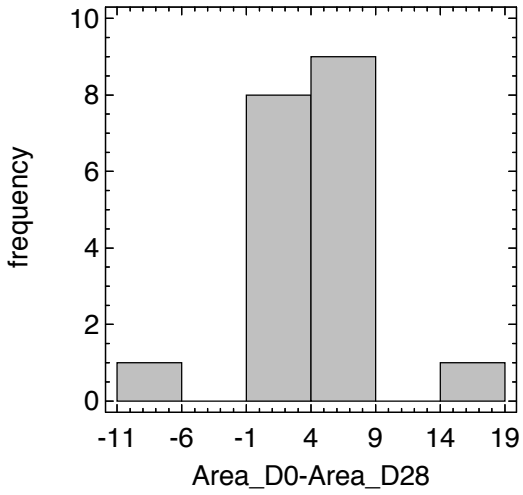
Normal Probability Plot



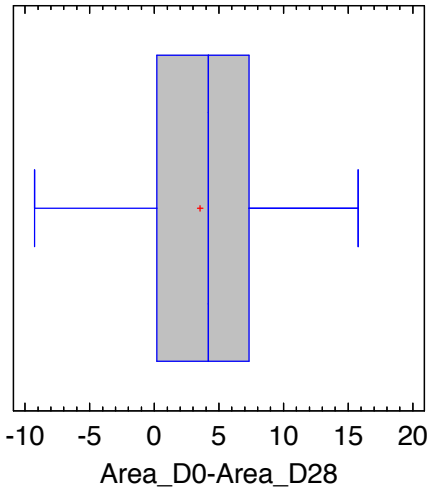
SnapStat: Paired Sample Comparison

Data variable: Area_D0-Area_D28
Count = 19
Average = 3,544
Standard deviation = 5,16588
Coeff. of variation = 145,764%
Minimum = -9,263
Maximum = 15,762
Range = 25,025
Stnd. skewness = -0,147926
Stnd. kurtosis = 1,82304

Histogram



Box-and-Whisker Plot

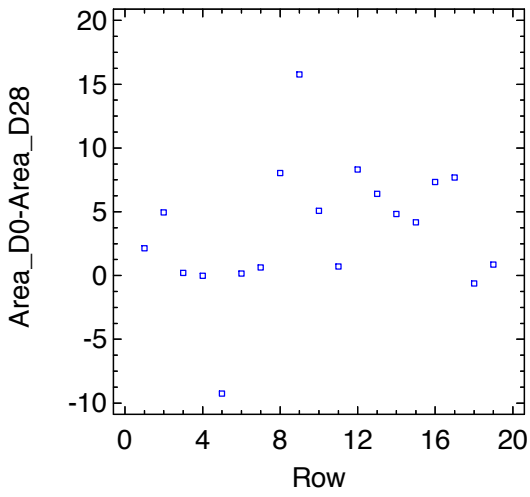


95% confidence intervals
Mean difference: 3,544 +/- 2,48988 [1,05412; 6,03388]
Sigma: [3,9034; 7,63942]

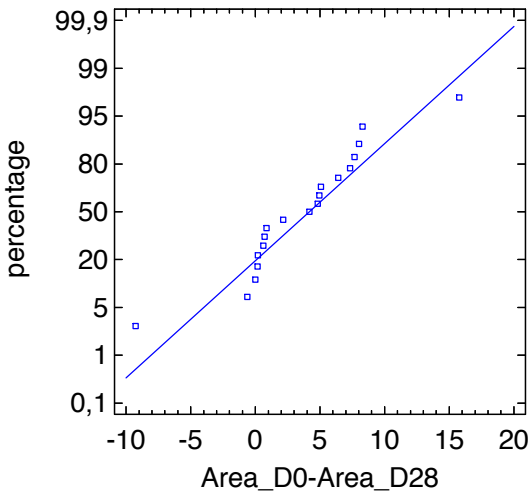
Comparison of Means
Null hypothesis: difference = 0
t statistic = 2,99038
Two-sided P-value = 0,0078

Diagnostics
Shapiro-Wilks P-value = 0,2132
Lag 1 autocorrelation = 0,367659 +/- 0,449647

Time Sequence Plot



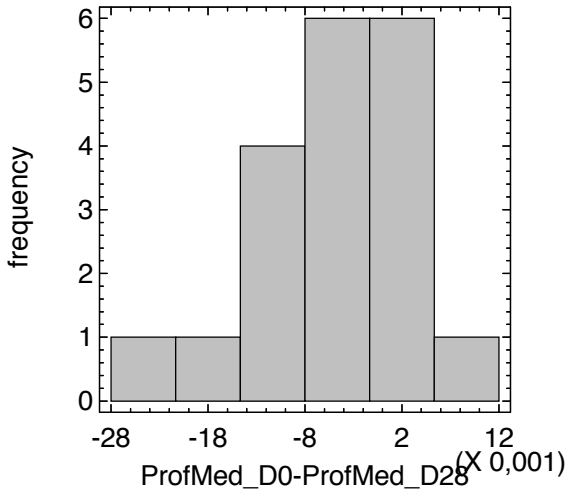
Normal Probability Plot



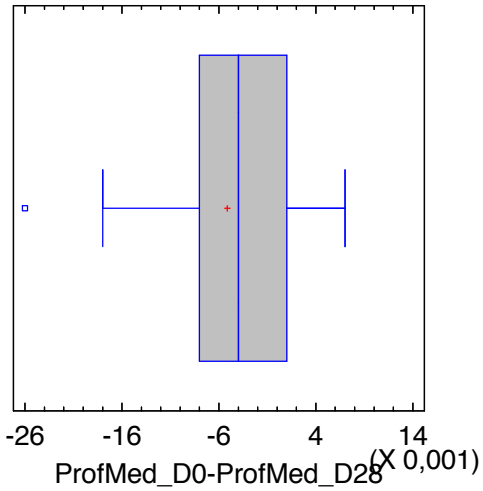
SnapStat: Paired Sample Comparison

Data variable: ProfMed_D0-ProfMed_D28
Count = 19
Average = -0,00515789
Standard deviation = 0,00822775
Coeff. of variation = -159,518%
Minimum = -0,026
Maximum = 0,007
Range = 0,033
Stnd. skewness = -1,50721
Stnd. kurtosis = 0,868937

Histogram



Box-and-Whisker Plot

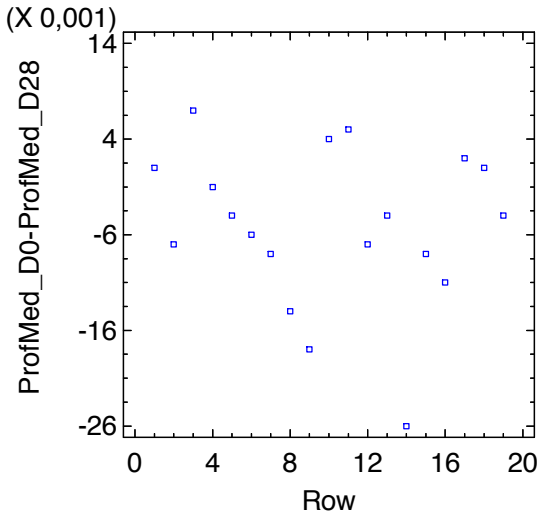


95% confidence intervals
Mean difference: -0,00515789 +/- 0,00396566 [-0,00912355; -0,0
Sigma: [0,00621699; 0,0121674]

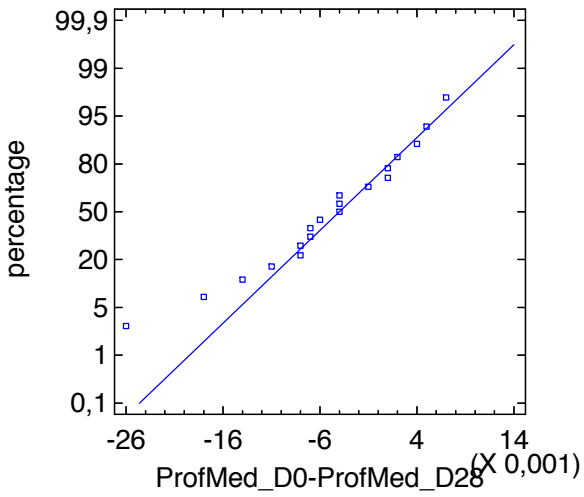
Comparison of Means
Null hypothesis: difference = 0
t statistic = -2,73255
Two-sided P-value = 0,0137

Diagnostics
Shapiro-Wilks P-value = 0,3870
Lag 1 autocorrelation = 0,145583 +/- 0,449647

Time Sequence Plot



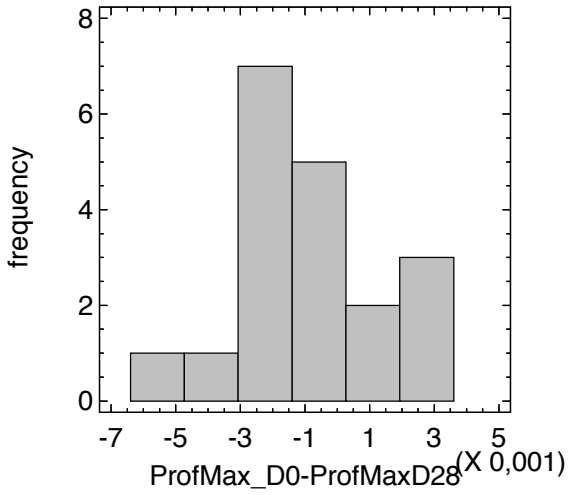
Normal Probability Plot



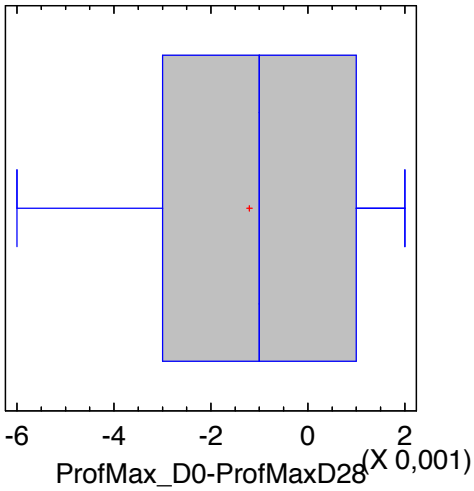
SnapStat: Paired Sample Comparison

Data variable: ProfMax_D0-ProfMaxD28
Count = 19
Average = -0,00121053
Standard deviation = 0,00222558
Coeff. of variation = -183,852%
Minimum = -0,006
Maximum = 0,002
Range = 0,008
Stnd. skewness = -0,315853
Stnd. kurtosis = -0,365627

Histogram



Box-and-Whisker Plot

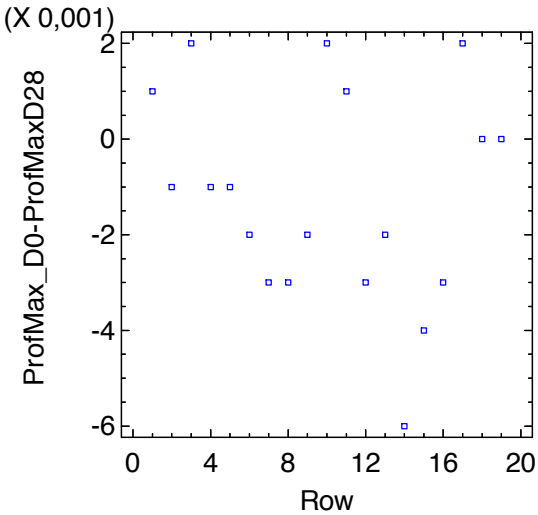


95% confidence intervals
Mean difference: -0,00121053 +/- 0,0010727 [-0,00228322; -0,00
Sigma: [0,00168168; 0,00329124]

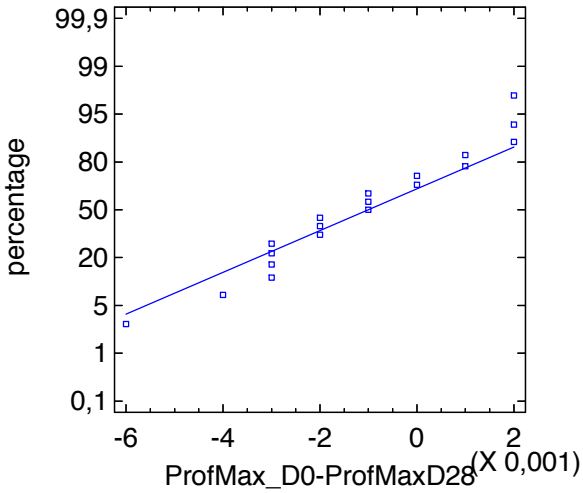
Comparison of Means
Null hypothesis: difference = 0
t statistic = -2,37087
Two-sided P-value = 0,0291

Diagnostics
Shapiro-Wilks P-value = 0,4040
Lag 1 autocorrelation = 0,353104 +/- 0,449647

Time Sequence Plot



Normal Probability Plot



Goodness-of-Fit Tests for Thick_EpiD0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,320086
DMINUS	0,167412
DN	0,320086
P-Value	0,0220405

The StatAdvisor

This pane shows the results of tests run to determine whether Thick_EpiD0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is less than 0,05, we can reject the idea that Thick_EpiD0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Thick_EpiD28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,154207
DMINUS	0,125346
DN	0,154207
P-Value	0,672188

The StatAdvisor

This pane shows the results of tests run to determine whether Thick_EpiD28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Thick_EpiD28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Thick_DermD0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,214988
DMINUS	0,125497
DN	0,214988
P-Value	0,261999

The StatAdvisor

This pane shows the results of tests run to determine whether Thick_DermD0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Thick_DermD0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Thick_Derm28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,270828
DMINUS	0,179516
DN	0,270828
P-Value	0,0793318

The StatAdvisor

This pane shows the results of tests run to determine whether Thick_Derm28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Thick_Derm28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Dens_EpiD0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,101145
DMINUS	0,169857
DN	0,169857
P-Value	0,549523

The StatAdvisor

This pane shows the results of tests run to determine whether Dens_EpiD0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Dens_EpiD0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Dens_EpiD28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,123999
DMINUS	0,223779
DN	0,223779
P-Value	0,221005

The StatAdvisor

This pane shows the results of tests run to determine whether Dens_EpiD28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Dens_EpiD28 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Dens_DermD0

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,128911
DMINUS	0,0702415
DN	0,128911
P-Value	0,858074

The StatAdvisor

This pane shows the results of tests run to determine whether Dens_DermD0 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Dens_DermD0 comes from a normal distribution with 95% confidence.

Goodness-of-Fit Tests for Dens_DermD28

Kolmogorov-Smirnov Test

	Normal
DPLUS	0,138099
DMINUS	0,0796783
DN	0,138099
P-Value	0,795502

The StatAdvisor

This pane shows the results of tests run to determine whether Dens_DermD28 can be adequately modeled by a normal distribution.

Since the smallest P-value amongst the tests performed is greater than or equal to 0,05, we can not reject the idea that Dens_DermD28 comes from a normal distribution with 95% confidence.

Paired Samples - Thick_EpiD0 & Thick_EpiD28

Data variable: Thick_EpiD0-Thick_EpiD28
22 values ranging from -28,34 to 155,67

The StatAdvisor
This procedure is designed to test for significant differences between two data samples where the data were collected as pairs. It will calculate various statistics and graphs for the differences between the paired data. Also included in the procedure are tests designed to determine whether the mean difference is equal to zero. Use the Tabular Options and Graphical Options buttons on the analysis toolbar to access these different procedures.

Summary Statistics for Thick_EpiD0-Thick_EpiD28

Count	22
Average	4,25864
Standard deviation	36,156
Coeff. of variation	849,005%
Minimum	-28,34
Maximum	155,67
Range	184,01
Stnd. skewness	7,16773
Stnd. kurtosis	15,4314

The StatAdvisor

This table shows summary statistics for Thick_EpiD0-Thick_EpiD28. It includes measures of central tendency, measures of variability, and measures of shape. Of particular interest here are the standardized skewness and standardized kurtosis, which can be used to determine whether the sample comes from a normal distribution. Values of these statistics outside the range of -2 to +2 indicate significant departures from normality, which would tend to invalidate any statistical test regarding the standard deviation. In this case, the standardized skewness value is not within the range expected for data from a normal distribution. The standardized kurtosis value is not within the range expected for data from a normal distribution.

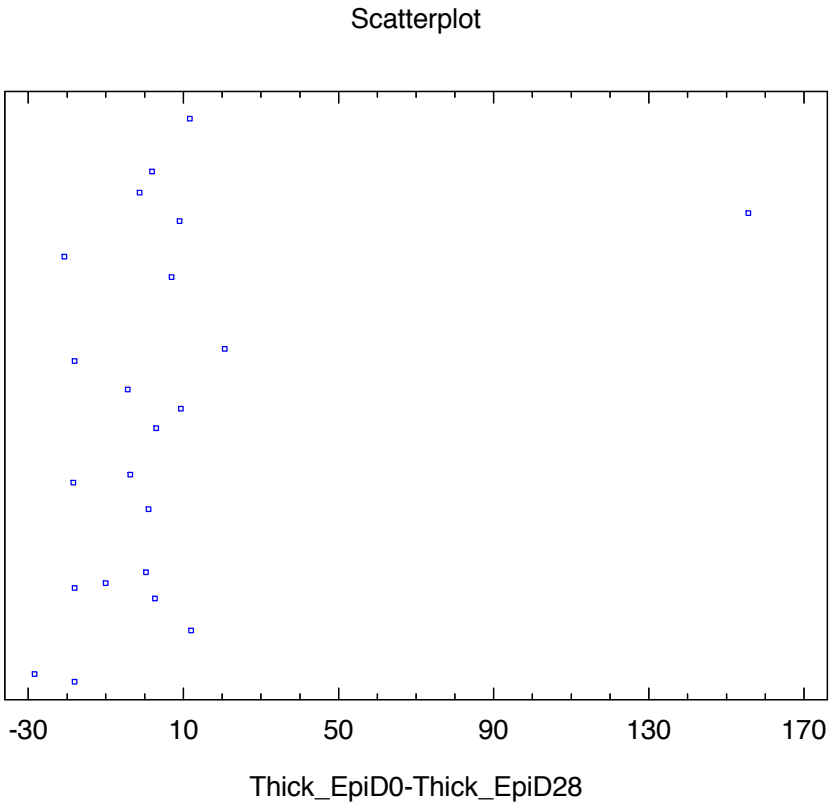
Hypothesis Tests for Thick_EpiD0-Thick_EpiD28
Sample mean = 4,25864
Sample median = 0,67
Sample standard deviation = 36,156

signed rank test
Null hypothesis: median = 0,0
Alternative: not equal

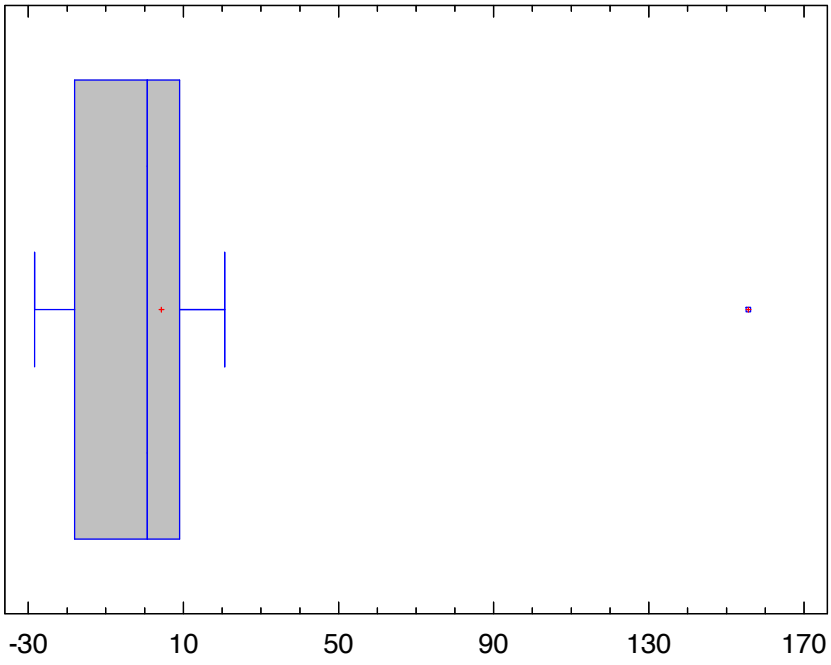
Average rank of values below hypothesized median: 13,65
Average rank of values above hypothesized median: 9,70833

Large sample test statistic = 0,308525 (continuity correction applied)
P-Value = 0,757679
Do not reject the null hypothesis for alpha = 0,05.

The StatAdvisor
This pane displays the results of tests concerning the population from which the sample of Thick_EpiD0-Thick_EpiD28 comes. The signed rank test tests the null hypothesis that the median Thick_EpiD0-Thick_EpiD28 equals 0,0 versus the alternative hypothesis that the median Thick_EpiD0-Thick_EpiD28 is not equal to 0,0. It is based on comparing the average ranks of values above and below the hypothesized median. Since the P-value for this test is greater than or equal to 0,05, we cannot reject the null hypothesis at the 95,0% confidence level. The sign and signed rank tests are less sensitive to the presence of outliers but are somewhat less powerful than the t-test if the data all come from a single normal distribution.


Scatterplot
-30
10
50
90
130
170
Thick_EpiD0-Thick_EpiD28

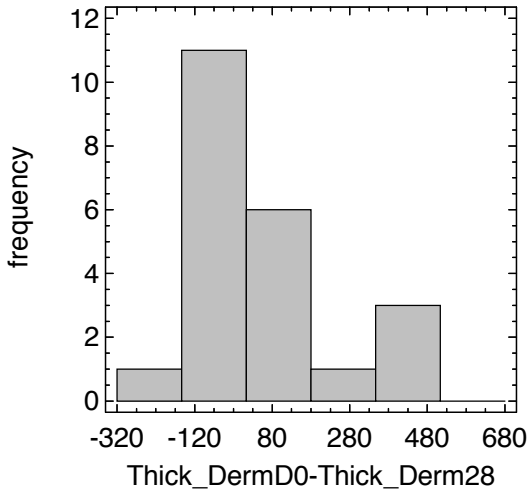
Box-and-Whisker Plot



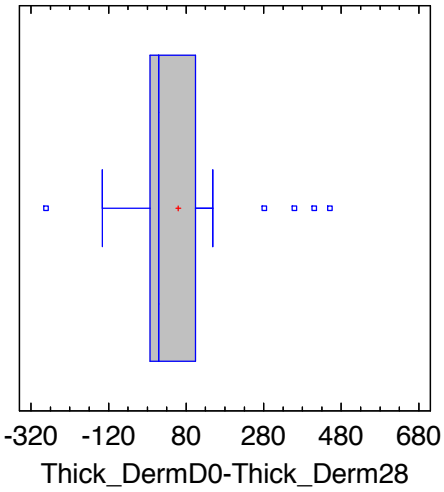
SnapStat: Paired Sample Comparison

Data variable: Thick_DermD0-Thick_Derm28
Count = 22
Average = 60,0005
Standard deviation = 177,042
Coeff. of variation = 295,068%
Minimum = -281,33
Maximum = 450,67
Range = 732,0
Stnd. skewness = 1,52765
Stnd. kurtosis = 0,691291

Histogram



Box-and-Whisker Plot

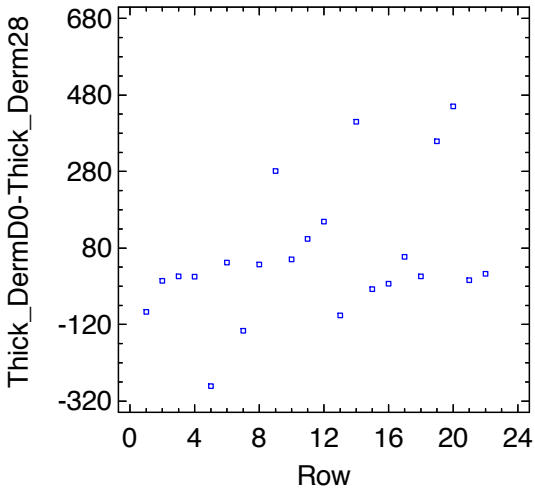


95% confidence intervals
Mean difference: 60,0005 +/- 78,4963 [-18,4958; 138,497]
Sigma: [136,208; 253,005]

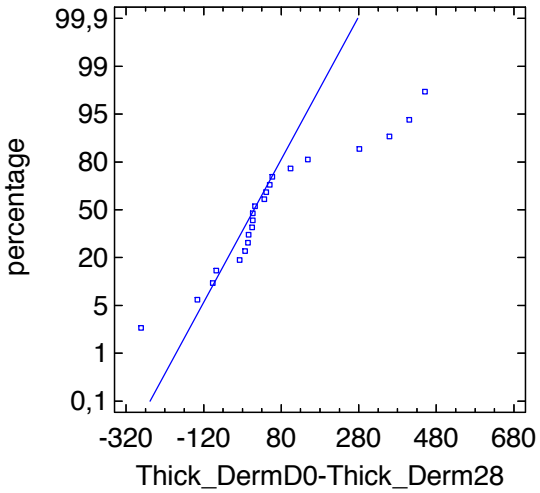
Comparison of Means
Null hypothesis: difference = 0
t statistic = 1,5896
Two-sided P-value = 0,1269

Diagnostics
Shapiro-Wilks P-value = 0,0217
Lag 1 autocorrelation = 0,0486733 +/- 0,417867

Time Sequence Plot



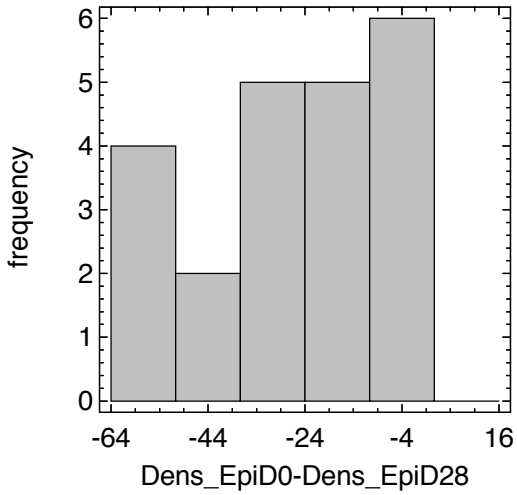
Normal Probability Plot



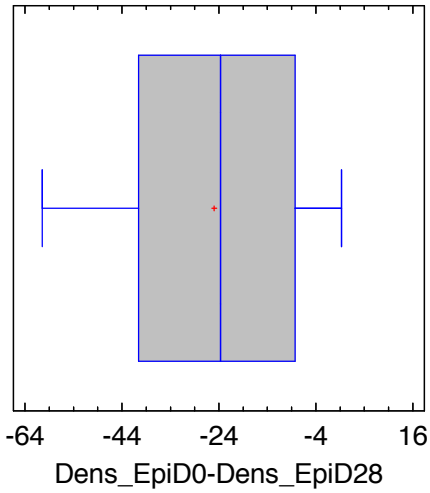
SnapStat: Paired Sample Comparison

Data variable: Dens_EpiD0-Dens_EpiD28
Count = 22
Average = -24,9977
Standard deviation = 19,2228
Coeff. of variation = -76,8981%
Minimum = -60,43
Maximum = 1,29
Range = 61,72
Stnd. skewness = -0,802765
Stnd. kurtosis = -0,904922

Histogram



Box-and-Whisker Plot

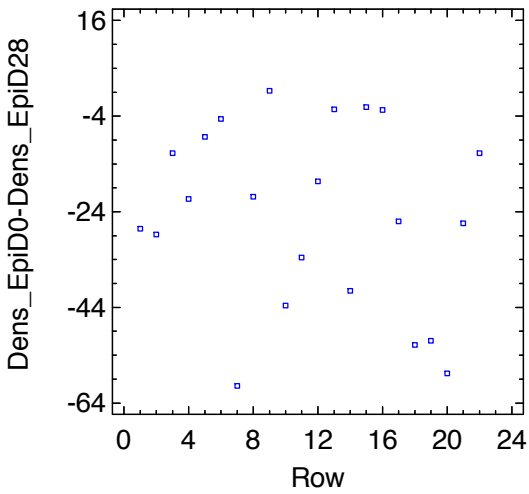


95% confidence intervals
Mean difference: -24,9977 +/- 8,52292 [-33,5206; -16,4748]
Sigma: [14,7891; 27,4706]

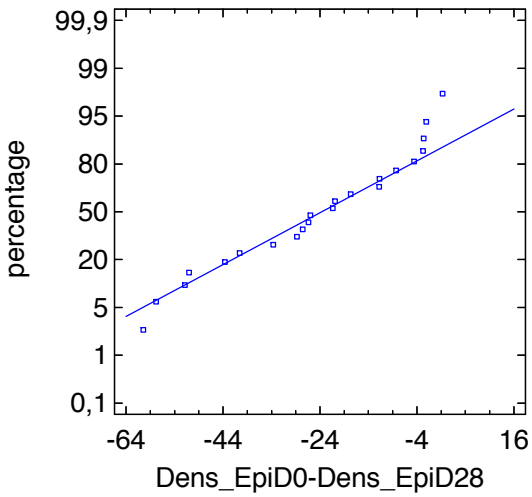
Comparison of Means
Null hypothesis: difference = 0
t statistic = -6,09952
Two-sided P-value = 0,0000

Diagnostics
Shapiro-Wilks P-value = 0,1720
Lag 1 autocorrelation = 0,104486 +/- 0,417867

Time Sequence Plot



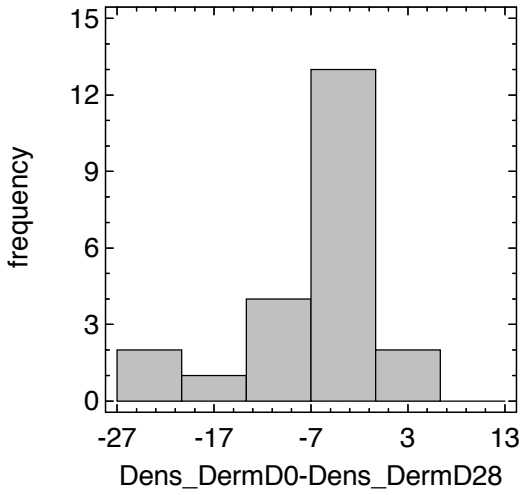
Normal Probability Plot



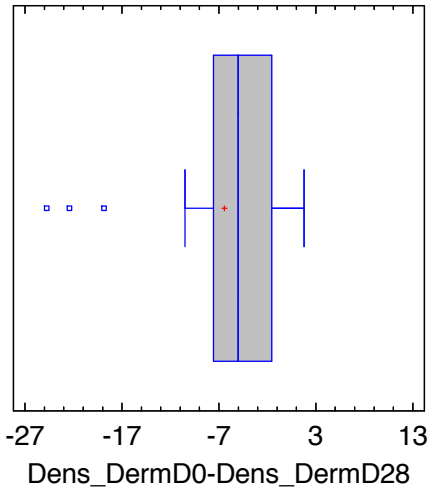
SnapStat: Paired Sample Comparison

Data variable: Dens_DermD0-Dens_DermD28
Count = 22
Average = -6,43318
Standard deviation = 7,06886
Coeff. of variation = -109,881%
Minimum = -24,75
Maximum = 1,79
Range = 26,54
Stnd. skewness = -3,00284
Stnd. kurtosis = 1,82721

Histogram



Box-and-Whisker Plot

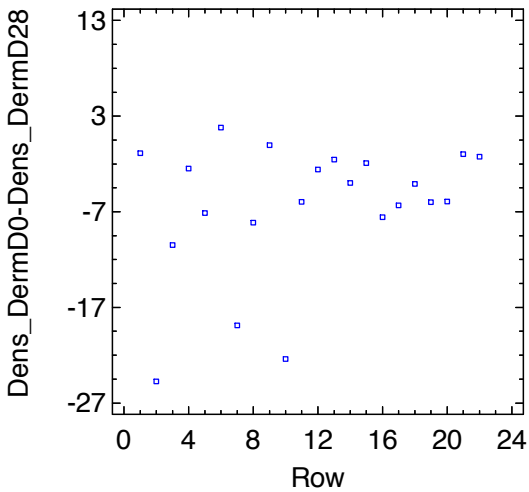


95% confidence intervals
Mean difference: -6,43318 +/- 3,13416 [-9,56734; -3,29902]
Sigma: [5,43843; 10,1019]

Comparison of Means
Null hypothesis: difference = 0
t statistic = -4,26862
Two-sided P-value = 0,0003

Diagnostics
Shapiro-Wilks P-value = 0,0005
Lag 1 autocorrelation = -0,17443 +/- 0,417867

Time Sequence Plot



Normal Probability Plot