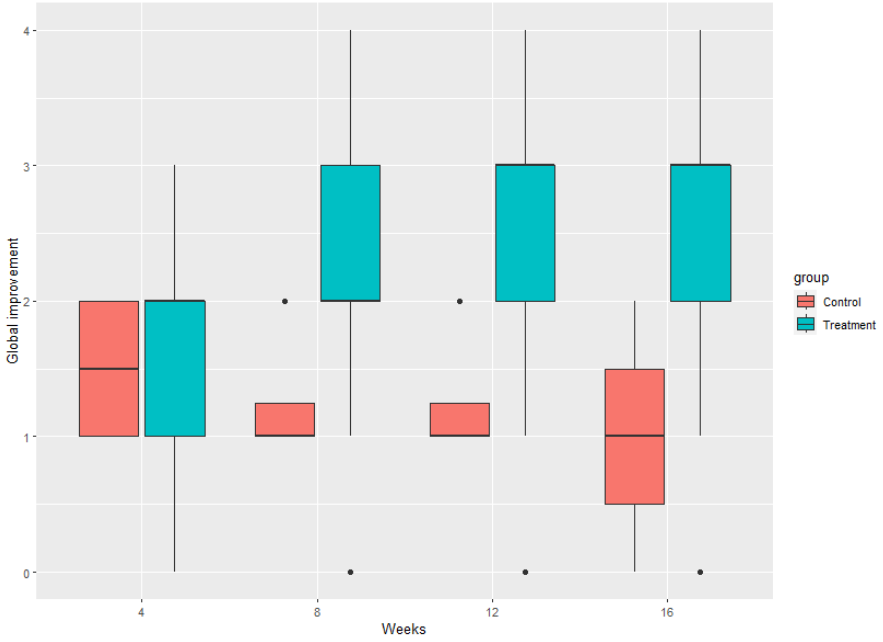
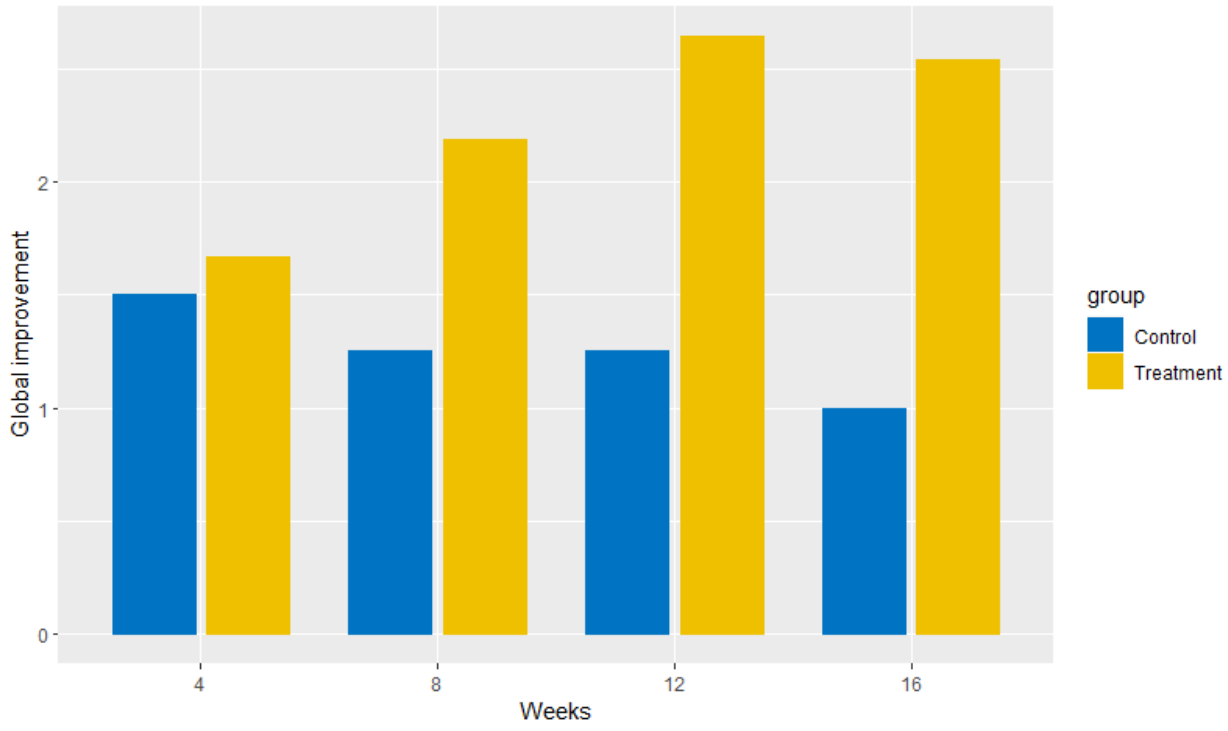
Patient demographics

There are 20 patients, 16 in the Treatment group (all females), and 4 in the control group (two males and two females). Mean age for the treatment group is 52.69, and the median is 54.5. For the control group mean/median are 45.25/47.5. In the treatment group Asian or Pacific Islander: 3 (19%), Caucasian / White 9 (56%), Multi-race 4 (25%). All patients in the control group are Caucasian / White 4 (100%). In the treatment group, Fitzpatrick skin type is distributed as: I (1): 2 (12.5%), II (2): 4 (25%), III (3): 5 (31%), IV (4): 5 (31%). In the control group: II (2): 1 (25%), III (3): 2 (50%), IV (4): 1(25%).

Change over time

1. **Overall improvement** in the treatment (red) and control (blue)group is show as boxplots. Comparing overall improvement at week 16 between the treatment and control groups, we see that the mean global improvement in the treatment group is 2.5 and in the control group is 1 (p-value=0.09306).

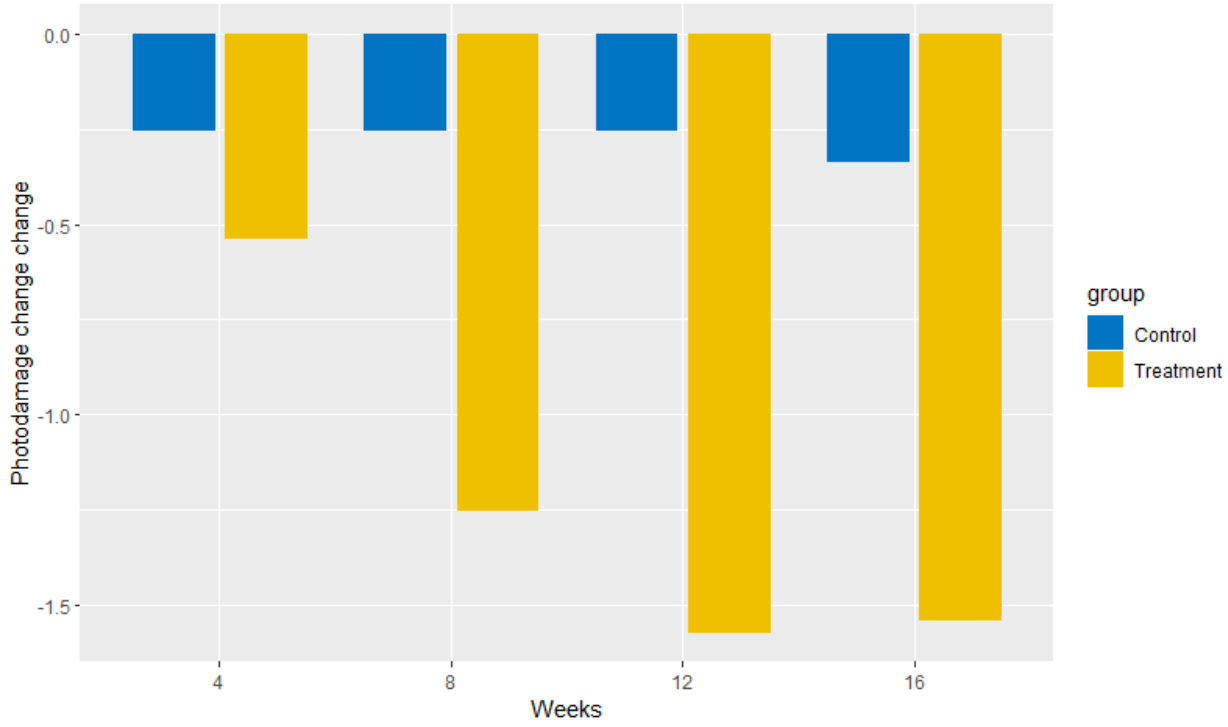


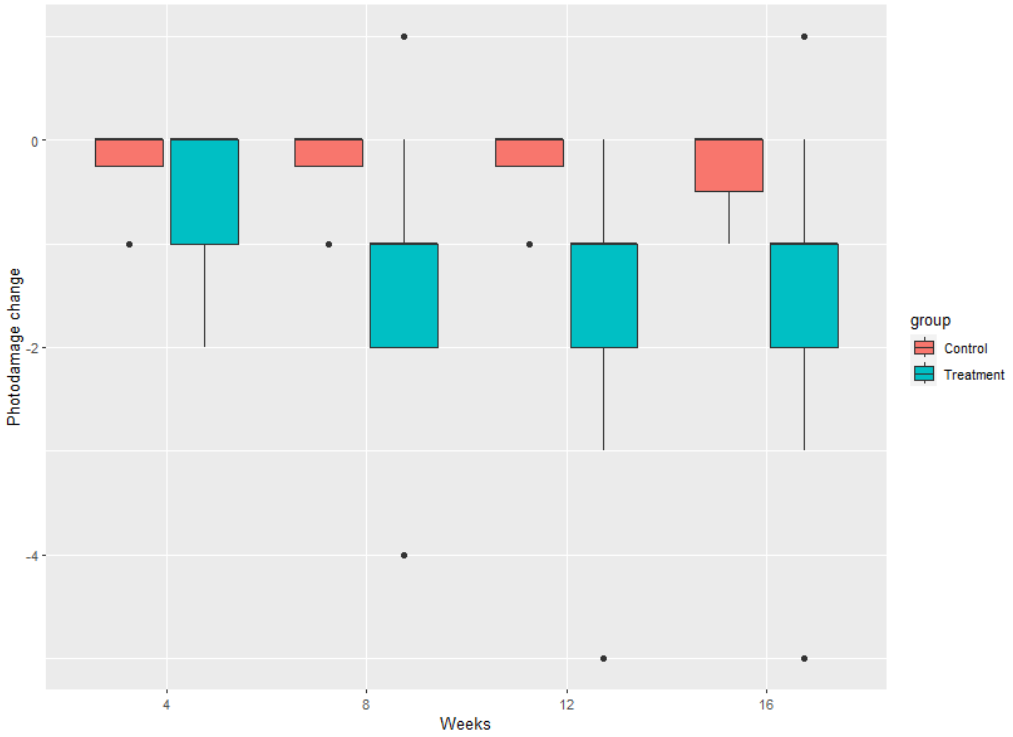


Week	**Treatment**	**Control**	**p-value**
4	1.66667	1.5	0.665621
8	2.1875	1.25	0.028157
12	2.64286	1.25	0.004073
16	2.53846	1	0.093057

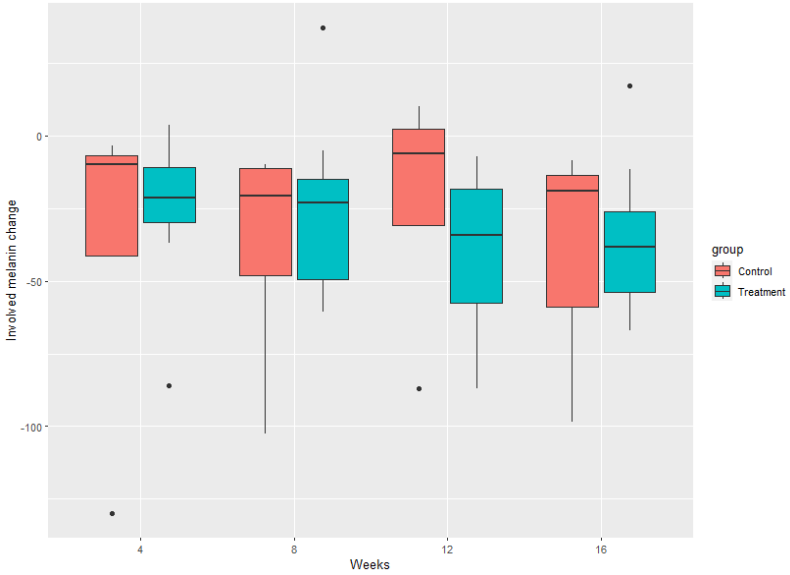
2. **Photodamage**. Analyzed the change in the photodamage with time. Photodamage is the photodamage at the day of the visit minus the photodamage at the first day of the study. Overall picture - photodamage is reduced with time spent using the product. The change between the first assessment and week 16 is significant, -1.538462, p-value = 0.002415, 95 percent confidence interval: [-2.414701, -0.662222]. In the control group the reduction of the photodamage measured at week 16 (-0.333) is less pronounced (p-value = 0.04672).

Week	**Treatment**	**Control**	**p-value**
4	-0.5333	-0.25	0.381205
8	-1.25	-0.25	0.021346
12	-1.5714	-0.25	0.0078
16	-1.5385	-0.33333	0.046723

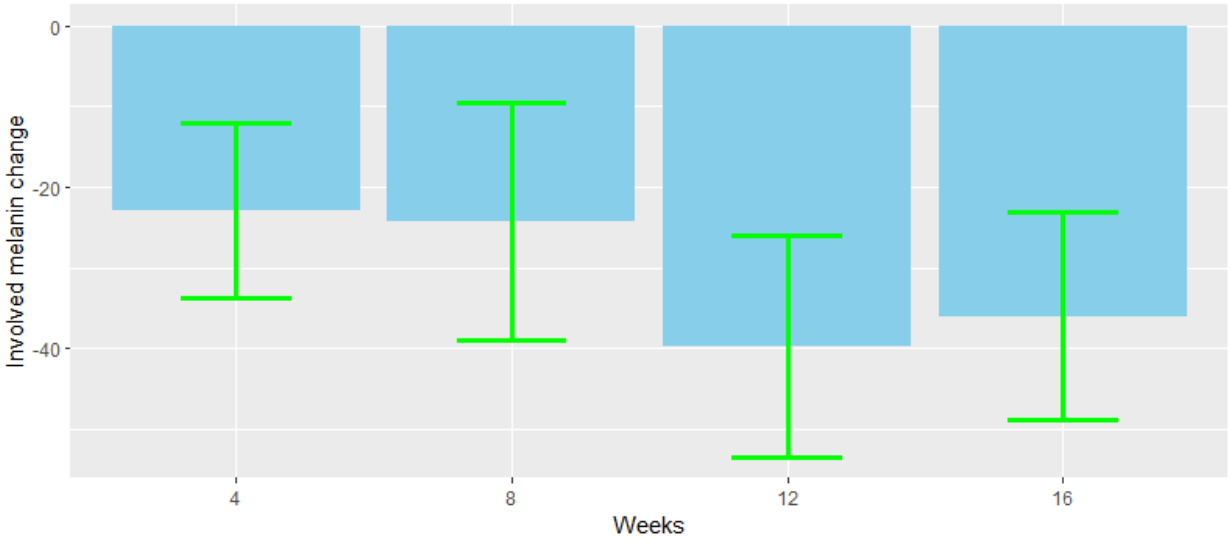


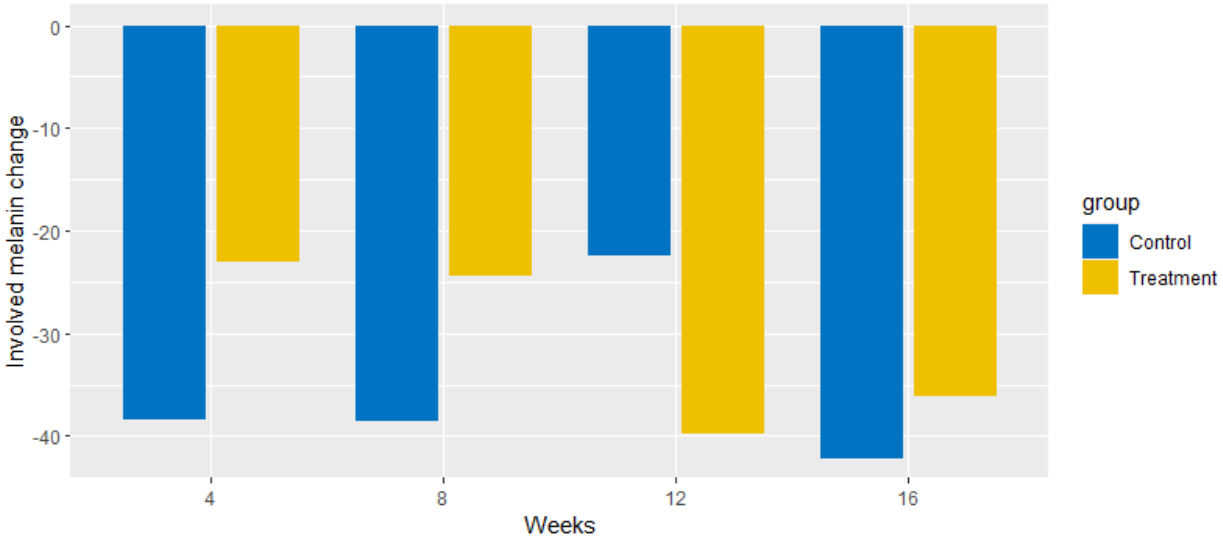

0
-2
-4
Photodamage change
4
8
12
16
Weeks
group
Control
Treatment

3. **Involved melanin** change. First, the change for all subjects between the first visit and week 16 is significant, p-value = 0.0001477, average change is -35.96692. 95 percent confidence interval for the change is [-50.34677, -21.58707]. Difference between treatment and control groups is not significant (p-value=0.8538).

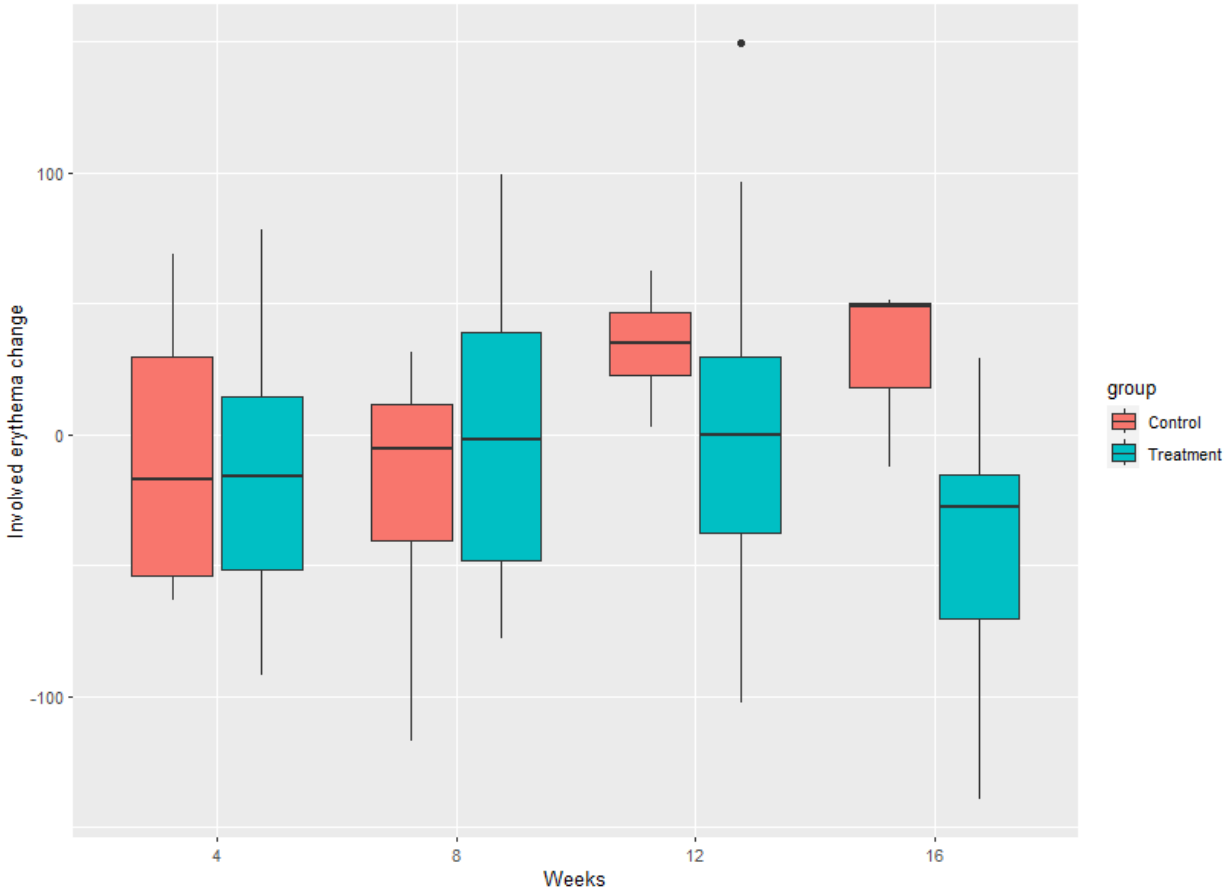


Week	**Treatment**	**Control**	**p-value**
4	-22.9153	-38.275	0.653491
8	-24.2269	-38.425	0.574282
12	-39.6614	-22.275	0.498157
16	-35.9669	-42.00	0.853838

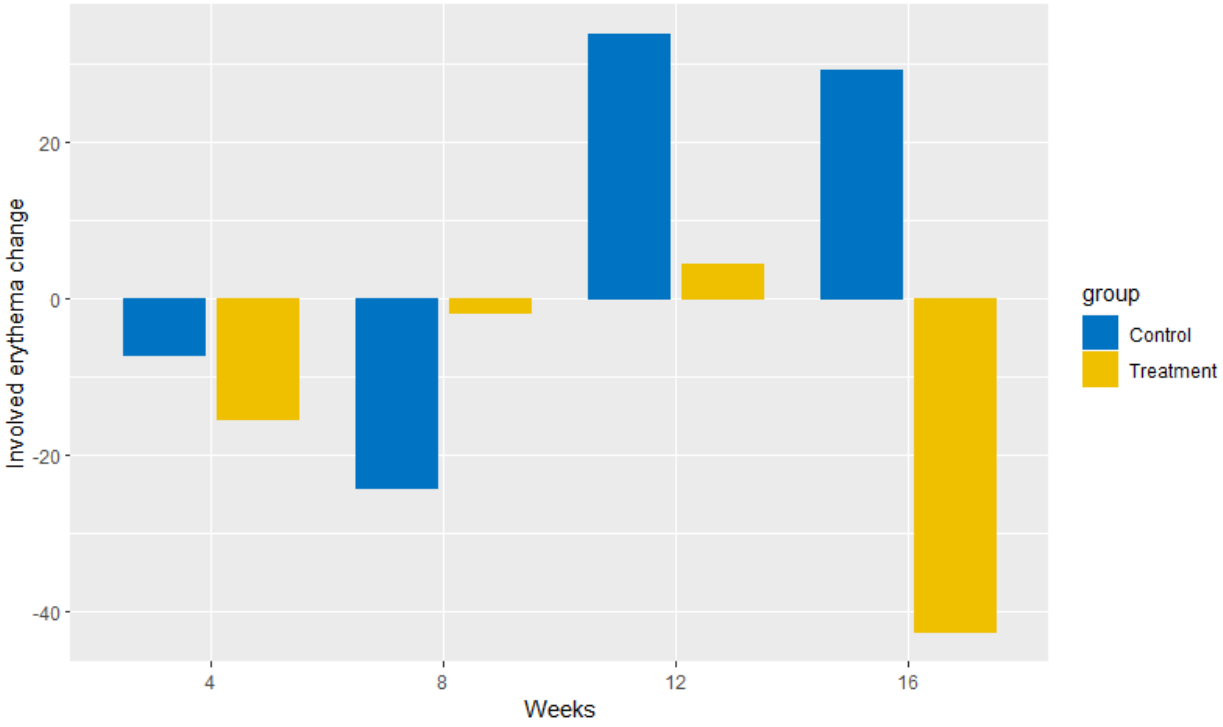

0
-20
-40
Involved melanin change
4
8
12
16
Weeks


0
-10
-20
-30
-40
Involved melanin change
4
8
12
16
Weeks
group
Control
Treatment

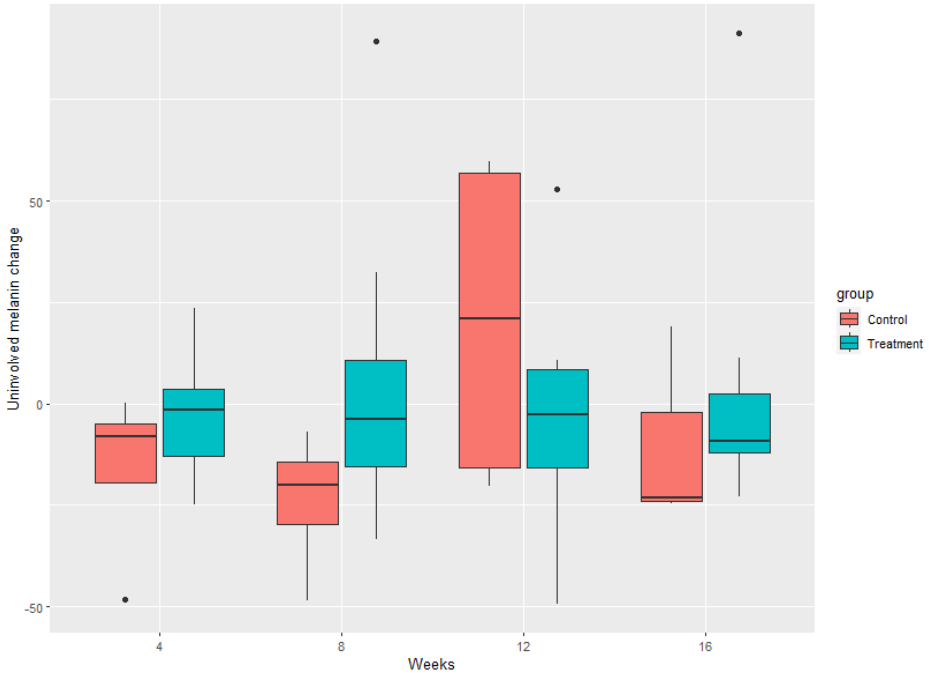
4. The change in **involved erythema** over 16 weesk is significant, -42.59154, p-value = 0.008564. 95 percent confidence interval for the change is: [-72.16447, -13.01860]. The difference between treatment and control group is also significant (p-value = 0.04513). During the week 16 visit, control group patients had average change in involved erythema of 29.26667.



Week	Treatment	Control	p-value
4	-15.267	-7.05	0.81793
8	-1.7188	-24.05	0.557614
12	4.50714	33.875	0.199639
16	-42.592	29.26667	0.045127

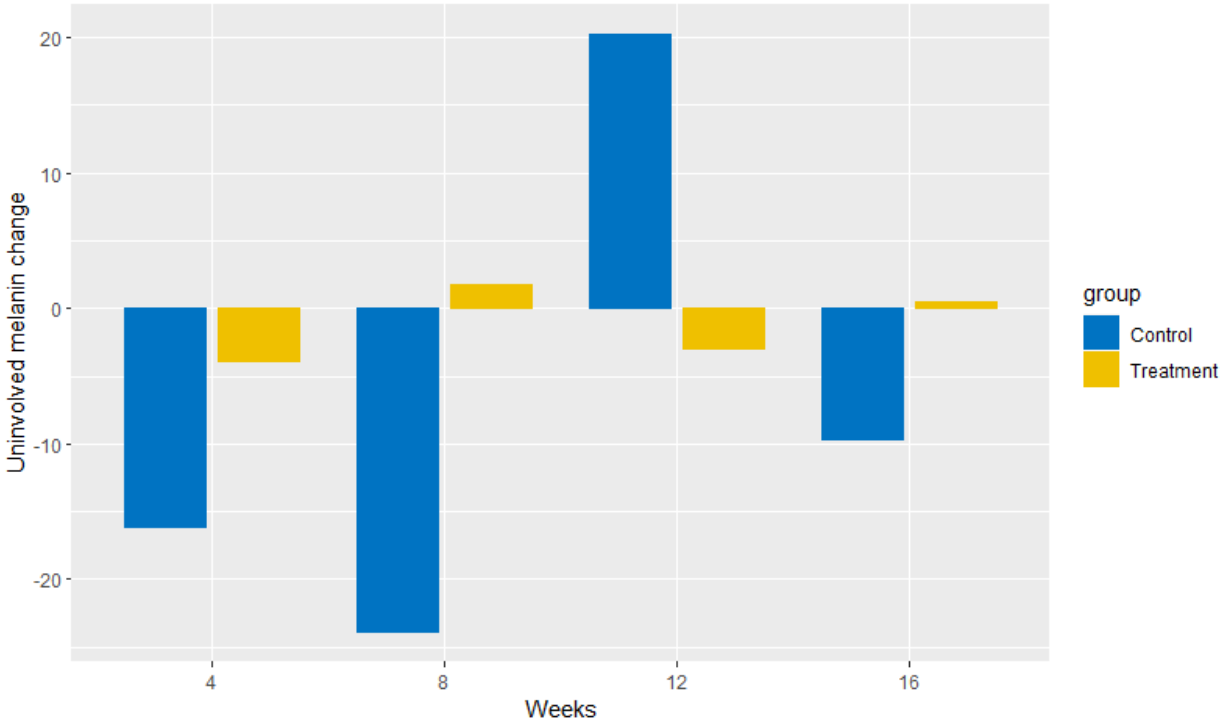


5. **Uninvolved melanin** change is not significant for all time points.

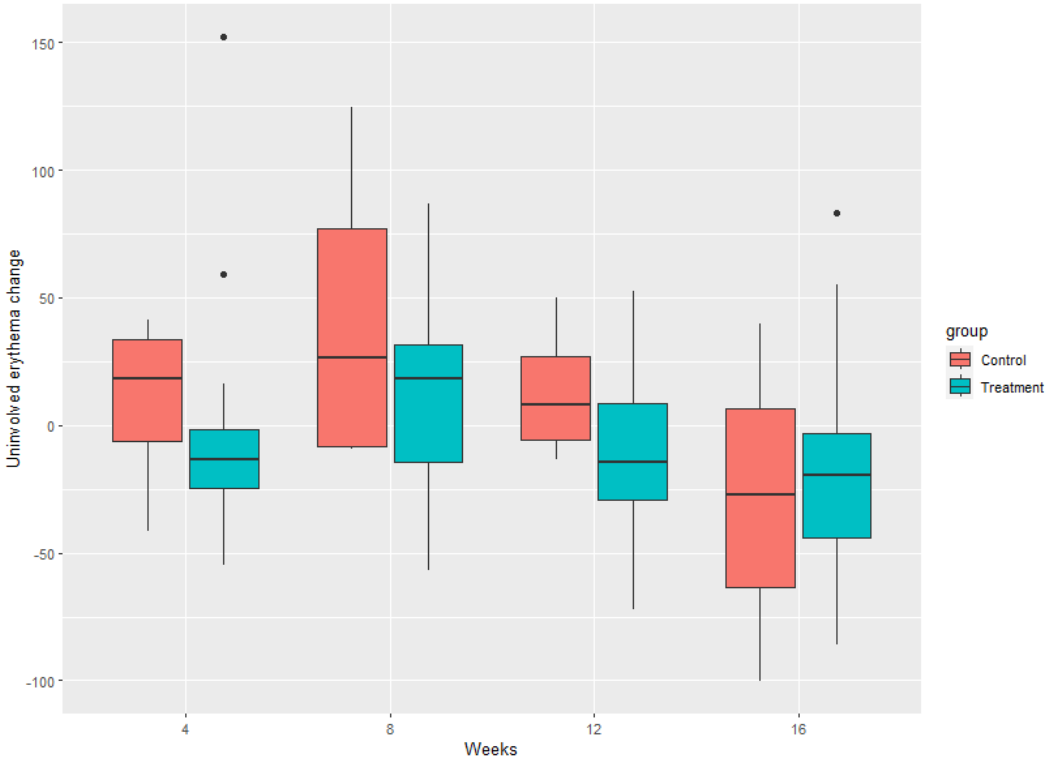


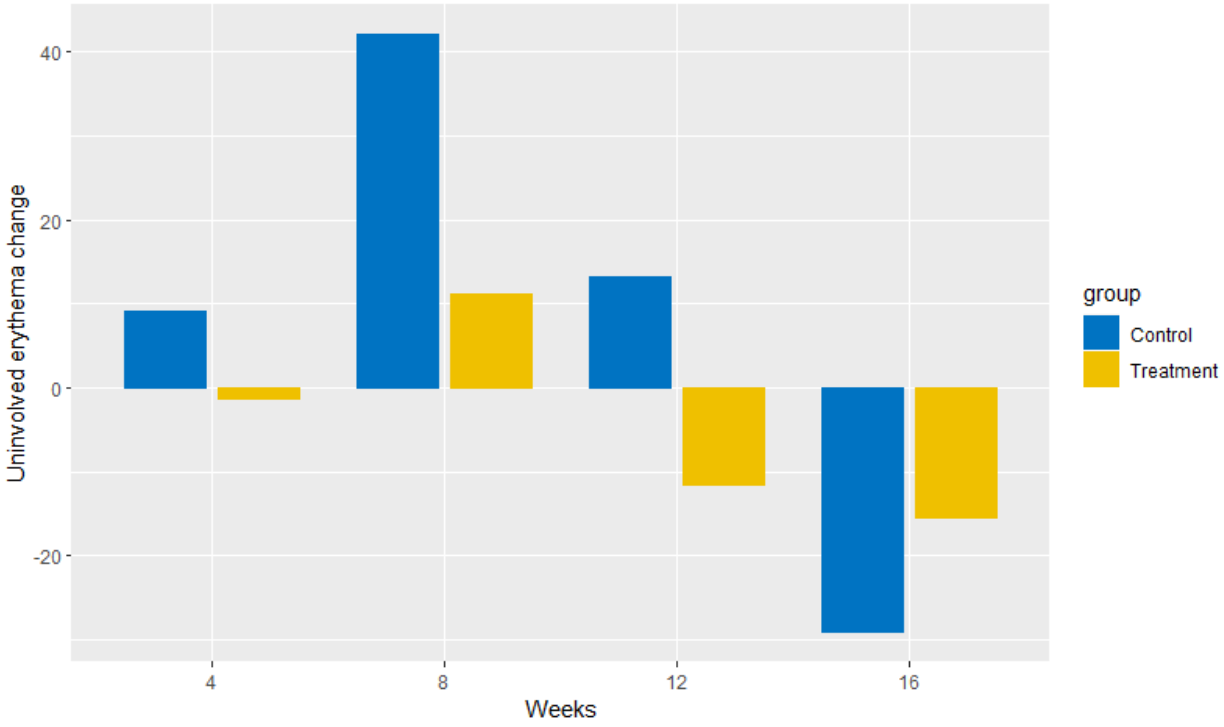
Week	Treatment	Control	p-value
4	-3.8467	-16.1	0.351755

8	1.71875	-23.9	0.057952
12	-2.9764	20.25	0.369524
16	0.52769	-9.66667	0.574529



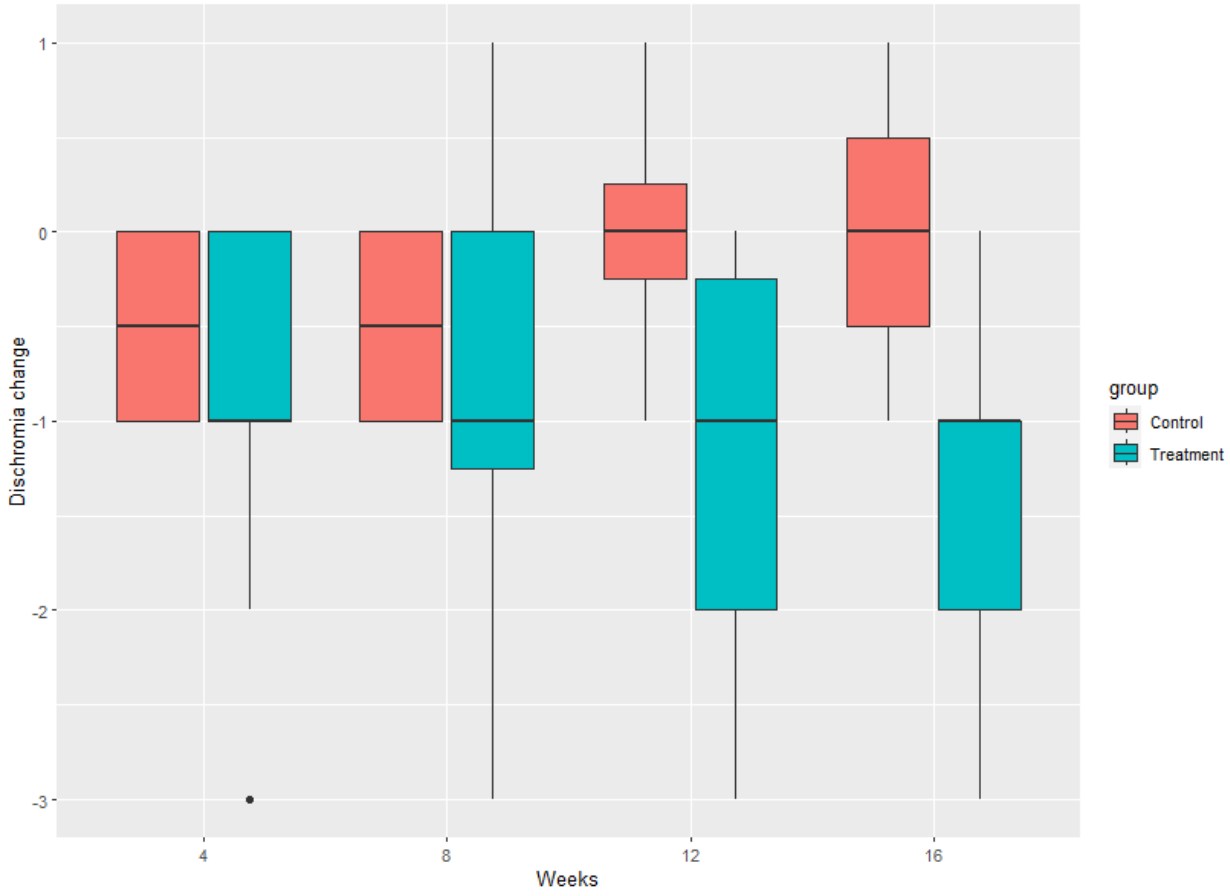
6. **Uninvolved erythema**, the change over 16 weeks of treatment is not significant (p-value 0.3). The difference between the treatment and control groups is also not significant (p-value = 0.7761)



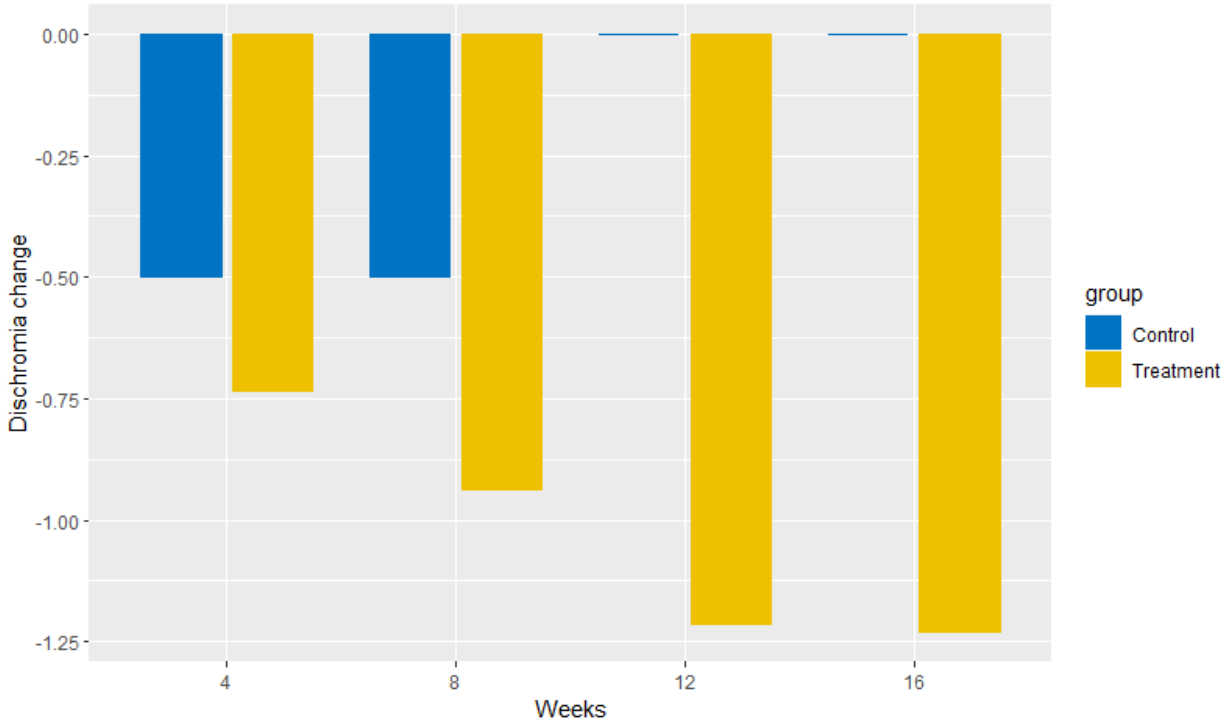


Week	Treatment	Control	p-value
4	-1.38	9.125	0.657122
8	11.1875	42.125	0.413424
12	-11.607	13.175	0.195182
16	-15.505	-29.1	0.776106

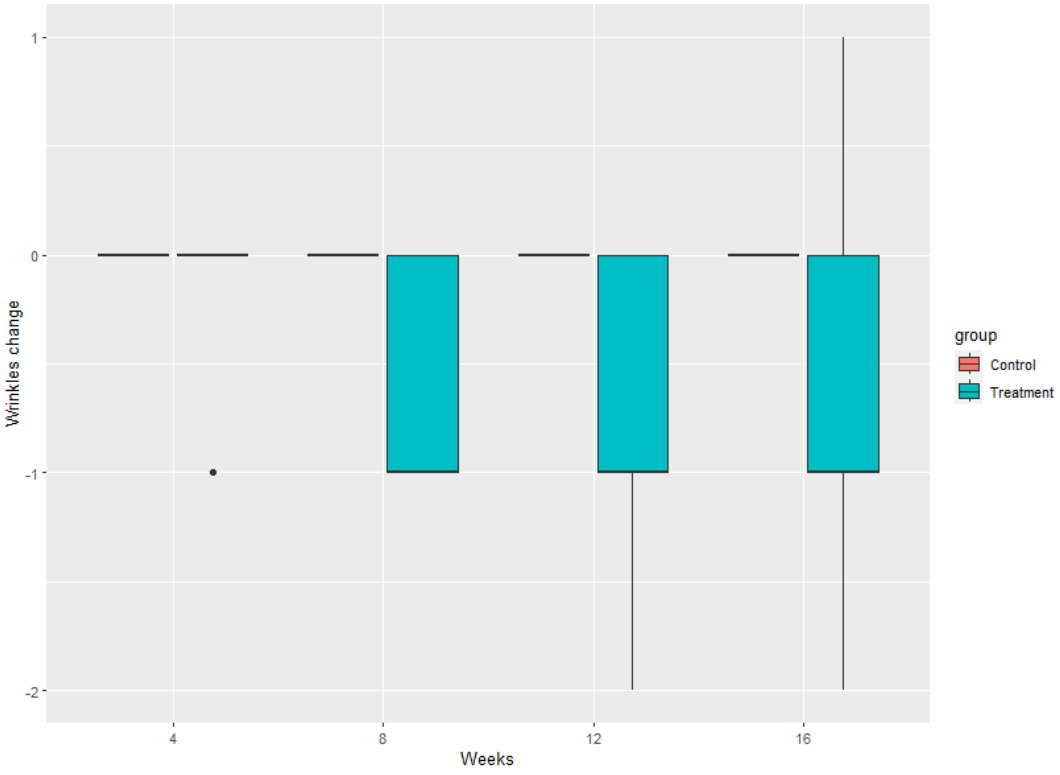
7. **Dyschromia** The change in dyschromia (-1.230769) is significant, p-value = 0.0004425. 95 percent confidence interval: [-1.7908341, -0.6707043].. During the week 16, mean change in dyschromia in the control group was 0. However, the difference between the treatment and control groups is not significant (p-value=0.1514) due to the low number of subjects in the control group.

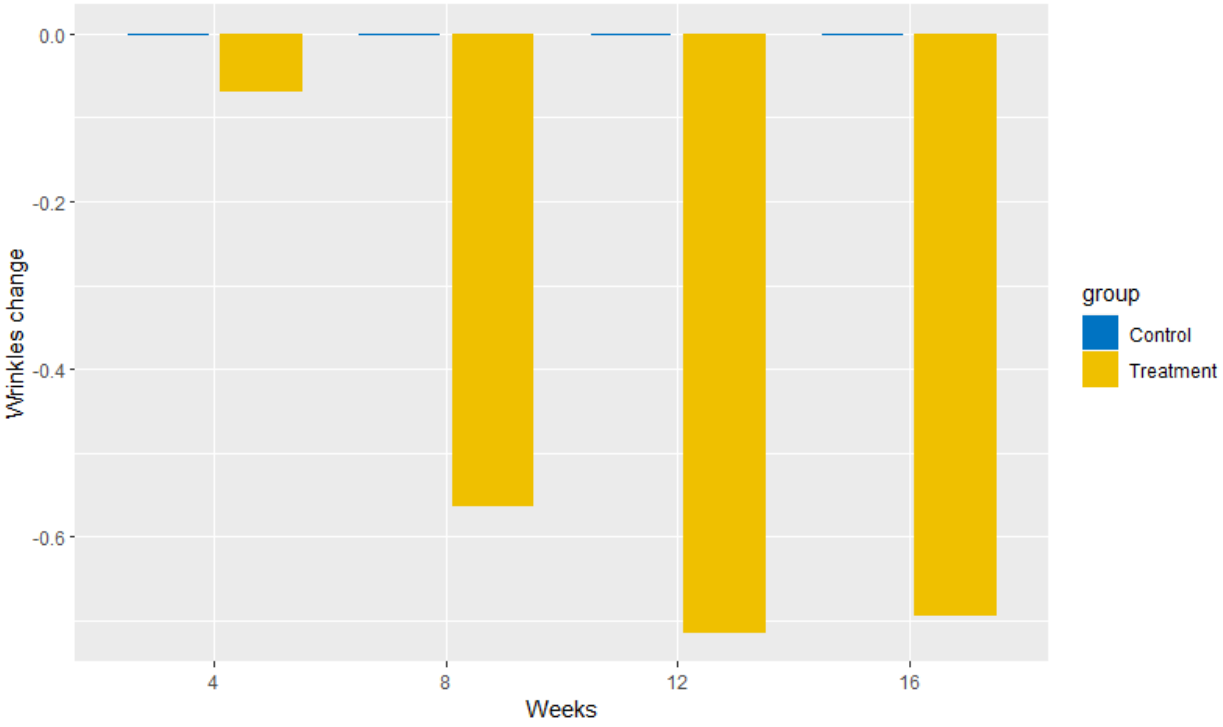


Week	Treatment	Control	p-value
4	-0.7333	-0.5	0.545331
8	-0.9375	-0.5	0.30381
12	-1.2143	0	0.047976
16	-1.2308	0	0.151358



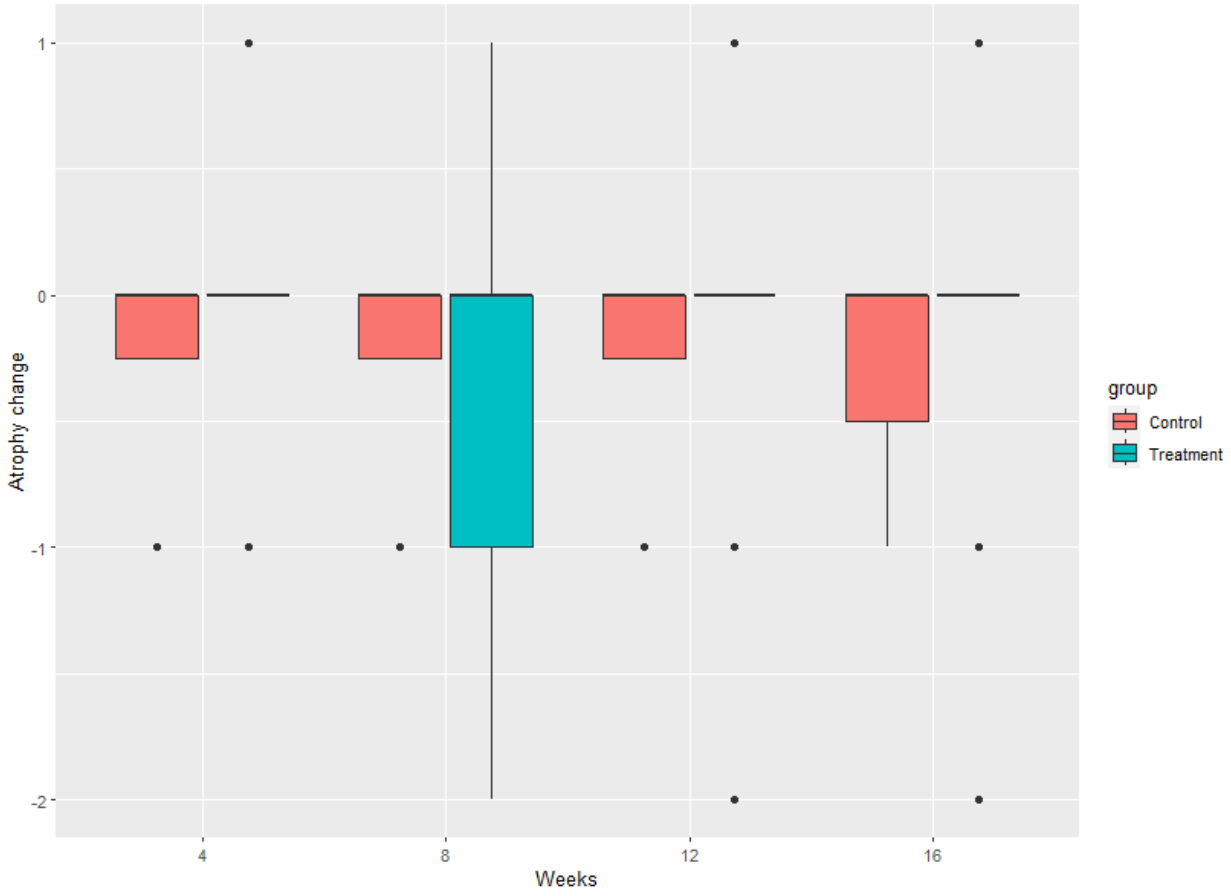
8. **Wrinkles**. Mean change in wrinkles over 16 weeks is -0.6923077, 95% CI [-1.1461733, -0.2384421], p-value = 0.006071. Mean change in the control group is 0.There is a significant difference between the treatment and control groups (p-value=0.006).=



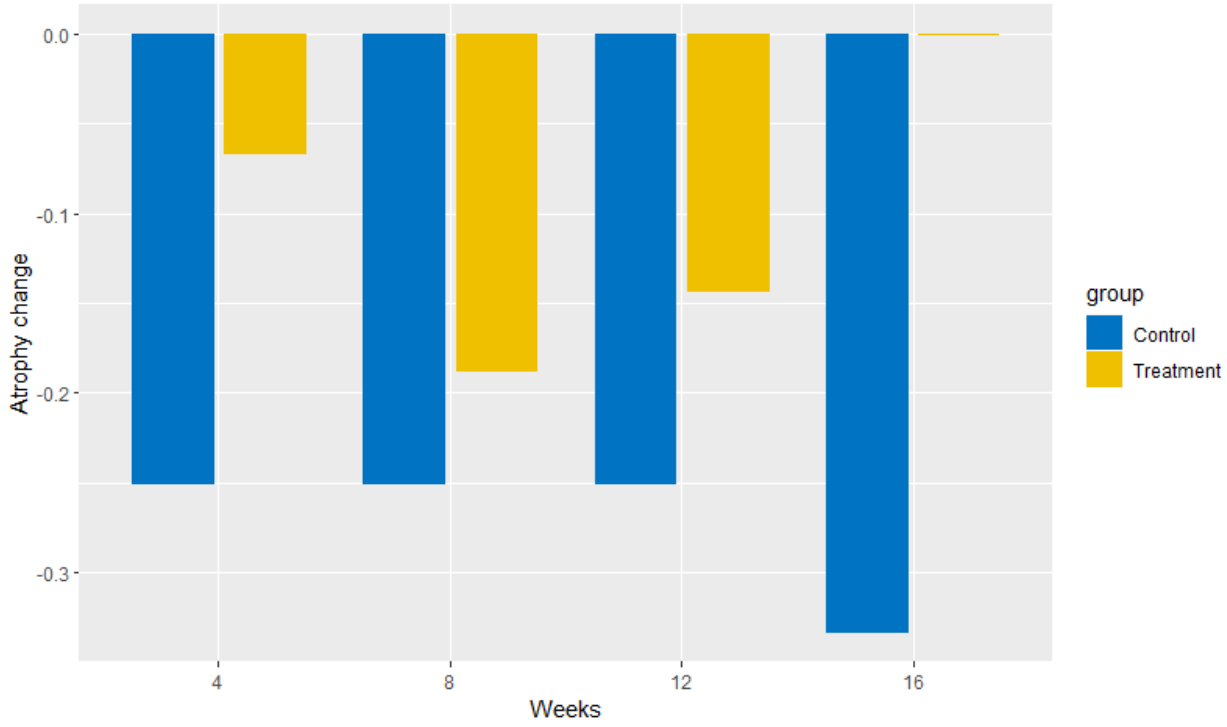


Week	Treatment	Control	p-value
4	-0.0667	0	0.334282
8	-0.5625	0	0.000526
12	-0.7143	0	0.000755
16	-0.6923	0	0.006071

9. **Atrophy.** There is no effect on atrophy and also no difference between the treatment and control groups (p-value=0.4533).



Week	Treatment	Control	p-value
4	-0.0667	-0.25	0.540169
8	-0.1875	-0.25	0.852624
12	-0.1429	-0.25	0.769762
16	0	-0.33333	0.453303



10. **Erythema**. Between weeks 0 and 16, proportions of the patients without Erythema increased from 25% to 69% (p-value = 0.0448). In the control group, at initial screening, 1 patient did not have eryhtema, 1 had minimal and 2 mild. At the conclusion of the study (week 16), 2 had no erythema and 1 was mild. We do not have enough samples to assess statistical significance.

Weeks	None	Minimal	Mild	Moderate
0	0.25	0.3125	0.3125	0.125
4	0.333333	0.6	0.066667	0
8	0.5	0.4375	0.0625	0
12	0.692308	0.230769	0.076923	0
16	0.692308	0.153846	0.153846	0

11. **Dryness scaling.** Proportions of the patients without **Dryness scaling** increased from 25% to 92.3% (p-value = 0.001157). In the control group, at initial screening, 1 patient did not have dryness scaling, and 3 had mild mild. At the conclusion of the study (week

16), 2 had no dryness scaling and 1 was mild (measurements for one control patient are missing). We do not have enough samples to assess statistical significance.

Weeks	None	Minimal	Mild	Moderate
0	0.25	0.1875	0.5	0.0625
4	0.466667	0.333333	0.133333	0.066667
8	0.625	0.3125	0.0625	0
12	0.923077	0	0.076923	0
16	0.923077	0	0.076923	0

12. Skin peeling and Edema did not change over the course of the study in treatment and control groups.

Regression analysis:
Explanatory variables:
The analysis considered the folllowing explanatory variables: Time, AGE, GENDER, RACE,ETHNICITY,dosage, FITZPATRICK_SKIN_TYPE. For all response variables, we subtract the baseline of measurements recorded during the week 0 visit.

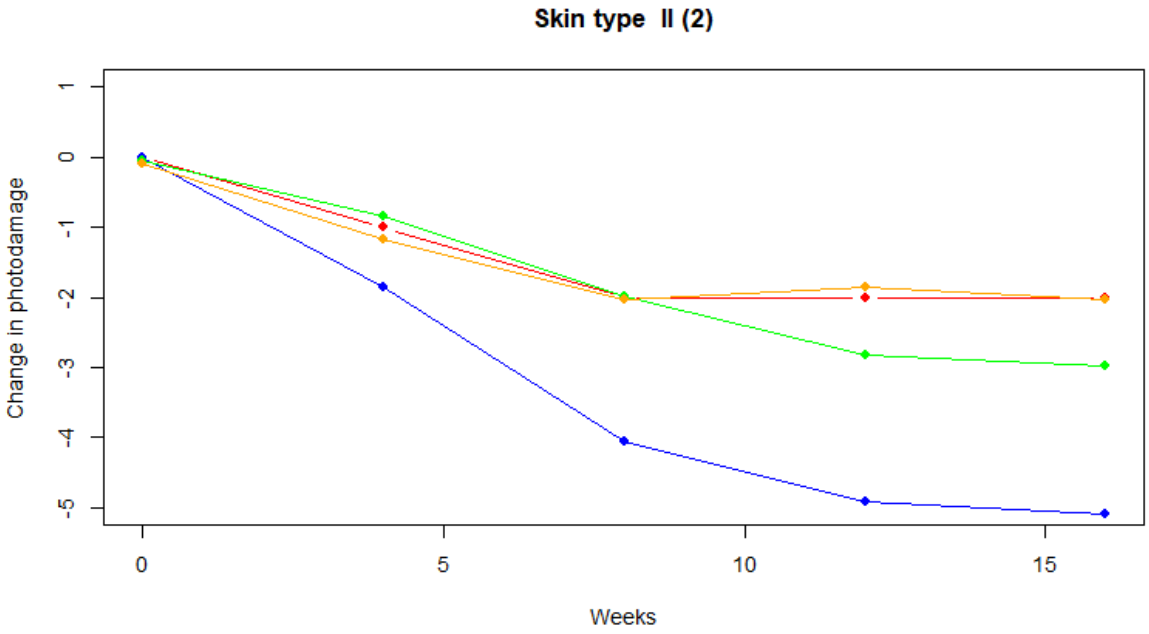
Photodamage
Analysis of the change in the photodamage with time. Photodamage is the photodamage at the day of the visit minus the photodamage at the first day of the study. Overall picture - photodamage is reduced with time spent using the product. The change between the first assessment and week 16 is significant, -1.538462, p-value = 0.002415, 95 percent confidence interval: [-2.414701, -0.662222]

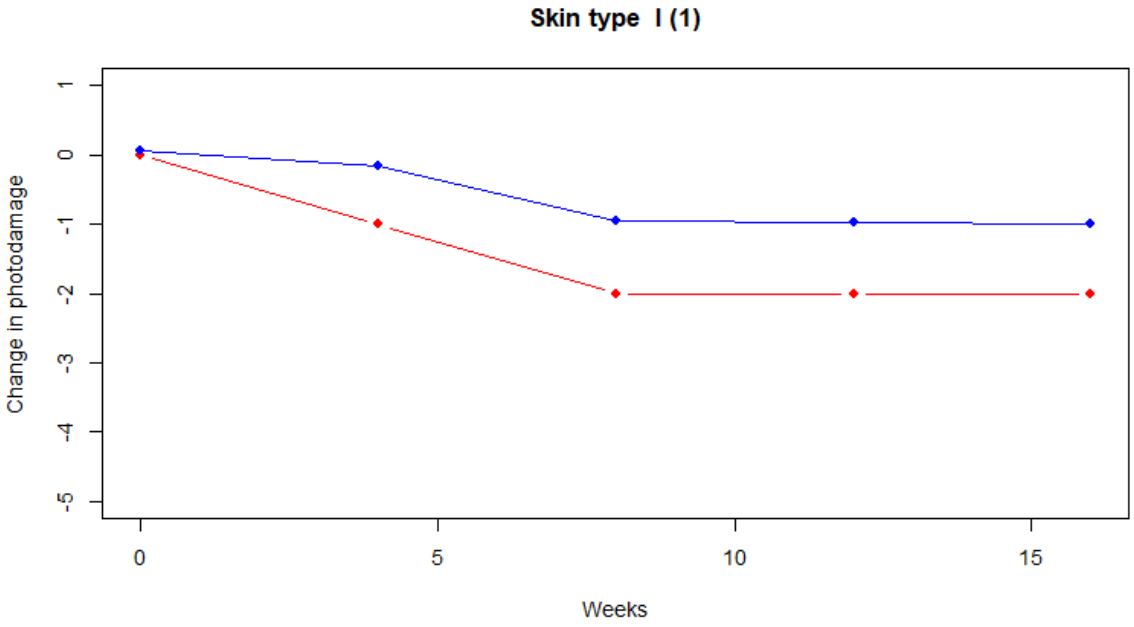
Regression model of the photodamage

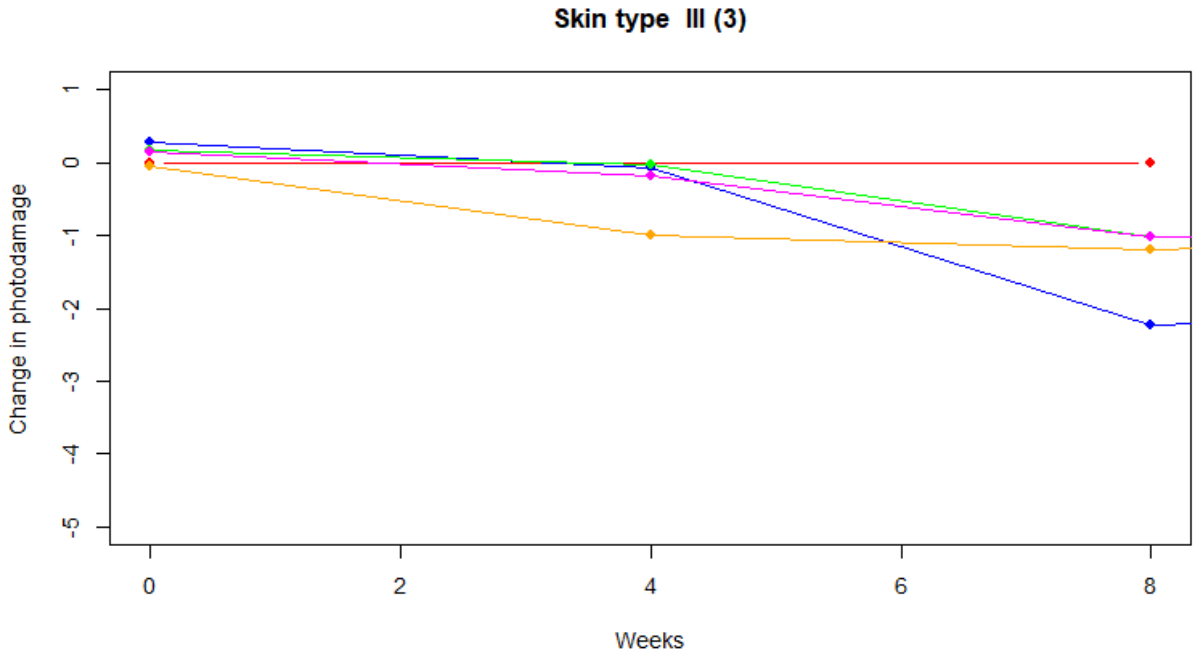
```
 Call:  glm(formula = photodamage ~ ., data = damage)

photodamage AGE       RACE Time FITZPATRICK_SKIN_TYPE
0  49 Multi-race    0             IV (4)
0  49 Multi-race   12             IV (4)
0  49 Multi-race   16             IV (4)
0  49 Multi-race    4             IV (4)
1  49 Multi-race    8             IV (4)
-2  64 Multi-race    8             II (2)

photodamage=
            (Intercept)                     AGE        RACECaucasian / White
                1.98854                 -0.02375                 -0.90332
          RACEMulti-race                    Time   FITZPATRICK_SKIN_TYPEII (2)
                -0.25946                 -0.09734                 -1.17645
FITZPATRICK_SKIN_TYPEIII (3)   FITZPATRICK_SKIN_TYPEIV (4)
                -0.23488                  0.16267

Degrees of Freedom: 73 Total (i.e. Null);  66 Residual
Null Deviance:     99.78
Residual Deviance: 35.25      AIC: 173.1

Significance
Coefficients:
                        Estimate Std. Error t value Pr(>|t|)
(Intercept)              1.98854    1.00360   1.981 0.051714 .
AGE                     -0.02375    0.01600  -1.484 0.142458
RACECaucasian / White   -0.90332    0.24390  -3.704 0.000436 ***
```

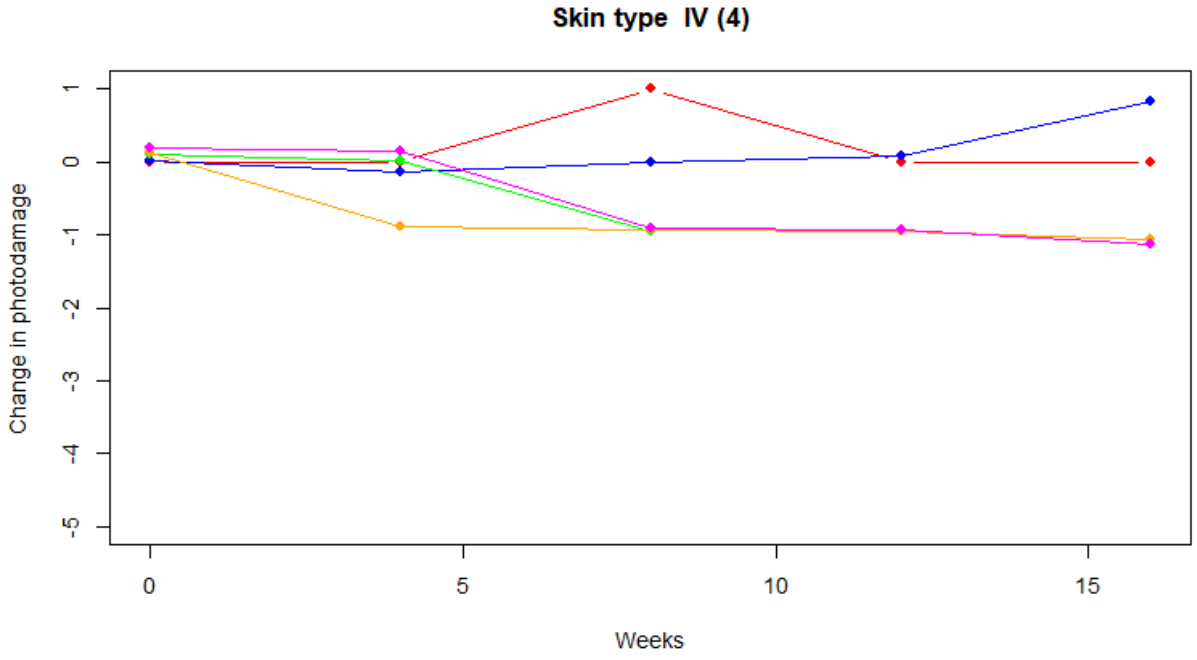
```
RACEMulti-race               -0.25946    0.26985  -0.962 0.339809
Time                         -0.09734    0.01547  -6.292 2.87e-08 ***
FITZPATRICK_SKIN_TYPEII (2)  -1.17645    0.31040  -3.790 0.000329 ***

0.5 %      99.5 %
(Intercept)                  -0.67340687  4.65048603
AGE                          -0.06620091  0.01869094
RACECaucasian / White        -1.55023339 -0.25640399
RACEMulti-race               -0.97519842  0.45628146
Time                         -0.13836803 -0.05630614
FITZPATRICK_SKIN_TYPEII (2)  -1.99975536 -0.35314179
FITZPATRICK_SKIN_TYPEIII (3) -1.03698454  0.56723389
FITZPATRICK_SKIN_TYPEIV (4)  -0.65491313  0.98025847

FITZPATRICK_SKIN_TYPEIII (3) -0.23488    0.30241  -0.777 0.440123
FITZPATRICK_SKIN_TYPEIV (4)   0.16267    0.30824   0.528 0.599450
```

It appears that the change is significant for Caucasian / White, FITZPATRICK_SKIN_TYPEII (2)

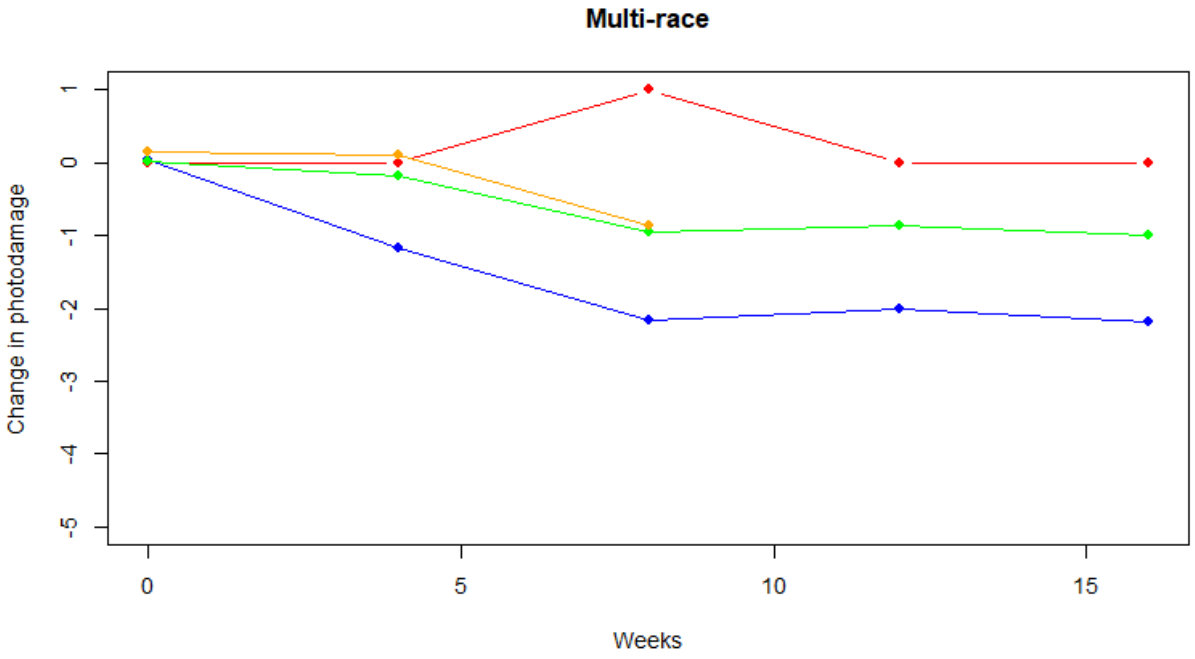

Skin type II (2)
Change in photodamage
1
0
-1
-2
-3
-4
-5
0
5
10
15
Weeks

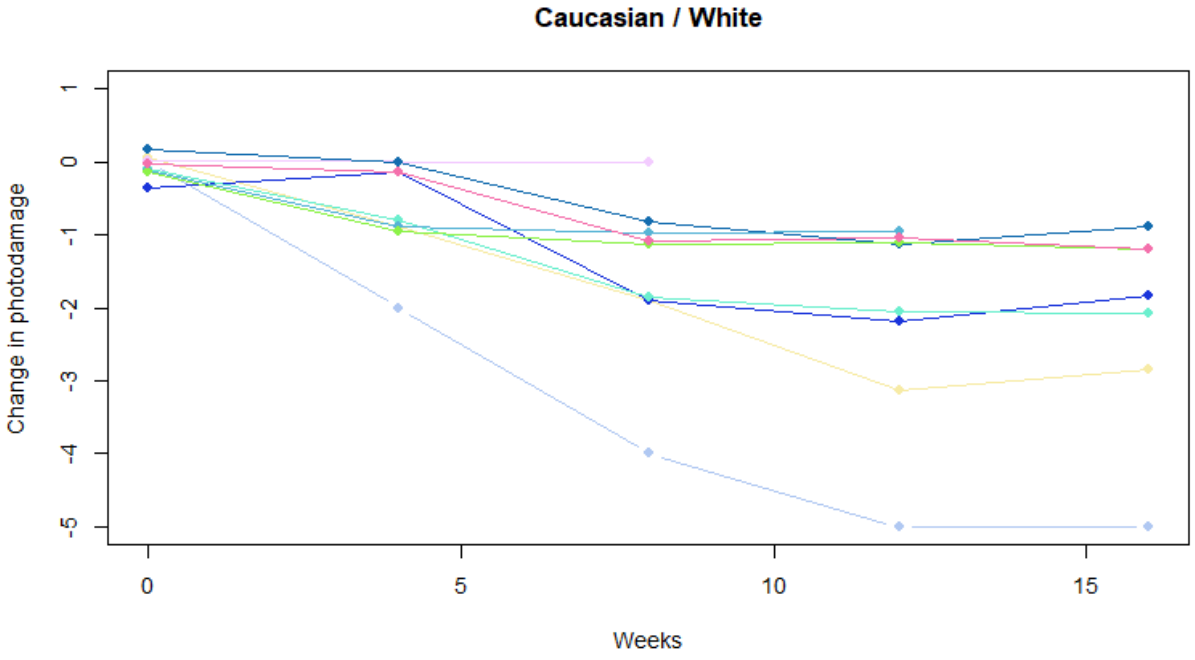

Skin type I (1)
Change in photodamage
1
0
-1
-2
-3
-4
-5
0
5
10
15
Weeks

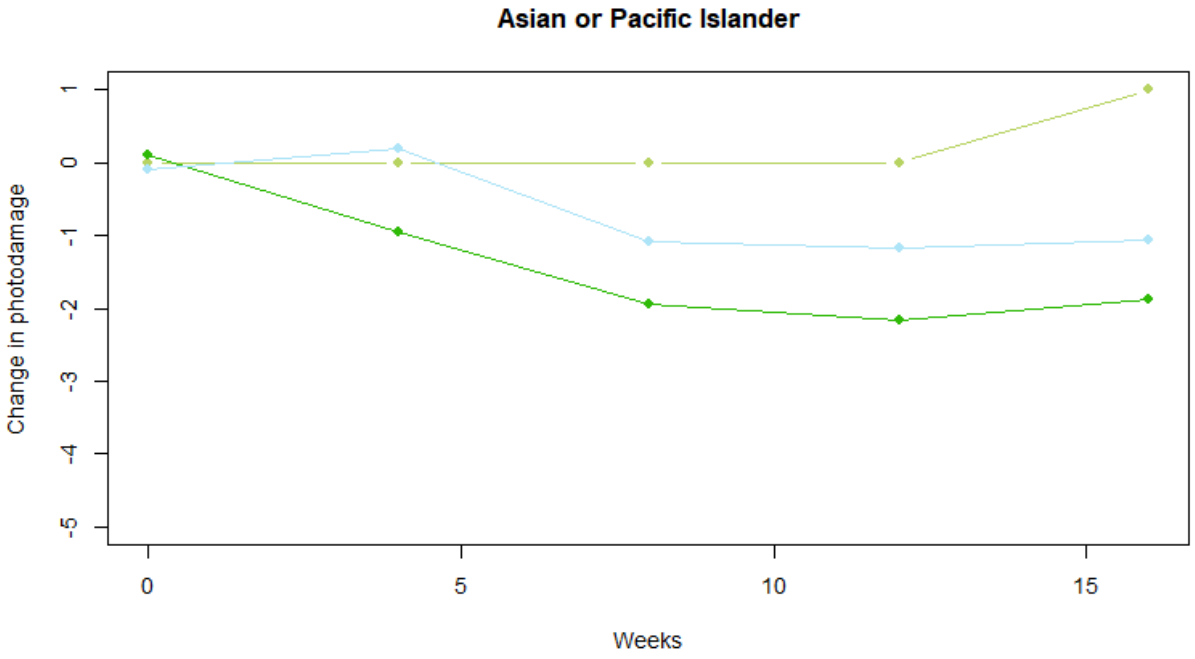




Splitting the subset by race


Multi-race
Change in photodamage
1
0
-1
-2
-3
-4
-5
0
5
10
15
Weeks


Caucasian / White
Change in photodamage
1
0
-1
-2
-3
-4
-5
0
5
10
15
Weeks


Asian or Pacific Islander
Change in photodamage
1
0
-1
-2
-3
-4
-5
0
5
10
15
Weeks

Involved melanin change regression analysis

Dividing the samples by skin type

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-6.5845	4.3263	-1.522	0.1326	
Time:FITZPATRICK_SKIN_TYPEI (1)	-1.4112	0.7961	-1.773	0.0807	.
Time:FITZPATRICK_SKIN_TYPEII (2)	-2.9890	0.6179	-4.837	7.72e-06	***
Time:FITZPATRICK_SKIN_TYPEIII (3)	-1.1471	0.6517	-1.760	0.0828	.
Time:FITZPATRICK_SKIN_TYPEIV (4)	-2.9153	0.6166	-4.728	1.16e-05	***

By Race

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-6.4827	4.5387	-1.428	0.157647	
Time:RACEAsian or Pacific Islander	-2.8811	0.7162	-4.023	0.000143	***
Time:RACECaucasian / White	-2.1824	0.5447	-4.007	0.000152	***
Time:RACEMulti-race	-1.8776	0.7111	-2.640	0.010207	*

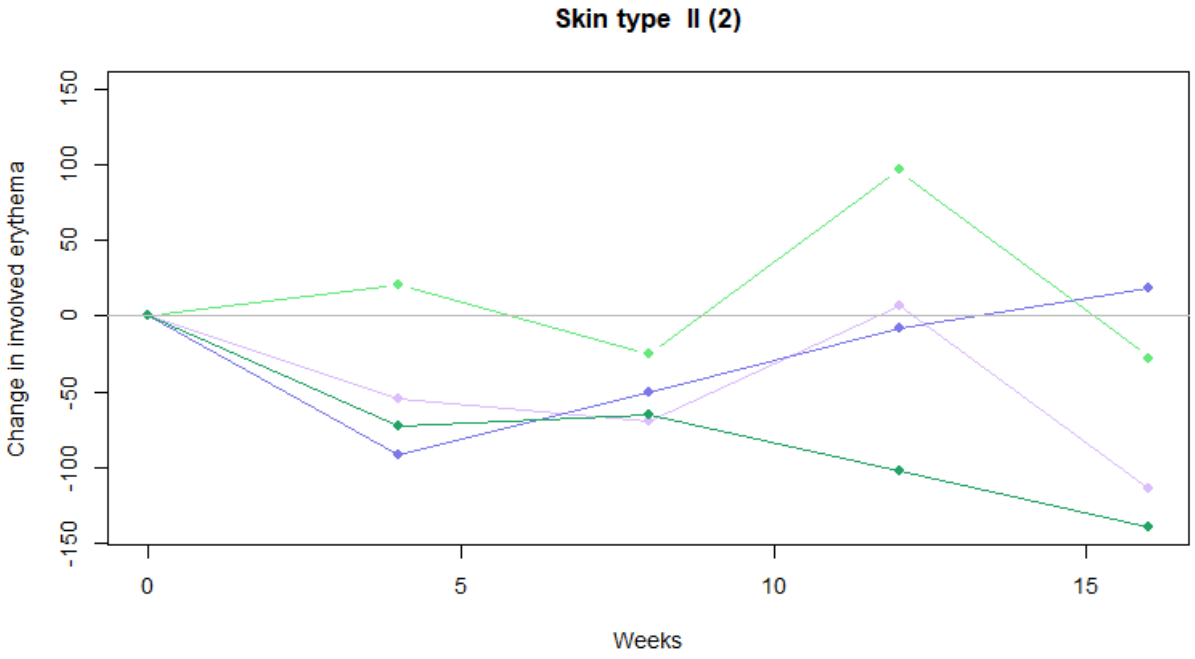
Involved erythema regression analysis

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-189.1031	82.9935	-2.279	0.026395	*
AGE	3.7662	1.1717	3.214	0.002138	**
RACECaucasian / White	23.6753	16.1714	1.464	0.148586	
RACEMulti-race	51.2561	18.8655	2.717	0.008671	**
FITZPATRICK_SKIN_TYPEII (2)	-78.0834	19.5349	-3.997	0.000183	***
FITZPATRICK_SKIN_TYPEIII (3)	-7.9377	20.8564	-0.381	0.704898	
FITZPATRICK_SKIN_TYPEIV (4)	-15.7471	21.8876	-0.719	0.474750	
Time	-2.3013	0.9926	-2.318	0.023976	*
Usage	-0.1297	0.5707	-0.227	0.821000	

It makes sense to consider skin types influence

Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	1.3119	9.6164	0.136	0.8919	
Time:FITZPATRICK_SKIN_TYPEI (1)	0.9023	1.7695	0.510	0.6117	
Time:FITZPATRICK_SKIN_TYPEII (2)	-3.6241	1.3735	-2.639	0.0103	*
Time:FITZPATRICK_SKIN_TYPEIII (3)	-0.6867	1.4485	-0.474	0.6370	
Time:FITZPATRICK_SKIN_TYPEIV (4)	-1.3495	1.3706	-0.985	0.3283	


Skin type II (2)
Change in involved erythema
150
100
50
0
-50
-100
-150
0
5
10
15
Weeks

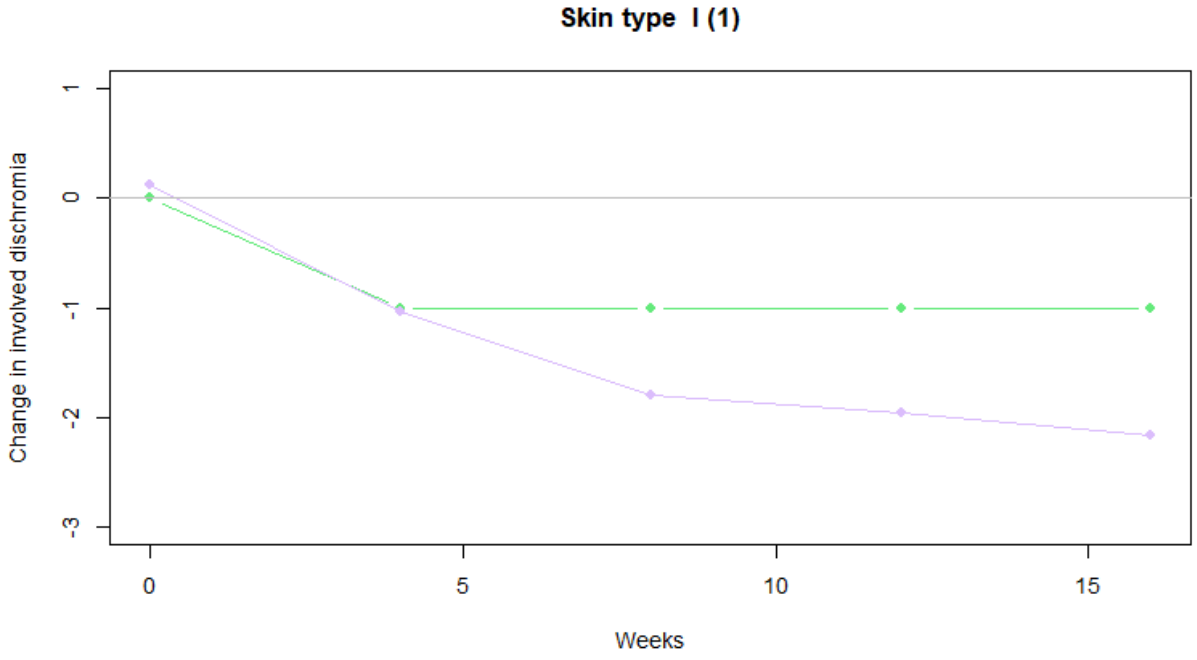
Regression analysis of the change in Dyschromia

Coefficients:

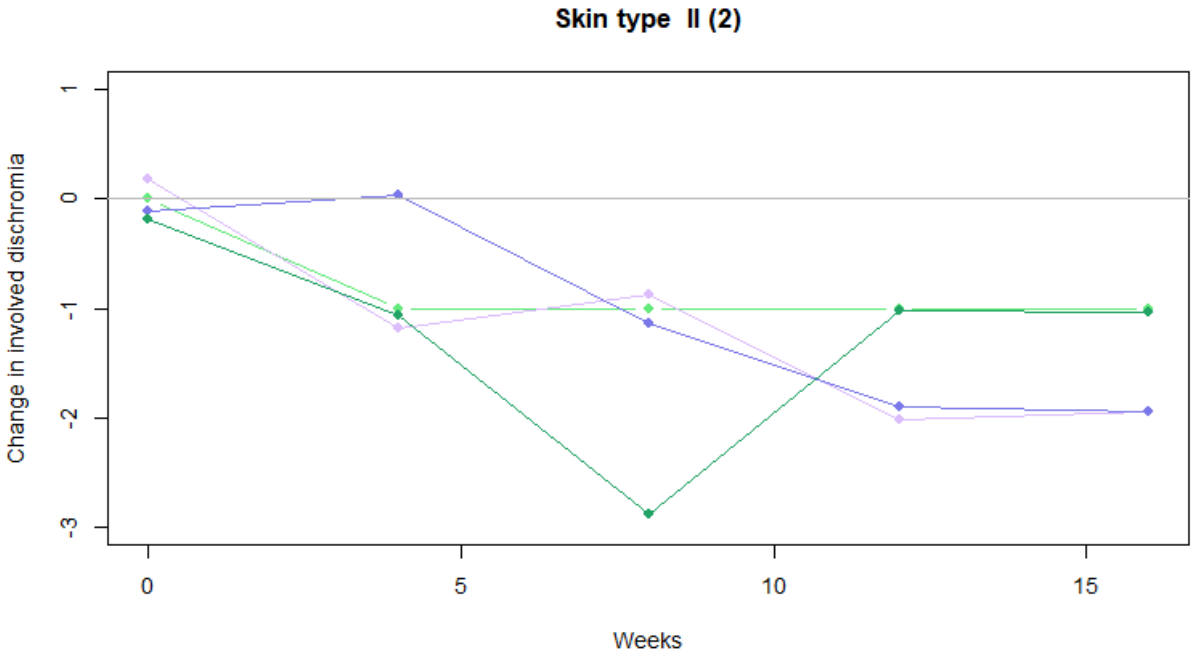
	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-2.726868	1.314548	-2.074	0.042492	*
AGE	0.041180	0.018559	2.219	0.030424	*
RACECaucasian / White	0.149036	0.256141	0.582	0.562921	
RACEMulti-race	-0.077463	0.298814	-0.259	0.796372	
FITZPATRICK_SKIN_TYPEII (2)	-0.160113	0.309417	-0.517	0.606799	
FITZPATRICK_SKIN_TYPEIII (3)	0.040135	0.330347	0.121	0.903719	
FITZPATRICK_SKIN_TYPEIV (4)	1.372008	0.346681	3.958	0.000209	***
Time	-0.083322	0.015723	-5.299	1.88e-06	***
Usage	-0.002239	0.009039	-0.248	0.805209	

Time and skin type

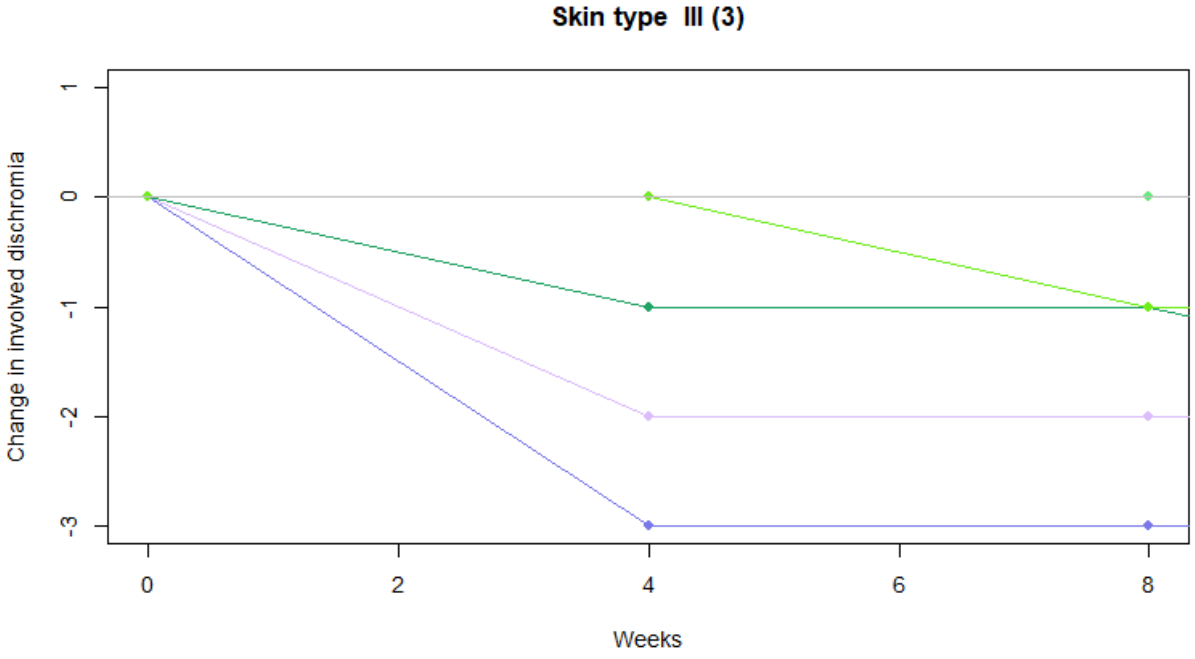
	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-0.22136	0.12928	-1.712	0.0913	.
Time:FITZPATRICK_SKIN_TYPEI (1)	-0.10239	0.02379	-4.304	5.42e-05	***
Time:FITZPATRICK_SKIN_TYPEII (2)	-0.10030	0.01847	-5.432	7.85e-07	***
Time:FITZPATRICK_SKIN_TYPEIII (3)	-0.13794	0.01947	-7.083	9.39e-10	***
Time:FITZPATRICK_SKIN_TYPEIV (4)	0.01504	0.01843	0.816	0.4173	



The change between week 0 and week 16 is -1.5, p-value =0.2. Not significant, due to insufficient number of subjects

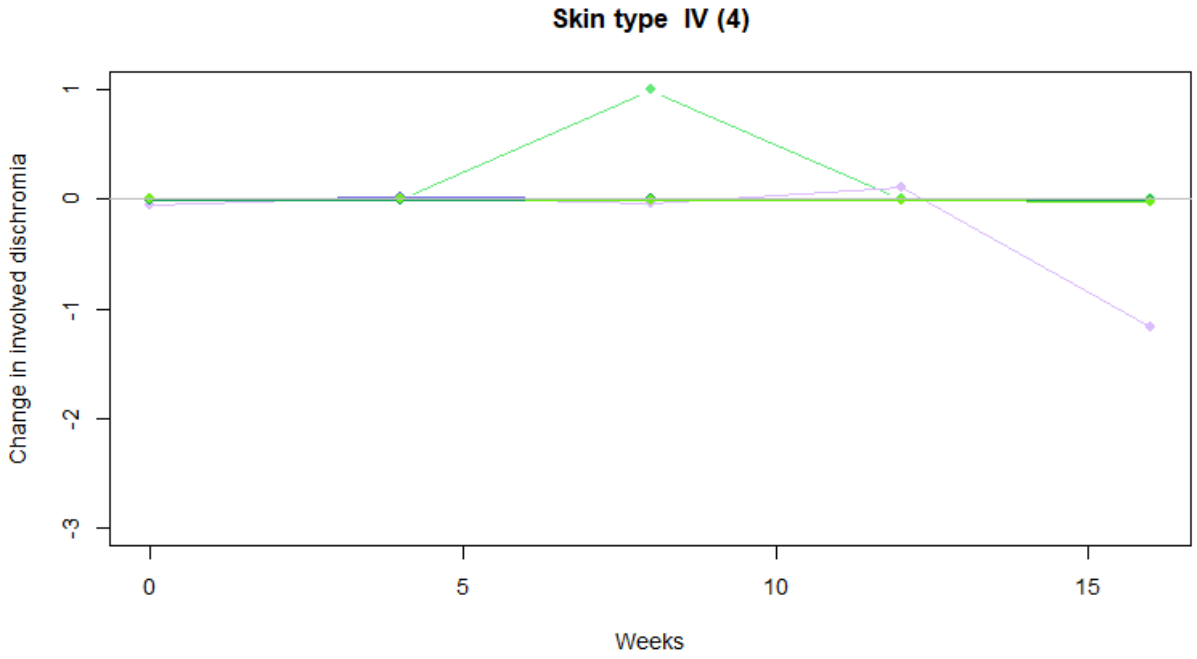


The change is significant p-value=0.01385
95 percent confidence interval:
[-2.4186931 -0.5813069]
mean of change in dyschromia is -1.5



p-value = 0.07418
alternative hypothesis: true mean is not equal to 0

95 percent confidence interval:
 -4.4841377 0.4841377
sample estimates:
mean of x
      -2



No effect on skin type 4, p-value = 0.391

Regression analysis of Wrinkles

Coefficients:

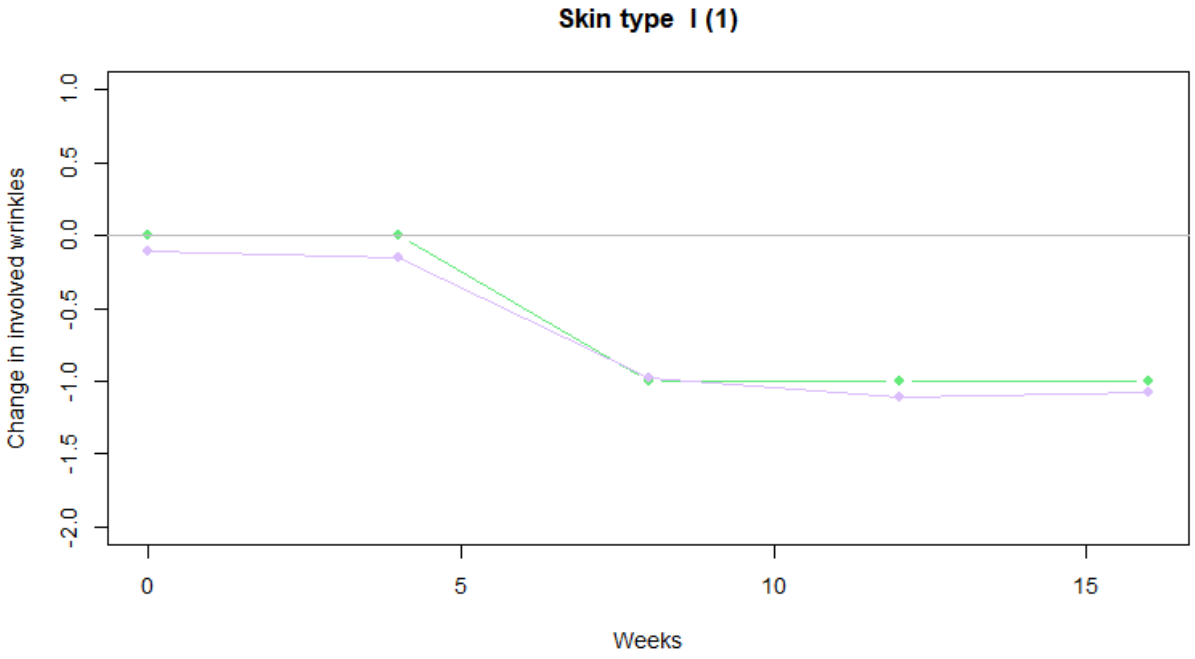
	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-1.018202	0.827218	-1.231	0.22334	
AGE	0.006800	0.011679	0.582	0.56266	
RACECaucasian / White	-0.256958	0.161184	-1.594	0.11633	
RACEMulti-race	0.093064	0.188037	0.495	0.62253	
FITZPATRICK_SKIN_TYPEII (2)	-0.038058	0.194709	-0.195	0.84572	
FITZPATRICK_SKIN_TYPEIII (3)	-0.166857	0.207881	-0.803	0.42545	
FITZPATRICK_SKIN_TYPEIV (4)	0.617327	0.218159	2.830	0.00639	**
Time	-0.054673	0.009894	-5.526	8.12e-07	***
Usage	0.013728	0.005688	2.413	0.01898	*

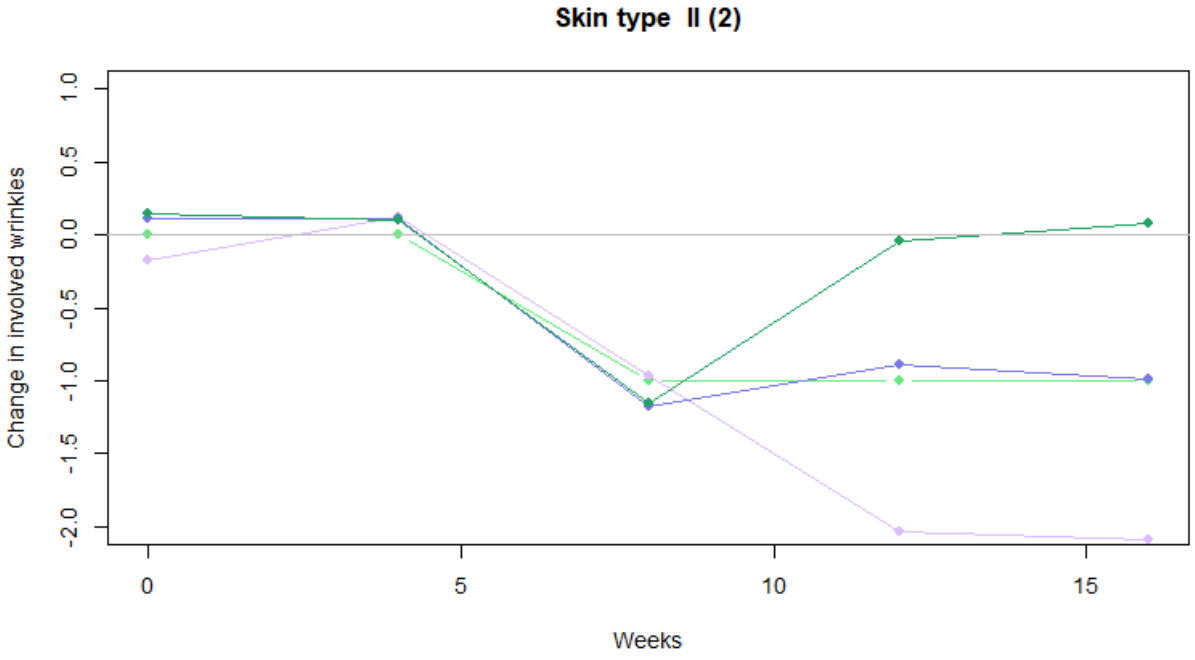
Looking at the skin types separately

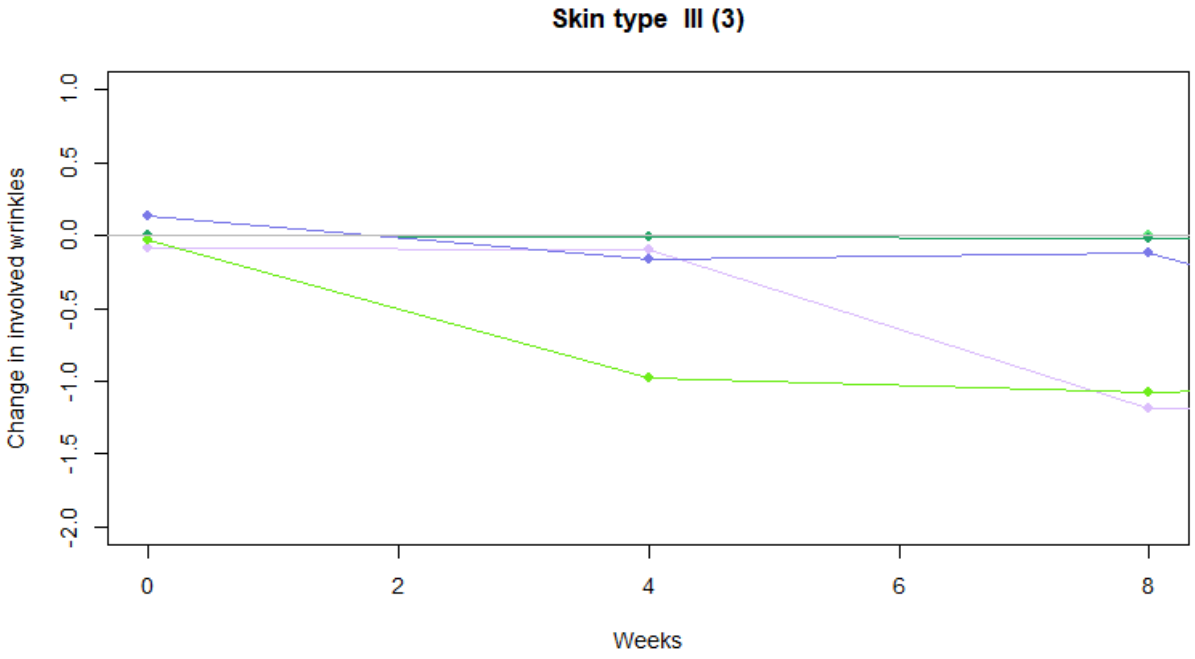
Coefficients:

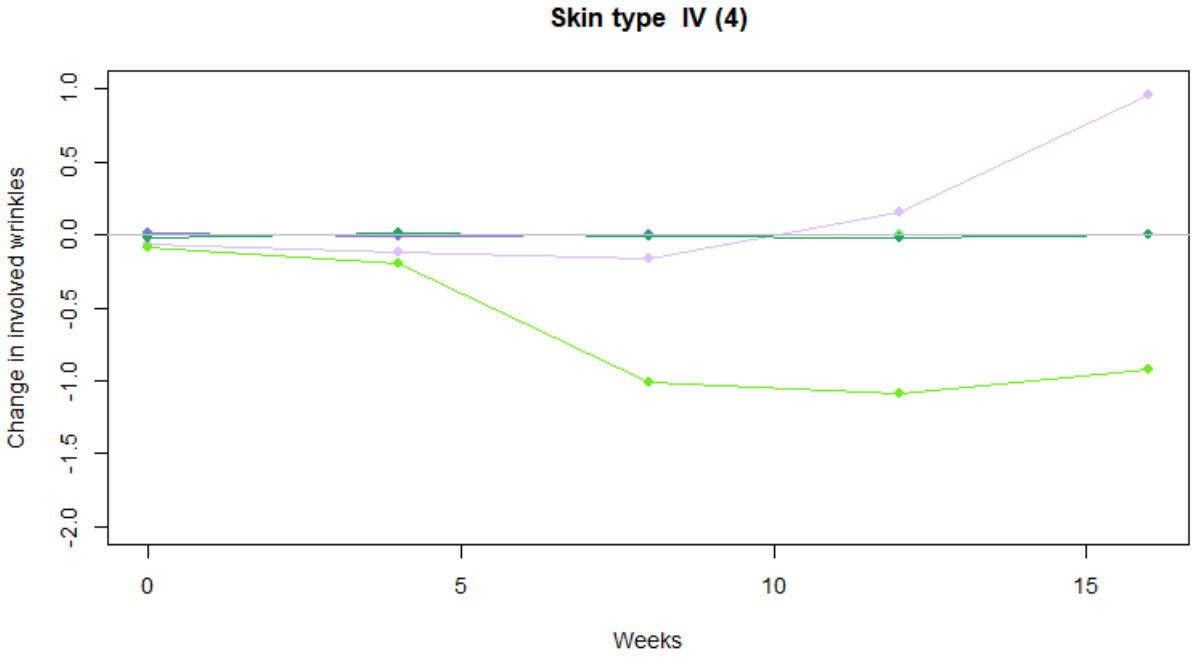
	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-0.005103	0.083197	-0.061	0.951	
Time:FITZPATRICK_SKIN_TYPEI (1)	-0.074575	0.015309	-4.871	6.79e-06	***
Time:FITZPATRICK_SKIN_TYPEII (2)	-0.074575	0.011883	-6.276	2.66e-08	***
Time:FITZPATRICK_SKIN_TYPEIII (3)	-0.059736	0.012532	-4.767	1.00e-05	***
Time:FITZPATRICK_SKIN_TYPEIV (4)	-0.009561	0.011858	-0.806	0.423	

Separate plots for skin types


Skin type I (1)
Change in involved wrinkles
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0
5
10
15
Weeks


Skin type II (2)
Change in involved wrinkles
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0
5
10
15
Weeks


Skin type III (3)
Change in involved wrinkles
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0
2
4
6
8
Weeks


Skin type IV (4)
Change in involved wrinkles
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0
5
10
15
Weeks

Regression analysis of Atrophy

No significant change

Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	0.5675068	0.9621840	0.590	0.55761	
AGE	-0.0180122	0.0135843	-1.326	0.19005	
RACECaucasian / White	-0.8927689	0.1874827	-4.762	1.32e-05	***
RACEMulti-race	-0.1466315	0.2187170	-0.670	0.50525	
FITZPATRICK_SKIN_TYPEII (2)	-0.1961811	0.2264776	-0.866	0.38993	
FITZPATRICK_SKIN_TYPEIII (3)	-0.2422350	0.2417979	-1.002	0.32060	
FITZPATRICK_SKIN_TYPEIV (4)	0.1495473	0.2537534	0.589	0.55792	
Time	-0.0004823	0.0115082	-0.042	0.96671	
Usage	0.0208140	0.0066163	3.146	0.00261	**

Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)	
(Intercept)	-0.638088	0.315857	-2.020	0.0477	*
Usage:FITZPATRICK_SKIN_TYPEI (1)	0.008234	0.006952	1.184	0.2408	
Usage:FITZPATRICK_SKIN_TYPEII (2)	0.008779	0.007425	1.182	0.2416	
Usage:FITZPATRICK_SKIN_TYPEIII (3)	0.014925	0.005980	2.496	0.0152	*
Usage:FITZPATRICK_SKIN_TYPEIV (4)	0.017676	0.008573	2.062	0.0434	*