SUMMARY STUDY REPORT
STUDY CODE: ACR/GLYCAD/1375
EudraCT-No: 2014-001796-31

Study title	A monocenter, double-blind, randomized study to assess the kinetic of antiperspirant efficacy of Glycopyrrolate 0.2% and 0.02% versus placebo during 4 days of topical applications on axilla of healthy volunteers.	
Study code	ACR/GLYCAD/1375	
Sponsor **L'OREAL SA** 14 rue Royale 75008 Paris **L'OREAL RESEARCH & INNOVATION** Advanced Clinical Research (ACR) Centre d'Aulnay-Chanteloup 1 Avenue Eugène Schueller 93600 Aulnay-sous-Bois Director of ACR: Benoit MULLER Ph.D. Head of Clinical Evaluation for Advanced Research Head of projects: Odette JAMMAYRAC Ph.D. Study manager & Monitor: Anne BIELICKI		**Investigational center** bioskin GmbH Burchardstrasse 17 20095 Hamburg, Germany Investigator: U.KRÖNCKE, M.D CRO Study manager: Martina EBBINGHAUS, M.S.
Principal Investigator	Heinrich SIEMETZKI M.D.	
Study date	**Start date:** 15th December 2014	**End date:** 16th February 2015
Duration of Treatment	4 days	
Study objective(s)	The main objective of this study was to assess the kinetic of antiperspirant efficacy of Glycopyrrolate 0.2% and 0.02% versus placebo on the axillae of healthy volunteers, during 4 days of topical applications. The secondary objectives were to assess: - the kinetic of antiperspirant efficacy of Glycopyrrolate 0.2% in comparison to 0.02% on the axillae of healthy volunteers, during 4 days of topical applications. - the safety of the different study products.	
Study design	Monocenter, randomized, double-blind compared to placebo. 66 volunteers were divided in 3 parallel groups of 22 subjects. Each subject received 2 different compounds in a randomized manner during 4 consecutive days on axillae as described below: 22 subjects: Glycopyrrolate 0.2% compared to Glycopyrrolate 0.02% 22 subjects: Glycopyrrolate 0.2% compared to placebo 22 subjects: Glycopyrrolate 0.02% compared to placebo Each subject was its own control for the 2 compounds. The investigational products were applied at the investigational site on the left and right axilla according to the randomization list.	

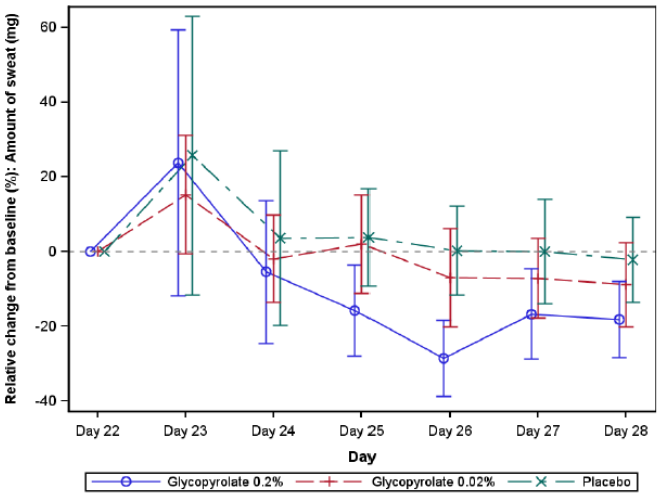
Flow chart

V = Visit	**Screening V1**	**Wash-out period**	**Inclusion V2**	**Treatment follow-up visits V3**	**V4**	**V5**	**Follow up visits V6**	**V7**	**End of study V8**
D = Day of assessment	**D0**	**D1 to D21**	**D22 baseline**	**D23**	**D24**	**D25**	**D26 24h***	**D27 48 h***	**D28 72 h***
Informed consent	X								
Demography	X								
Medical examination	X								X
Urine Pregnancy test	X		X						X
Casual heart rate & blood pressure	X		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Inclusion/non inclusion criteria eligibility	X		X						
Conditioning period		X**							
Thermal challenge (warm-up and 2 sweat collection periods)			X [1,2]	X [3]	X [3]	X [3]	X[3]	X[3]	X[3]
Gravimetric measurement			X[2]	X	X	X	X	X	X
Randomization			X						
Investigational products application			X[4]		X[5]				
Concomitant medications	◄								►
Adverse Events (including local intolerances)		◄							►

* ± 4 hours **: Washing axillae at home twice a day with unscented soap and use deodorant provided by the site.
X[1]: washing axillae at the center one hour before thermal challenge.
X[2]: thermal challenge performed one hour before the first application of investigational product (baseline).
X[3]: no washing axillae before thermal challenge.
X[4]: at least one hour after the thermal challenge, no washing axillae before application.
X[5]: at least one hour after thermal challenge, washing axillae before application.
X[6]: measurements of heart rate and blood pressure before and at least 30 min after thermal challenge.

Population	Subjects were healthy male and female volunteers, 18 to 45 years old. Volunteers showed a variety of sweating rates. The difference between the highest and lowest sweat output among the subjects exceeded 600 mg of sweat in one 20 min collection per axilla after warm-up period. 127 subjects were screened and among them, 61 subjects were considered as screening failure. 66 subjects were randomized in the study and 60 subjects completed the study. Full analysis set (FAS) and Per Protocol Set (PPS) were respectively including 63 and 60 subjects. The mean age of the 66 adults was 32.7 years (range 18 to 45 years). Overall, 31 (47%) women and 35 (53%) men were randomized. 7 (11%) of the subjects had Fitzpatrick phototype II whereas 59 (89%) of the subjects had phototype III. Moreover, 1 woman was not of childbearing potential. For the 30 other women, their contraceptive states were acceptable. All randomized subjects met the inclusion criteria and none of the exclusion criteria.
Investigational products	**Active:** Glycopyrrolate 0.2% (solution in Natrosol, Ethanol, Water) batch number: 1345614221 Glycopyrrolate 0.02% (solution in Natrosol, Ethanol, Water) batch number: 1345614220 Glycopyrrolate: (3RS)-3-[(2SR)-(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide. Molecular formula: $C_{19}H_{28}NO_3^+$ **Placebo:** vehicle without active batch number: 1345614219
Investigational areas	Both axillae of each subject served as investigational areas. Axillae were washed at the center in a standardized manner with a standard soap for 10 seconds, and then dried with a paper towel. Washing was performed at baseline on Day 22 one hour before entering the thermal challenge, and before each application of investigational products from Day 23 to Day 25. Washing of the axillae at home was not allowed from Day 22 to the end of study (D28). From the last application of investigational products on Day 25 until Day 28, washing of the axillae was neither be allowed at home nor at the center.
Treatment Allocation	Route of administration: topical administration at the study site by a technician under medical supervision. Dose: application once daily for 4 days of 0.4 g on treatment areas (one hour after thermal challenge). The products were conditioned in a flask of 5 ml and applied with a micropipette. Investigational products were applied on treatment areas (according to randomization), with a rest of 5 minutes at ambient temperature for product penetration.

Evaluation criteria	• **Primary criteria** **Efficacy:** Antiperspirant efficacy by assessment of the relative reduction % of sweat with Glycopyrrolate 0.2% and 0.02% in comparison to sweat output in a placebo (vehicle without active) treated field. • **Secondary criteria** **Efficacy:** Antiperspirant efficacy by assessment of the relative reduction % of sweat in comparison to Glycopyrrolate 0.02% vs Glycopyrrolate 0.2%. The amount of sweat was measured gravimetrically at baseline (D22) before the first application of investigational products, before application at D23; D24 and D25 as well as on D26 (24h after the last application), D27 (48h after the last application) and D28 (72h after the last application). • **Safety :** Safety was assessed by recording Adverse Events, including cutaneous reactions (local intolerance), from the informed consent signature date until the end of the study
Statistical methodology	The aim of this study was to evaluate in vivo the kinetic of the antiperspirant efficacy of Glycopyrrolate at 2 concentrations 0.2% and 0.02% as compared to the placebo (vehicle without active) during 4 days of topical applications (from day 23 to day 25), and to evaluate the remanence 24h, 48h and 72h after the last application. • **Assessment criteria** For all subjects the individual quantities of sweat at all measurements time and the calculated Z values were recorded. The amount of sweat was evaluated by gravimetric measurement of the absorbed sweat per absorbance pad. The variable Z-value was calculated according to the following formula (according the FDA guideline) see below: $Z[\%] = \frac{\frac{PC}{PT}}{\frac{C}{T}} \times 100$ The calculated Z-value is the ratio of test axilla to control axilla adjusted for the ratio of right-to-left area sweating rate. **PT:** pre-treatment measure for the test axilla (product area) **PC**: pre-treatment measure for control axilla (reference area) **T:** treated measure for test axilla (product area) **C:** treated measure for control axilla (reference area) Sweat reduction % value was calculated according the following formula: **r =sweat reduction % = 100 – Z *** ** Median Z according to the FDA guideline.* • **Assessment methodology** - In case of abnormality, values were log-transformed. - For the statistical analysis of Z, the Wilcoxon signed-rank test was used (Z<0.8 ; Z<1). - Analysis of covariance (ANCOVA) was also performed on log-transformed values (Murphy & Levine,1991) o to test the difference between products taking into account all variation factors. o to estimate the relative difference between products with the possibility to

	have excluded previously variation factors. - T-tests were also performed on log-transformed values to estimate the relative reduction of each product according to baseline. The analyses were performed based on the per protocol (PP) population.
Major Protocol deviations & modifications to the study conduct	No subjects were entered into the study who did not fully satisfy entry criteria. A protocol amendment was written and approved before the start of the study (Protocol V 2.0 October 07, 2014) to change the storage temperature of the IMPs from room temperature (15-25°C) to 2-8°C. No major protocol deviation was noted during the study duration.
Efficacy Results	The efficacy analyses for this study are based on the 60 subjects of the per-protocol set (66 randomized subjects). The main objective of this study was to assess the kinetic of antiperspirant efficacy of Glycopyrrolate 0.2% and 0.02% versus placebo on the axillae of healthy volunteers, during 4 days of topical applications (Day 22 to Day 25). ➢ **Relative reduction (%) of sweat from baseline :** ▪ Glycopyrrolate 0.2% is efficient with a moderate time effect from Day 24 (-16.59% p=0.016) and with a stronger time effect after the 3 rd application at D25 (-24.03%, p-value < 0.001). ▪ Glycopyrrolate 0.2% is efficient on remanence on the following days 24h, 48h and 72h after last application (-36.81%, p-value < 0.001), Day 27 (-25.59%, p-value < 0.001) and Day 28 (-24.56%, p-value < 0.001 ▪ For Glycopyrrolate 0.02% the time effect is significant moderate at Day 26 (-15.71%, p-value 0.028) Day 27 (-12.73%, p-value 0.026) and Day 28 (-15.45%, p-value 0.013) in favor of a sweat reduction. ▪ The statistical indicators did not allow to conclude on a time effect of the Placebo.  ▪ ➢ **FDA guideline : Z- Value : r = sweat reduction % = 100-Z :** ▪ For Glycopyrrolate 0.2% vs Placebo the Median Z value is significantly < 100% after 3 applications on Day 25 (86.35%, p= 0.0006; r=13.65%), and on the following days 24h _Day 26 (78.25%, p < 0.0001; r=21.75%), 48h_Day 27 (83.22%, p= 0.0035; r=16,78%) and 72h_ Day 28 (91.68%, = 0.0003; r=8,32%) after last application but not significantly different from 80% from Day 26 to Day 28 inclusive.

	▪ For Glycopyrrolate 0.02% vs Placebo the Z-value is not significantly different from 100% on any of the days considered and is significantly different from 80% but not inferior on all days considered. ➢ **Relative difference treatment estimates (%) from model Murphy & Levine** ▪ Sweat reduction is significantly superior with Glycopyrrolate 0.2% than with placebo after the 3rd application on Day 25 (-15.73%, p-value < 0.001; moderate effect), Day 26 (-23.58%, p-value < 0.001; strong effect), Day 27 (-17.14%, p-value < 0.001; moderate effect) and Day 28 (-12.77%, p-value < 0.001; moderate); ▪ Sweat reduction is significantly superior with Glycopyrrolate 0.2% than with Glycopyrrolate 0.02% on Day 25 (-11.50%, p-value 0.001), Day 26 (-18.93%, p-value < 0.001), Day 27 (-13.58%, p-value < 0.001) and Day 28 (-7.76%, p-value 0.028). ▪ Sweat reduction is not significantly different with Glycopyrrolate 0.02% than placebo.
Safety Results	No serious adverse events were reported during the study. 2 adverse events (headache) were experienced by the randomized subjects, 1 with moderate and 1 with mild intensity. The relation for both adverse events was assessed as unlikely to the study procedures. Both adverse events resolved without sequelae. No local intolerance was experienced by the subjects.
Conclusion	This study shows that Glycopyrrolate 0,2% is efficient vs vehicle after 3 applications on day 25 and shows a remanence vs vehicle till 72h after the last application.. For Glycopyrrolate 0.02 there is no significant treatement effect at any timpoint observed compared to placebo. Glycopyrrolate 0,2% compared to Glycopyrrolate 0,02% provides a significant efficacy in in terms of sweat reduction . The test products were assessed as safe in the present clinical study.