

	<table><tr><th>Title</th></tr><tr><td>CTN 43BBJ1911 US Jawline, Clinical Investigation Plan</td></tr></table>	Title	CTN 43BBJ1911 US Jawline, Clinical Investigation Plan	
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A randomized, evaluator-blinded, parallel group, no treatment controlled, multicenter study to evaluate effectiveness and safety of GP0109 for Jawline definition

Study products: GP0109

NCT ID: NCT05110287

Clinical trial number (CTN): 43BBJ1911

Sponsor: Q-Med AB, part of the Galderma Group
Seminariegatan 21
SE-752 28 Uppsala, Sweden
Telephone: +46 18 474 90 00
Facsimile: +46 18 474 90 01



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Investigators and Study Administrative Structure

Sponsor: Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala, Sweden
Telephone: +46 18 474 90 00



Further details on all participating Investigators and the complete administrative structure of the study are found in the study files. Note that administrative changes are to be documented in the study files without requiring a Clinical Investigation Plan (CIP) amendment.

Sponsor Signatures

The CIP is electronically signed in the document management system within the Q-Med AB quality management system by the representatives listed below.



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PPD

Signed Agreement of the Clinical Investigation Plan

CTN: 43BBJ1911

Title of the CIP: A randomized, evaluator-blinded, parallel group, no treatment controlled, multicenter study to evaluate effectiveness and safety of GP0109 for Jawline definition

We, the undersigned, have read and understand the CIP specified above, and agree on the contents. The CIP, the clinical trial agreement (CTA) and the additional information given in the Instructions for use (IFU) and Report of Prior Investigations (ROPI) will serve as a basis for co-operation in this study.

Principal Investigator

Printed name



Signature



Date





Study site


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Synopsis



	<p data-bbox="371 58 405 76">Title</p> <p data-bbox="371 120 1011 147">CTN 43BBJ1911 US Jawline, Clinical Investigation Plan</p>	
Title of study	A randomized, evaluator-blinded, parallel group, no treatment controlled, multicenter study to evaluate effectiveness and safety of GP0109 for Jawline definition	
Indication	GP0109 is an injectable implant intended to be used to restore and enhance jawline definition in subjects over the age of 21	
Clinical Trial Number (CTN)	43BBJ1911	
Study population:	Adult population with Grade 2 to 4 (moderate to very severe) on the Galderma Jawline Scale (GJS) with the intent to undergo bilateral jawline treatment	
Countries involved	USA	
Number of sites	Approximately 15 sites. Approximately five of the sites will be using needle for injection, approximately five sites cannula for injection, and approximately five sites with combination of needle and cannula for injection.	
Number of subjects	<p>Approximately 224 subjects will be randomized (3:1) to treatment or to no treatment group.</p> <p>At least 45 subjects will be Fitzpatrick skin type (FST) IV through VI. This includes at least 23 subjects with FST V-VI, where at least 12 subjects will be FST V and at least 11 subjects will be FST VI.</p> <p>The aim is to achieve an even distribution of subjects between the assigned sites.</p>	
Study Design	<p>This is a prospective, randomized, evaluator-blinded, no treatment controlled, parallel group, multicenter study in the USA.</p> <p>A total of approximately 224 subjects will be included in the study. In the treatment group approximately 56 subjects will receive injections with needle, 56 with cannula and 56 with both needle and cannula combined. Approximately 56 subjects will be randomized to no treatment at baseline.</p> <p>The study enrollment will be conducted in two stages. Stage 1 includes the first approximately 50 eligible subjects that will be randomized to treatment or to no treatment. At least 10 of these subjects will be FST IV-VI, where at least 3 subjects will be FST V, and at least 2 subjects will be FST VI. The aim is to achieve even distribution of subjects to minimum one site using needle for injection, one site with cannula for injection, and one site with combination of needle and cannula for injection. The Sponsor will submit the 3-month data after baseline, from subjects in stage 1 to the Food and Drug Administration (FDA) for review and await the agency's agreement prior to continued enrollment into Stage 2. Approximately 174 eligible subjects will be randomized and enrolled in Stage 2.</p> <p>Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. A follow-up telephone call should be made 72 hours after treatment and a follow-up visit should be completed 14 days after treatment. Optional touch-up treatment may be administered 1 month after initial treatment, if deemed necessary by Treating Investigator and the subject to obtain optimal aesthetic improvement. Optimal aesthetic improvement is defined as at least 1 grade improvement, from baseline, on the GJS, and best correction that can be achieved as agreed by the Treating Investigator and the subject. If optional touch-up is performed, a 72-hour follow-up telephone call, a 14day follow up visit, and a 1-month follow-up visit should be scheduled.</p> <p>At the Month 12 visit, subjects in the no treatment group will be offered optional treatment. Subjects in the no treatment control group that do not receive treatment at month 12 will end the study at month 12. The subjects who received treatment at baseline will also be offered an optional additional treatment at the month 12 visit if aesthetic improvement is not maintained (as determined by the Treating Investigator and subject). If optional</p>	

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	<p data-bbox="448 224 1414 282">treatment is performed, a 72-hour follow-up telephone call, a 14-day follow up visit, and a 1-month follow-up visit should be scheduled.</p> <p data-bbox="448 300 1414 448">Investigator blinding will be accomplished by having a Treating Investigator administer the treatments and having a Blinded Evaluator, to whom randomization and treatment are concealed, conduct blinded assessments. Safety assessments will be performed by nonblinded personnel. The Blinded Evaluator is not blinded to study treatment following the Month 12 visit.</p> <p data-bbox="448 468 1414 616">Effectiveness and safety data will be collected for up to 24 months from baseline. A subject will be involved in the study for up to 25 months, including a 30-day screening period. For subjects in the control group that do not receive treatment at Month 12, the clinical study participation is approximately 13 months including the screening period. The study visits are illustrated in Figure 1.</p> <p data-bbox="448 636 823 665"><u>General study safety stopping rule:</u></p> <p data-bbox="448 672 1414 730">Enrollment and treatment in the study will be temporarily halted if a serious adverse event (SAE) occurs for the following:</p> <ul data-bbox="496 739 1414 857" style="list-style-type: none"> any unanticipated SAE which is possibly related to the study device or procedure including but not limited to a vascular embolic event that leads to skin necrosis, vision loss or stroke, damage to facial nerves which may result in facial paralysis or injury to internal facial structures. <p data-bbox="448 878 1414 936">The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:</p> <ul data-bbox="496 945 1414 1176" style="list-style-type: none"> was unanticipated, directly related to the study product or device injection procedure, and presents an unreasonable risk to study subjects, the study will be terminated, and the Investigators will be notified. The institutional review board (IRB) and regulatory authority (RA) will also be notified if the study is prematurely terminated due to safety concerns. If the SAE does not meet the above criteria, then enrollment in the study will continue. <p data-bbox="448 1196 620 1225"><u>Randomization:</u></p> <p data-bbox="448 1232 1414 1485">Approximately 224 subjects will be randomized in a 3:1 ratio to treatment with GP0109 or no treatment. Before starting the study, a computer-generated randomization list will be prepared under the supervision of a designated statistician from the Sponsor. The randomization list will be stratified by injection tool (needle, cannula, and combination) and FST group (I-III, IV, and V-VI). The FST I-III group will be further stratified by study site. Randomization numbers will be allocated in ascending sequential order to each subject. Randomization will be performed using an Interactive Response System by assigning each subject to GP0109 or no treatment according to the randomization list.</p>	
<p data-bbox="204 1507 368 1630">Primary Effectiveness Objective and Endpoint</p>	<p data-bbox="448 1507 1414 1565">The primary objective of the study is to demonstrate superiority of GP0109 versus no treatment/control in jawline definition.</p> <p data-bbox="448 1585 555 1615">Endpoint:</p> <p data-bbox="448 1621 1414 1680">Responder rate based on the Blinded Evaluators' live assessment using the GJS, at 3 months after baseline.</p> <p data-bbox="448 1700 1414 1758">A responder is defined as a subject with at least 1 grade improvement from baseline on both jawlines concurrently.</p>	

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Safety Objectives and Endpoints	<div data-bbox="448 1294 1417 1355">To evaluate the incidence, intensity, time to onset, and duration of adverse events (AEs) collected throughout the study period.</div> <div data-bbox="438 1361 1422 1464"></div>	
Subgroup analyses:	<div data-bbox="448 1473 1417 1534">To evaluate the consistency of the primary analysis results across different subgroups, specifically:</div> <div data-bbox="496 1541 1401 1832"><ul style="list-style-type: none">• Injection with needle, cannula, and combination• Study site• Fitzpatrick skin types (I-III and IV-VI)• Race• Ethnicity• Gender• Age (\leq median age, and $>$ median age)• Injection volume (\leq median total injection volume, and $>$ median total injection volume)</div> <div data-bbox="448 1865 1299 1895">To evaluate the consistency of AE data across different subgroups, specifically:</div> <div data-bbox="496 1901 1054 1995"><ul style="list-style-type: none">• Study site• Injection with needle, cannula and combination• Fitzpatrick skin types (I-III and IV-VI)</div>	





	<p data-bbox="371 56 405 73">Title</p> <p data-bbox="371 118 1011 147">CTN 43BBJ1911 US Jawline, Clinical Investigation Plan</p>	
	<ul style="list-style-type: none"> • Injection volumes (\leq median total injection volume, and $>$ median total injection volume) • Gender • Age (\leq median age, and $>$ median age) 	
<p data-bbox="201 421 435 483">Duration of Subject Participation:</p>	<p data-bbox="451 421 1409 483">Clinical study participation for each subject is approximately 25 months, including 30 days screening period.</p> <p data-bbox="451 499 1273 528">One month is defined as 4 weeks in the study; 4 weeks is defined as 28 days.</p>	
<p data-bbox="201 555 368 618">Clinical Study Duration:</p>	<p data-bbox="451 555 1409 678">The planned clinical study duration (from First Subject First Visit to Last Subject Last Visit) is approximately 33 months. This includes approximately 4 months of recruitment time and approximately 4 months for data collection and the FDA review of Stage 1 prior to enrollment of subjects in Stage 2.</p>	
<p data-bbox="201 701 416 730">Inclusion criteria:</p>	<p data-bbox="451 701 1257 730">The subjects must meet all the following criteria to be eligible for the study:</p> <ol style="list-style-type: none"> <li data-bbox="507 745 1409 842">1. Subject is willing to comply with the requirements of the study, including being photographed, following post-treatment care instructions, attending all study visits and providing a signed written informed consent. <li data-bbox="507 857 1305 887">2. Males or non-pregnant, non-breastfeeding females, over the age of 21. <li data-bbox="507 902 1409 999">3. Moderate to very severe (Grade 2 to 4) on the Galderma Jawline Scale (GJS) with no more than one grade difference between the left and right side at baseline as assessed by the Blinded Evaluator. <li data-bbox="507 1014 1134 1043">4. Intent to receive bilateral jawline definition treatment. <li data-bbox="507 1059 1409 1133">5. Subject is willing to abstain from any other facial, submental, and/or neck aesthetic procedure(s) or implant for the duration of the study. <p data-bbox="499 1149 1086 1178">Inclusion criteria 6 - 7 apply to female subjects only</p> <ol style="list-style-type: none"> <li data-bbox="507 1193 1409 1715">6. If the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test (UPT) at the screening/enrollment visit and prior to treatment. Acceptable forms of effective birth control include: <ul style="list-style-type: none"> • Barrier methods of contraception: • Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository. • Bilateral tubal ligation. • Combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1. • Hormonal or copper intra uterine device (IUD) inserted at least 28 days prior to Day 1. • Vasectomized partner (in monogamous relationship) for at least 3 months prior to screening. • Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form of birth control). <li data-bbox="507 1709 1409 1783">7. Negative urine pregnancy test for females of childbearing potential at screening and all injection visits. 	
<p data-bbox="201 1816 416 1845">Exclusion Criteria</p>	<p data-bbox="451 1816 1409 1879">The presence of any of the following exclusion criteria excludes a subject from enrollment in the study:</p> <ol style="list-style-type: none"> <li data-bbox="507 1895 1409 1957">1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins. <li data-bbox="507 1973 1409 2036">2. Known/previous allergy or hypersensitivity to local anesthetics, e.g. lidocaine or other amide-type anesthetics. 	



	<div data-bbox="371 56 406 78">Title</div> <div data-bbox="371 120 1013 152">CTN 43BBJ1911 US Jawline, Clinical Investigation Plan</div>	<div data-bbox="1161 11 1264 35">CCI</div> <div data-bbox="1315 11 1490 35"></div> <div data-bbox="1209 56 1508 224"></div>
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		<ol style="list-style-type: none"> 3. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions. 4. Prior surgery in the treatment area or neck surgery that in the Treating Investigator's opinion could interfere with the study safety and/or effectiveness assessments. 5. Any previous aesthetic procedures or implants: <ul style="list-style-type: none"> • Previous permanent filler or implant, lifting threads, or autologous fat in the face or neck regardless of time. • Previous Calcium Hydroxylapatite (CaHA), poly L-lactic acid (PLLA) below the level of the horizontal line from subnasale including the neck within 24 months. • Previous HA filler or collagen filler below the level of the horizontal line from subnasale including the neck within 12 months. • Previous botulinum toxin treatment below the level of the horizontal line from subnasale including the neck and in the masseter area within 6 months. • Previous energy based aesthetic procedures (e.g. laser, intense pulsed light, radiofrequency and ultrasound) below the level of the horizontal line from subnasale, in the submental area and neck within 6 months. • Previous mechanical (e.g. dermabrasion, needling) or chemical aesthetic procedures (e.g. chemical peel) below the level of the horizontal line from subnasale, in the submental area and neck within 6 months. • Previous treatment with cryotherapy below the level of the horizontal line from subnasale, in the submental area and neck within 6 months. 6. Deoxycholic acid treatment in the submental region within the last 6 months. 7. Presence of any disease or lesions near or on the area to be treated, e.g.: <ul style="list-style-type: none"> • Inflammation, active or chronic infection (e.g. in mouth, dentals, head and neck region); • Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes simplex or herpes zoster; • Scars or deformities; • Cancer, or precancer such as actinic keratosis or actinic cheilitis. 8. Evidence of scar-related disease or delayed healing activity within 12 months, or subjects susceptible to keloid formation, hyperpigmentation, or hypertrophic scarring. 9. History of cancer or previous radiation in the treatment area. 10. Subjects with temporomandibular joint dysfunction, jaw pain, chewing pain, muscular related pain in the treatment area, and pain from opening and closing the mouth. 11. Presence of a dental, oral, or facial condition which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment, e.g. has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities. Any planned procedure (e.g. dental implants, tooth extractions, orthodontia) during the study period, that would make the subject unsuitable for inclusion in the opinion of the Investigator. 12. Presence of abnormal rating in jaw mobility and function; jaw mobility restrictions or inability to pronounce at least 80% of the pre-selected words. 13. Presence of abnormal rating in jawline sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the jawline, or abnormal rating of facial nerve function. 14. Detection of any abnormal jawline structure, such as unexpected lump or nonuniform density.


	<ol style="list-style-type: none"> 15. Any past or current history of severely impaired/absent eye function in 1 or both eyes and/or uncontrolled retinal disease, retinal vascular occlusion (e.g. vein or arterial occlusion), narrow angle glaucoma, neovascular eye disease, detached retina, or any other condition with the potential to cause a decline of visual acuity (e.g. uncontrolled diabetes). 16. Poor visual acuity; with an absolute score on the Snellen chart of 20/50 or worse in one or both eyes using the prescribed correction (e.g. contacts or eyeglasses) or the other visual function assessment tests with abnormal clinical findings according to Treating Investigator. 17. An underlying known disease, a surgical or medical condition that would expose the subject to undue risk, e.g. HIV, active hepatitis, autoimmune disease, history of bleeding disorders, connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, or scleroderma. 18. Use of concomitant medications that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation, e.g. aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs), Omega 3, or Vitamin E within 2 weeks (i.e. 14 days) before treatment. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation. 19. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., immunosuppressive monoclonal antibodies, antiviral treatment for HIV or hepatitis) within 3 months. 20. Treatment with systemic corticosteroids within 3 months before treatment (inhaled corticoids are allowed). 21. Use of topical facial corticosteroids or prescription retinoids (below the level of the horizontal line from subnasale) within 1 month of the baseline visit or systemic retinoid treatment within 6 months of the baseline visit, or plan to receive such treatment during participation in the study. 22. Presence of tattoo, piercing, beard or facial hair, which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment. 23. Presence of any condition which, in the opinion of the Treating Investigator, makes the subject unable to complete the study per protocol, e.g.: 24. Subject is not likely to avoid other prohibited facial cosmetic treatments 25. Subject is not likely to complete the study because of other commitments 26. Subject is anticipated to be unavailable for visits, incapable of understanding the investigational assessments, or has unrealistic expectations of treatment result 27. Subject who has a concomitant condition (e.g. acute viral or bacterial infection with fever) that might interfere with study treatments or assessments 28. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period. 29. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company. 30. Participation in any other interventional clinical study within 30 days before treatment.
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Investigational product:	<p>GP0109 1 mL in a glass syringe.</p> <p>The sterilized gel contains 25 mg/mL crosslinked HA CCI and 3 mg/mL lidocaine hydrochloride in a physiological buffer.</p> <p>Needle TSK Steriject 27G x 3/4" (19 mm) and Cannula TSK Steriglide 25G x 2" (50 mm). Both are commercially available.</p>
Reference therapy:	No treatment control group
Treatment regimen and location of treated area:	<p>In the study, the treatment area extends from the mandibular angle, through the jawline and including the post- and pre-jowl area (from tip of ear to tip of chin) in order to create a smooth correction that blends well with the adjacent structures.</p> <p>Subjects in the treatment group will receive one GP0109 treatment at baseline and one optional touch-up treatment at 1 month.</p> <p>Subjects in the no treatment group will be offered an optional GP0109 treatment at 12 months. The subjects who received treatment at baseline will also be offered an optional re-treatment at the month 12 visit, if aesthetic improvement is not maintained (as determined by the Treating Investigator and subject).</p> <p>Sites will be selected to use either needle, cannula or a combination for injection of all subjects at their site. The injection technique is at the Treating Investigator's discretion in the deep subcutaneous tissue or supraperiosteal plane. Depending on the location and injection tool, serial puncture (needles), tunneling, and linear threading among other techniques can be used to safely and effectively enhance the contour, shape and definition of this aesthetic region. The injection technique and the use of needle/cannula per treated area will be recorded.</p> <p>Aspiration is recommended prior to each injection.</p> <p>It is recommended to start injection with small aliquots at the edge of the angle of the mandible in the deep subcutaneous tissue or supraperiosteal to enhance the mandibular angle. Once the mandibular angle is defined, continue the correction with the mandible body with a threading technique medially and inferior to the masseter and the post-jowl sulcus using needle or cannula. The antegonial notch injection where facial artery is should be avoided; in this area, subcutaneous injection is recommended. The ascending mandibular ramus is recommended to be treated in the subcutaneous plane to avoid the parotid gland.</p> <p>Injection into the masseter muscle should be avoided and attempts should be made to inject superficial to or deep below the masseter muscle. Care must be taken to avoid facial artery and vein, mental nerve and artery, parotid gland, superficial temporal artery and vein, marginal mandibular nerve.</p> <p>Slow injection is recommended, and overcorrection should be avoided.</p> <p>After each injection, the treated tissue may be massaged for a smooth placement of the filler and optimal jawline contouring.</p> <p>Allowed maximum injection volume is 4 mL per treatment session and side of face, with a total maximum volume of 8 mL per treatment session. The injection can bridge all the way from the mandibular angle, post-jowl and to the pre-jowl area (from tip of ear to tip of chin). Treatment of chin area is allowed for achieving a smooth contour, however treatment of chin retrusion is not within the scope of the study.</p>

	<div data-bbox="1161 11 1264 38">CCI</div> <div data-bbox="1315 11 1490 38"></div> <div data-bbox="1203 60 1506 224"></div> <div data-bbox="371 60 405 76">Title</div> <div data-bbox="371 120 1011 150">CTN 43BBJ1911 US Jawline, Clinical Investigation Plan</div>
<div data-bbox="204 271 352 327">Effectiveness Assessments</div>	<div data-bbox="453 271 1321 645"></div>
<div data-bbox="204 651 424 678">Safety Assessments</div>	<div data-bbox="496 651 1390 779"><p>1. Adverse Event reporting: AEs will be obtained from signs and symptoms reported by the subject or detected during each examination. Any ongoing AEs related to product or injection procedure will be followed until resolved or chronic/stable through end of study participation.</p></div> <div data-bbox="485 786 1401 1547"></div> <div data-bbox="496 1554 1401 1951"><p>3. Palpation, jaw mobility and functionality tests, at screening, baseline and at each physical follow-up visit.</p><p>4. Facial nerve function test at screening, baseline and at each physical follow-up visit.</p><p>5. Changes in hair growth (e.g. loss or growth) in the treated area, at each physical follow-up visit after baseline.</p><p>6. Visual function assessments (i.e. Snellen visual acuity test, extraocular muscle function test, and confrontation visual field test) will be performed at baseline and all following physical visits. At treatment visits the assessments will be performed both prior to and post injection of the study product.</p><p>7. Device deficiencies will be assessed at treatment visits.</p></div>

	<p data-bbox="371 58 405 73">Title</p> <p data-bbox="371 118 1011 147">CTN 43BBJ1911 US Jawline, Clinical Investigation Plan</p>	
<p data-bbox="204 275 432 300">Statistical Methods</p>	<p data-bbox="451 275 675 300"><u>Analysis populations</u></p> <ul data-bbox="507 311 1409 562" style="list-style-type: none"> • Intention-to-treat (ITT) population will include all subjects who are randomized and will be analyzed according to the randomization scheme • Per protocol (PP) population will include all subjects in ITT who complete the 3 months after baseline visit, without any deviations considered to have substantial impact on the primary effectiveness outcome • Safety population will include all subjects who were treated with GP0109 or randomized to the control group, and will be analyzed according to as-treated principle <p data-bbox="451 584 775 609"><u>Primary effectiveness analysis</u></p> <p data-bbox="451 618 1409 734">Responder rate based on the GJS, as assessed live by the Blinded Evaluator at Month 3 after baseline, will be the primary effectiveness endpoint. A responder will be defined as a subject with at least 1 grade improvement from baseline on both sides of the face concurrently.</p> <p data-bbox="451 757 1409 904">The null hypothesis will be that there is no relationship between responder rate and treatment group (i.e. the responder rate is the same in treated and untreated subjects). The alternative hypothesis will be that there is a relationship between responder rate and treatment group (i.e. the responder rate is different in treated subjects compared to untreated subjects).</p> <p data-bbox="451 927 1409 1043">The estimates of the responder rate in each treatment group will be presented as well as the difference in responder rates. Corresponding confidence intervals for responder rates and the difference in responder rates along with the p-value for the difference will also be presented.</p> <p data-bbox="451 1066 1409 1429">First, the Breslow-Day test for homogeneity of odds ratios will be used to assess consistency of GJS odds ratios across all strata (the needle-treated group, the cannulatreated group, and the combination group). A significance level of 0.05 will be used to determine if the responder rates are non-homogenous. If the Breslow-Day p-value is less than or equal to 0.05, the primary analysis will be stratified (i.e. conducted separately) for the needle-treated group, the cannula-treated group, and the combination group, using a significance level of 1.7% to account for multiplicity. If the Breslow-Day p-value is greater than 0.05, the analysis will be carried out on pooled groups, using a significance level of 5%. Regardless of whether the primary analysis will be based on pooled injection tool groups, or done separately, the no treatment control subjects will be pooled across all study sites. Fisher's exact test will be used to compare the responder rates between the treated and untreated subjects at Month 3.</p> <p data-bbox="451 1451 1409 1536">In order to assess the poolability of study sites, a Breslow-Day test for homogeneity of odds ratios across sites will be performed. If the p-value of the sites test is <0.05, then subgroup analysis by study sites will be done.</p> <div data-bbox="451 1547 1409 2029">  </div> <p data-bbox="451 2040 611 2065"><u>Safety analysis</u></p>	

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	<p data-bbox="371 56 405 73">Title</p> <p data-bbox="371 118 1011 147">CTN 43BBJ1911 US Jawline, Clinical Investigation Plan</p>	
	<p data-bbox="448 275 852 304">This analysis will be descriptive only.</p> <p data-bbox="448 322 651 351"><u>Subgroup analyses</u></p> <p data-bbox="448 356 1407 508">In order to investigate the homogeneity of the results of the primary analysis across different subgroups, subgroups defined by injection tool, study site, Fitzpatrick skin types (I-III and IV-VI), race, ethnicity, injection volume, age, and gender will be used. Fisher's exact tests will be used as in the primary analysis, as well as confidence intervals for the difference in responder rates. These will be displayed in graphs.</p> <p data-bbox="448 526 1407 613">In addition, the consistency of AE data across different subgroups will be evaluated. Subgroups will be defined by study site, injection tool, Fitzpatrick skin types (I-III and IV-VI), gender, age, and injection volumes.</p> <p data-bbox="448 631 866 660"><u>Handling of dropouts and missing data</u></p> <p data-bbox="448 665 1254 694">Number of missing values will be summarized and reported as appropriate.</p> <p data-bbox="448 712 1407 864">For ITT analysis of the Blinded Evaluator GJS responder rate at 3 months after baseline (primary endpoint), missing values will be assumed to be missing due to lack of effect. Therefore, the primary method of imputation will use the baseline observation carried forward (BOCF) method. Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the observed cases in the ITT set.</p> <p data-bbox="448 882 1378 911">All other effectiveness endpoints will be evaluated based on the observed cases in ITT.</p> <p data-bbox="448 929 1398 987">Descriptive statistics of all safety data will be performed on observed cases in the Safety population.</p> <p data-bbox="448 1005 579 1034"><u>Sample size</u></p> <p data-bbox="448 1039 1407 1191">A total sample size of approximately 224 subjects will be included in this study. Approximately 168 subjects will be randomized to treatment with GP0109 (~56 will be injected using needle, ~56 will be injected using cannula, and ~56 will be injected using both combined) and approximately 56 will be randomized to no treatment. Sample size justifications are given below.</p> <p data-bbox="448 1209 595 1238"><u>Previous data</u></p> <p data-bbox="448 1243 1407 1272">Since the primary endpoint will be based on a new scale, no existing data is available.</p> <p data-bbox="448 1272 1407 1361">CCI</p> <p data-bbox="448 1379 592 1408"><u>Assumptions</u></p> <p data-bbox="448 1413 1407 1565">Based on results in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a responder rate of at least 70% in the GP0109 treatment group at 3 months after baseline. For the no treatment control group, responder rates up to almost 30% have been observed in the data on file. Based on this, it is assumed that the response rate will be maximum 32% in the no treatment control group at 3 months after baseline.</p> <p data-bbox="448 1565 1407 1776">CCI</p> <p data-bbox="448 1787 584 1816"><u>Calculations</u></p> <p data-bbox="448 1821 1407 1937">Using a two-sided test at the 5% significance level will have more than 99% power to demonstrate difference between a responder rate of 70% in the GP0109 group and a responder rate of 32% in the no treatment control group when the sample sizes are 150 and 50, respectively.</p> <p data-bbox="448 1955 1407 2045">Performing the same test, but in needle, cannula, and combination subjects separately (at the 1.7% level of significance for each test to account for multiplicity), the power will be approximately 90% (assuming the same responder rate of 70% in all GP0109 groups</p>	

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	<div>(needle, cannula, and combination). All no treatment subjects will be included in each of the by strata tests.</div> <div>Accounting for approximately 10% dropouts at 3 months after baseline, approximately 224 subjects need to be randomized in a 3:1 ratio (GP0109 to no treatment).</div> <div>CCI</div> <div><div><u>Safety considerations</u></div><div>With 168 treated subjects, there will be a probability of approximately 80% for the study to detect at least one subject having an adverse event with an assumed population incidence of 1%.</div></div>	


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Abbreviations and Definitions of Terms

AE	Adverse Event
Blinded Evaluator	An evaluator responsible for independent evaluation of treatment result(s). The evaluator should be a Health Care Professional and must not be involved in the treatment of the subject.
BDDE	1,4-butanediol diglycidyl ether
BOCF	Baseline Observation Carried Forward
CaHa	Calcium Hydroxylapatite
CRF	United States Code of Federal Regulations
Childbearing Potential	A female (including pre-menopausal subjects) capable of becoming pregnant; this includes women on oral, injectable, or mechanical contraception or women whose male partners have been vasectomized or are utilizing mechanical contraceptive devices. A female that had a surgical sterilization procedure is not considered to be of childbearing potential.
CIP	Clinical Investigation Plan
CCI	
CIs	Confidence intervals
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CTA	Clinical trial agreement
CTN	Clinical trial number
CV	Curriculum vitae
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance (includes malfunctions, use errors, and inadequate labelling)
DMP	Data management plan
eCRF	Electronic case report form
EOS	End of Study
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
FST	Fitzpatrick skin type
G	Gauge
CCI	
GCP	Good clinical practice
GJS	Galderma Jawline Scale
GDPR	General Data Protection Regulation

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HIV	Human Immunodeficiency Virus	
HA	Sodium hyaluronate often referred as Hyaluronic acid	
IB	Investigator's Brochure, i.e. compilation of the current clinical and non-clinical information on the investigational product, relevant to the clinical study	
ICF	Informed Consent Form	
ICH	International Conference on Harmonisation	
IFU	Instructions for use	
Investigational product	Medical device being assessed for safety or performance in a study. "Investigational product" is the same as "study device," "investigational device," or "investigational medical device."	
Institution	Any public or private entity or agency or medical or dental facility where a clinical study is conducted.	
Investigator	The Principal Investigator (PI) or other qualified person, i.e. sub-Investigator, designated and supervised by the PI at a study site to perform critical study-related procedures or to make important study-related decisions as specified on the signature and delegation log. An Investigator should be a Physician.	
Investigator file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Investigator.	
IRB	Institutional review board	
ISO	International Organization for Standardization	
ITT	Intention-to-treat	
IUD	Intra uterine device	
MedDRA	Medical Dictionary for Regulatory Activities	
MDR	Medical Devices Regulation	
NSAID	Non-steroidal anti-inflammatory drug	
PI	Principal Investigator; qualified person responsible for conducting the study at a study site	
PLLA	Poly L-lactic acid	
PP	Per protocol	
PT	Preferred term	
RA	Regulatory authority	
Reference product	Medical device, therapy (e.g. active control), placebo, or no treatment, used in the reference group in a study	
ROPI	Report of Prior Investigations	

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SAE	Serious Adverse Event	
SAP	Statistical Analysis Plan	
SDV	Source data verification	
SMP	Safety Management Plan	
SOC	System organ class	
Sponsor file	Essential documents relating to a clinical study as defined in applicable GCP guidance document and maintained by the Sponsor	
Study files	The Investigator file and the Sponsor file	
Study products	The investigational product and the reference product under study	
Study site	Institution or site where the study is carried out	
TC	Telephone Call	
Touch-up/TU	Repeated injection to be performed after treatment, if necessary to achieve optimal correction	
Treating Investigator	Qualified physician to perform the study injections, should be aware of important neurovascular and anatomical structures near injection sites	
Tx	Treatment	
UPT	Urine pregnancy test	
WHO	World Health Organization	

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1. Ethical Considerations

1.1 Statement of ethical compliance

The study shall be conducted in compliance with the clinical trial agreement (CTA), the clinical investigation plan (CIP), good clinical practice (GCP), and applicable regional or national regulations. The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1964, and its amendments in force at the initiation of the study) insofar as such revisions are consistent with US treaty obligations and in accordance with US law.

The study shall follow the international standard for clinical study of medical devices for human subjects, International Organization for Standardization (ISO) 14155:2020 or later updates as applicable for US regulations, and the International Conference on Harmonisation (ICH) guideline for GCP (E6(R2)) as applicable for medical device.

The study related medical care provided to the subjects during the study is the responsibility of an appropriately qualified medical doctor (i.e. the Principal Investigator) or, where appropriate any other person entitled by national law to provide the relevant patient care.

1.2 Application to institutional review board; IRB and/or regulatory authorities

It is the responsibility of the Principal Investigator (PI) to obtain approval of the CIP/CIP amendment(s) from the institutional review board (IRB). The study shall not begin until the required favorable opinion from the IRB has been obtained. The PI shall file all correspondence with the IRB in the Investigator file and copies of IRB approvals shall be forwarded to the Sponsor. Any additional requirements imposed by the IRB or regulatory authorities (RA) shall be followed.

The study requires application for approval from the US Food and Drug Administration (FDA).

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The study will not be started until the Sponsor has received written approval or until the statutory waiting period from the appropriate authority has elapsed. The Sponsor will provide the PI with a copy of the relevant document.

The collection, access to, processing, and transfer of protected health information or sensitive personal data shall be carried out in accordance with applicable rules and regulations.

2. Background Information

2.1 Indication and population description

GP0109 is an injectable implant intended to be used to restore and enhance jawline definition in subjects over the age of 21 years.


The target population for this product is male and female adults for treatment according to the intended use. The study population is defined in the study inclusion and exclusion criteria. The plan is to include study subjects representative of the target population; both male and female subjects of different ages and with different skin types. Race and ethnicity will be evaluated as subgroups in the study. The exclusion criteria are chosen to, in a safe manner, evaluate the product.

2.2 Study Product Profile

2.2.1 Investigational product description

The investigational product GP0109 is a new medical device, currently not approved for use in any country and there is no clinical experience to date.

GP0109 is a new member of the Restylane family and is manufactured using the NASHA™ technology. The Restylane® family of products are injectable, sterile, transparent and biodegradable gels of sodium hyaluronate (HA) generated by Streptococcus species of bacteria, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and suspended in phosphate buffered saline pH 7. Some of the products in the Restylane family are manufactured with the addition of 3 mg/mL lidocaine for pain reduction during treatment.

GP0109 shares many properties with the already marketed and clinically established product Restylane® Lyft™ Lidocaine. In order to build a defined and straight jawline an injectable filler with high lifting potential is required. The gel in GP0109 is therefore slightly modified to be optimal for the intended use. The main difference is that instead of 20 mg HA/mL, GP0109 has a higher HA concentration, 25 mg/mL  after crosslinking. The purpose of the higher HA concentration is to increase the lifting potential of the gel, while the purpose of adding non-crosslinked HA is to reduce the extrusion force of the product needed to facilitate the injection.

GP0109 in 1 mL syringes will be used in the study and will be injected with needle, cannula or a combination of both.

2.2.1.1 Pre-clinical documentation

NASHA™ gels, with and without lidocaine hydrochloride, have been tested for cytotoxicity, genotoxicity, sensitization and irritation and for local and systemic toxicity in accordance with ISO 10993 (Biological Evaluation of Medical devices). The conclusion of these studies was that the products fulfilled the current biocompatibility requirements for medical devices.

Additional studies for cytotoxicity, irritation, sensitization, pyrogenicity and implantation in accordance with ISO 10993, were performed to finalize the biological evaluation of GP0109 despite the very small differences in the physicochemical properties (HA concentration, addition of non-crosslinked HA, gel particle size) and the equivalence found at the chemical characterization between GP0109 and Restylane Lyft Lidocaine. The data collected and tests performed show no new risks for GP0109 when compared to the already marketed and clinically used Restylane Lyft Lidocaine. Thus, the risk for biocompatibility issues with GP0109 should be minimal.

2.2.1.2 Clinical documentation

As GP0109 shares many properties with Restylane Lyft Lidocaine, the reported PostMarketing Adverse Events (AEs) for Restylane Lyft Lidocaine has been chosen as basis for risks anticipated for GP0109. Please refer to the GP0109 study specific Instructions for Use (IFU) which summarizes AEs experienced with Restylane Lyft Lidocaine injections and expected for this new gel, along with precautions that can minimize these potential complications.

For intravascular complications or embolic event, the treating physician should provide prompt medical attention and follow relevant clinical practice guidelines¹ for handling these symptoms. The treating physician should also review the Intravascular Treatment Protocol² provided separately in the Investigator file, as a support tool.

Please refer to the study Report of Prior Investigations (ROPI) for a description of clinical studies completed in the jawline area with Restylane products, post-market reporting of the Restylane products in total as well as separately in the jawline area, and available clinical data from publications with HA fillers in the jawline area.

2.2.2 Reference product description

Not applicable. The reference in this study is a no treatment control.

2.3 **Study rationale and justification for design**

The rationale for performing this study is to obtain evidence of safety and effectiveness of GP0109 for restoration and enhancement of jawline definition, to support future marketing applications.

From an aesthetic perspective, the jawline contributes significantly to facial proportional appearance and is a critical component in the perception of facial attractiveness in both men and women. An attractive jawline constitutes a well-defined, straight jawline. Aging across the mandibular border may be described by several mechanisms: Fat atrophy and volume loss; shifting of subcutaneous fat compartments; and mandibular septum dehiscence with submandibular fat hypertrophy.³ With aging, bone recession, combined with mid-face laxity, may produce sagging skin below the jawline as the supporting systems diminish. In the lower face, this age-associated volume loss leads to loss of definition of the jawline.⁴ Individuals are looking to create or enhance an attractive appearance by improving their natural definition of the jawline. In Europe, a consumer survey revealed that the jawline is a preferred feature to change for one-third of women aged 46-63 years.⁵ Further, enhancing to achieve a welldefined, "strong", masculine jawline is also desired by men.⁶ Rejuvenation of the jawline is becoming part of routine aesthetic practice with injectable dermal fillers containing hyaluronic acid or calcium hydroxylapatite.

No treatment has been chosen as control as there is no approved dermal filler for this indication in the US. No treatment control is a commonly accepted comparator in aesthetic injectable filler trials for new indications.

The effectiveness of GP0109 for jawline definition will be evaluated by demonstrating superiority in responder rates (defined as at least 1 grade improvement from baseline on both jawlines concurrently on the Galderma Jawline Scale [GJS]) relative to no treatment. The GJS was developed as a quantitative assessment of the jawline area in clinical trials. For the GJS to be considered a reliable and valid tool for assessing aesthetic improvements, live subjects were rated by an independent panel at two sessions separated at least two weeks apart in order to assess the intra- and inter-rater reliability. Based on the validation results, the GJS was determined to be fit for use in clinical settings to detect changes to treatment by improving the jawline definition as a result of volume correction.

2.4 Risks and benefits

The benefits of treatment of the jawline with HA fillers have been documented in clinical studies, post-market surveillance, and published literature. Treatment with HA fillers are less invasive than surgical options and may offer less downtime from swelling and bruising. Adding volume in the jawline may improve subject satisfaction and restore youth by creating definition. HA fillers are becoming more popular for the treatment of jawline and have a good safety profile.

Restylane products have been proven safe and well tolerated in animal studies as well as in human clinical studies. The non-clinical data collected, and tests performed, show no new risks for GP0109 when compared to the already marketed and clinically used Restylane Lyft Lidocaine. Thus, the risk for biocompatibility issues with GP0109 should be minimal.

There is no previous clinical experience of GP0109 since this is a new product to the Restylane family. To establish the safety profile of GP0109 in a clinical setting and to mitigate any unforeseen risks, study enrollment will be conducted in two stages. Stage 1 includes the first approximately 50 eligible subjects who will be randomized to treatment or to no treatment. The Sponsor will submit 3-month-after-baseline data from subjects in stage 1 to the FDA for review and await the agency's agreement to continue enrollment into Stage 2.

Overall, clinical studies demonstrated that treatment with Restylane products in the jawline area were effective and well tolerated, and satisfactory aesthetic outcome results were obtained. No treatment-related Serious Adverse Events (SAEs) were reported in the studies.

Safety data obtained from published literature confirm that the risks of injecting HA filler in the jawline and chin area are acceptable and that HA fillers are a good alternative for jawline aesthetic treatment. The risk of vascular compromise always needs to be taken into consideration. Bone resorption and osteomyelitis are extremely rare and unique case reported events, these theoretical events need additional studies and monitoring in order to draw further conclusions. Adverse reactions can occur, but many can be prevented with proper planning and detailed understanding of treatment anatomy to avoid vulnerable areas. Appropriate injection technique can further reduce the risk. Generally, any suspected granuloma should be confirmed by biopsy.

The most common medical complaints received from post marketing surveillance after treatment with Restylane NASHA fillers in jawline/chin are swelling, mass/induration, and pain/tenderness. Serious adverse events are rarely reported (reporting frequency <0.001%

based on post-market surveillance data) following treatment with Restylane Lyft Lidocaine (reference product to GP0109) in any indication. Among the few case reports assessed as serious and related to treatment with Restylane Lyft Lidocaine, events of infection/abscess, swelling and ischemia/necrosis were the most commonly reported. Serious adverse events following treatment in the jawline/chin area showed a similar reporting pattern as that for treatment with Restylane Lyft Lidocaine in any treatment area.

The product contains the local anaesthetic lidocaine to reduce pain. To further reduce pain, subjects can receive additional local anaesthetics. Lidocaine can, in rare cases, cause allergic reactions. Therefore, subjects with known allergy or hypersensitivity to local anesthetics should not be included in the study.

Additional information about expected AEs and anticipated risks are included in the product specific IFU and ROPI.

To mitigate these risks, only study Investigators qualified by education and experience, who are skilled in the use of dermal fillers from their clinical practice and involvement in clinical research, and with knowledge of facial anatomy, understanding of the depth and plane of injection, as well as knowledge of the signs and symptoms and management of potential complications, will be chosen to participate in this study. This further ensures proper device implantation and management of study risk.

In light of the recent pandemic, Treating Investigators should be mindful of the risk posed by the interaction of hyaluronic acid dermal filler with SARS-CoV-2 and vaccination. The current data does not support the concern for an increased risk of developing severe adverse reactions following soft tissue filler injections associated with the COVID-19 vaccines compared to that risk associated with other previously described triggers or the default risk following soft tissue filler injections.

Potential hazards related to treatment with GP0109 are assessed, evaluated, and managed in accordance with the requirements in ISO 14971 standard and in-house established risk management procedures. To date, no unacceptable risks have been identified for the use of GP0109 in the setting of a clinical study.

It is concluded that there is reasonable assurance from a safety perspective for conducting an IDE clinical trial in the USA, using GP0109 for injection into the jawline in subjects over the age of 21 years.

Given the anticipated low level of transient and acceptable AEs in connection with the injection, the protocol-required safety assessments, and the injection technique training provided, it was determined the risk-benefit assessment for use of GP0109 for jawline definition offer a clinical benefit at reasonable risk.

3. Objective(s) and Endpoint(s)

3.1 Objectives and endpoints

3.1.1 Primary objective and endpoint


The primary objective of the study is to demonstrate superiority of GP0109 versus no treatment control in jawline definition.

Endpoint:

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- ☐ Responder rate based on the Blinded Evaluators’ live assessment using the GJS, at 3 months after baseline.
- A responder is defined as a subject with at least 1 grade improvement from baseline, on both jawlines concurrently.



- 3.1.3 Safety objectives The safety objectives and endpoints are:
- To evaluate the incidence, intensity, time to onset and duration of adverse events (AEs) collected throughout the study period.
- 

4. Design of the Study

4.1 General outline

This is a prospective, randomized, evaluator-blinded, no treatment controlled, parallel group, multicenter study in United States to evaluate the effectiveness and safety of GP0109 for jawline definition. Approximately 224 subjects will be included in the study, randomized (3:1) to treatment or to no treatment group.

In the treatment group, approximately 56 subjects will receive injections with needle, 56 with cannula, and 56 with both needle and cannula combined. Approximately 56 subjects will be randomized to no treatment at baseline.

The study enrollment will be conducted in two stages. Stage 1 includes the first approximately 50 eligible subjects that will be randomized to treatment or to no treatment. The aim is to achieve an even distribution of subjects to a minimum one site using needle for injection, one site with cannula for injection, and one site with combination of needle and cannula for injection. The Sponsor will submit the 3 months after baseline data collected on subjects in stage 1 to the FDA for review and await the agency's agreement to continue enrollment into Stage 2. In Stage 2, approximately 174 eligible subjects will be enrolled and randomized.

All randomized subjects will have a GJS grade of 2 (moderate) to 4 (very severe) at baseline.

Investigator blinding will be accomplished by having a Treating Investigator administer the treatments and having a Blinded Evaluator, to whom randomization and treatment are concealed, conduct blinded assessments using the GJS. Safety assessments will be performed by non-blinded personnel.

Eligible subjects randomized to receive treatment will be injected by the Treating Investigator at Day 1. A follow-up telephone call should be made 72 hours after treatment and a follow-up visit should be completed 14 days after treatment. Optional touch-up treatment may be administered 1 month after initial treatment, if deemed necessary by Treating Investigator and the subject to obtain optimal aesthetic improvement. Optimal aesthetic improvement is defined as at least 1 grade improvement from baseline on the GJS, and best correction that can be achieved as agreed by the Treating Investigator and the subject.

If optional touch-up is performed, a 72-hour follow-up telephone call, a 14-day follow up visit, and a 1-month follow up visit should be scheduled. At the Month 12 visit, subjects in the no treatment group will be offered optional GP0109 treatment. Subjects in the no treatment/control group that do not receive treatment at month 12 will end the study at month 12. The subjects who received treatment at baseline will also be offered an optional additional treatment at the month 12 visit if aesthetic improvement is not maintained (as determined by the Treating Investigator and the subject). If optional treatment is performed, a 72-hour follow-up telephone call, a 14-day follow up visit, and a 1-month follow up visit should be scheduled. *Note: The Blinded Evaluator is not blinded to study treatment following the Month 12 visit.*

Effectiveness and safety data will be collected for up to 24 months from baseline. A subject will be involved in the study for up to 25 months, including a 30-day screening period.

The study visits are illustrated in Figure 1.

General study safety stopping rule:

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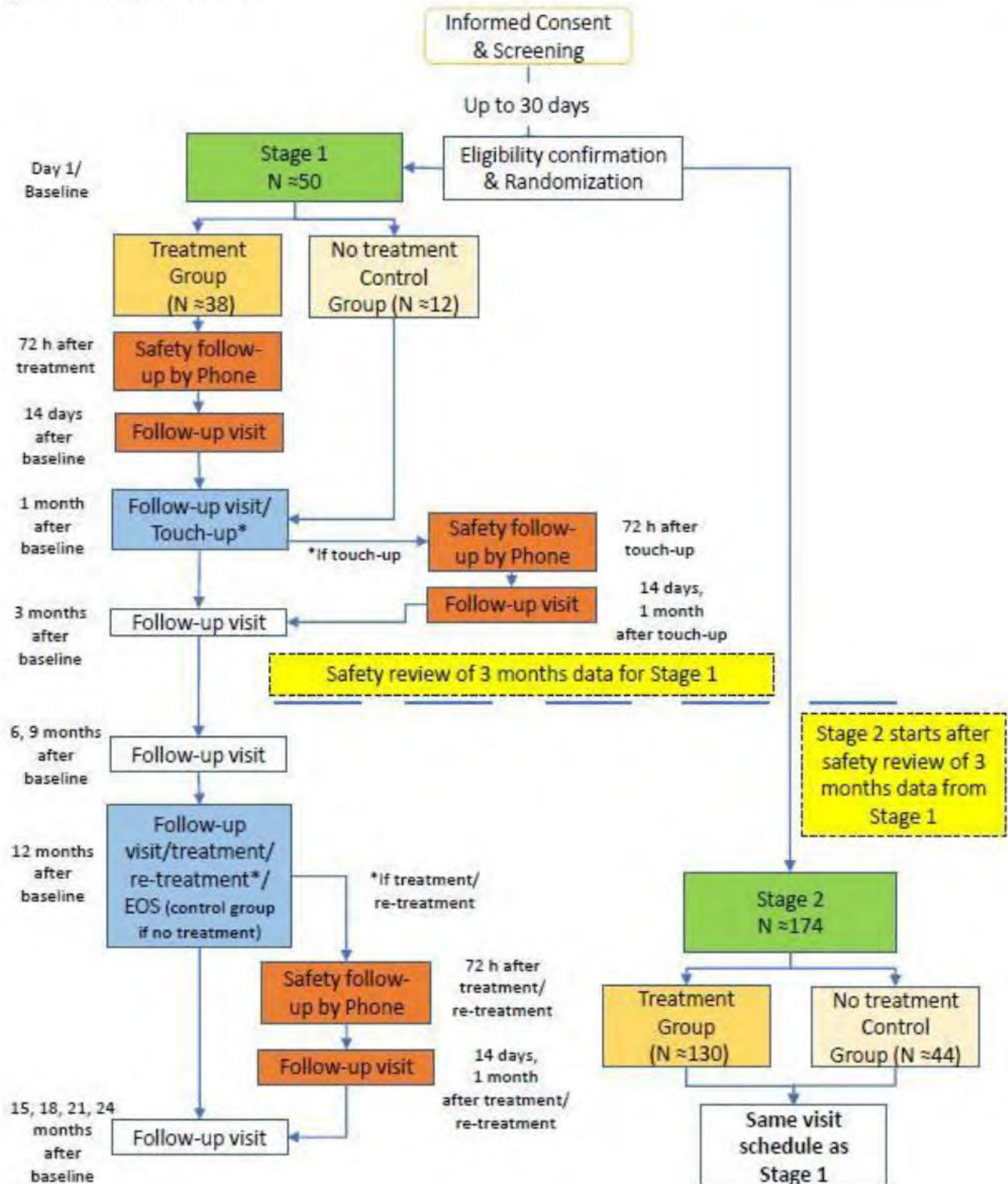
Enrollment and treatment in the study will be temporarily halted if a serious adverse event (SAE) occurs for the following:

- any unanticipated SAE which is possibly related to the study device or procedure, including but not limited to a vascular embolic event that leads to skin necrosis, vision loss or stroke, damage to facial nerves which may result in facial paralysis, or injury to internal facial structures.

The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:

- was unanticipated,
- directly related to the study product or device injection procedure,
- and presents an unreasonable risk to study subjects, the study will be terminated, and the Investigators will be notified. The IRB and RA will also be notified if the study is prematurely terminated due to safety concerns. If the SAE does not meet the above criteria, then enrollment in the study will continue.

Figure 1: Study Flow Chart



4.2 Number of subjects

Approximately 224 subjects will be enrolled at approximately 15 sites in the US. At least 45 subjects will be Fitzpatrick Skin Type (FST) IV through VI. This includes at least 23 subjects with FST V-VI, where at least 12 subjects will be FST V and at least 11 will be FST VI.

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Stage 1 includes the first approximately 50 eligible subjects that will be randomized to treatment or to no treatment. At least 10 of these subjects will be FST IV-VI, with at least 3 subjects with FST V and at least 2 subjects with FST VI.

The duration of the enrollment period for Stage 2 is expected to be 4 months. Approximately 15 subjects will be included and treated at each site. The aim is to achieve an even distribution of subjects between the assigned sites.

4.3 Duration of subject participation

The total duration of the study is approximately 33 months. This includes approximately 4 months recruitment time and approximately 4 months for data collection and the FDA review of Stage 1 prior to enrollment of subjects in Stage 2.

Clinical study participation for each subject is approximately 25 months, including 30 days screening period. For subjects in the control group that do not receive treatment at month 12, the clinical study participation is approximately 13 months including the screening period.

The screening visit and baseline visit can be combined and performed on the same day if no drug washout is needed.

One month is defined as 4 weeks in the study; 4 weeks is defined as 28 days.

End of Study is when enrollment has reached the target number of subjects and all ongoing subjects have completed their last study visit (i.e. month 24, or month 12 for control subjects who do not receive optional treatment).

4.4 Randomization and blinding

4.4.1 Randomization

Approximately 224 subjects will be randomized in a 3:1 ratio to treatment with GP0109 or no treatment. Before starting the study, a computer-generated randomization list will be prepared under the supervision of a designated statistician from the Sponsor. The randomization list will be stratified by injection tool (needle, cannula, and combination) and FST group (I-III, IV, and V-VI). The FST I-III group will be further stratified by study site. Randomization numbers will be allocated in ascending sequential order to each subject. Randomization will be performed using an Interactive Response System by assigning each subject to GP0109 or no treatment according to the randomization list.

4.4.2 Blinding

The Treating Investigator will not be blinded to study treatments.

A Blinded Evaluator, to whom randomization and treatment are concealed, will conduct the blinded assessments. To the extent possible, the same Blinded Evaluator should assess an individual subject throughout the study.

The Blinded Evaluator is not allowed to be present during the injections or to discuss treatments with the Treating Investigator or subjects. All documents with information regarding study products and randomization assignment should be kept in a separate file not available to the Blinded Evaluator.

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Safety assessments will be performed by non-blinded personnel as treatment-related AEs are expected to occur during a few days after treatment, thereby revealing which subjects have received the study product.

4.4.3 Emergency unblinding

Not applicable as the Treating Investigator is not blinded to treatment.

4.5 **Medical history**

History of relevant surgical events and medical conditions should be documented (including any prior dermatological procedures or implants) in the electronic Case Report Forms (eCRF) using medical terminology.

4.6 **Prior and concomitant therapies**

4.6.1 Definition

Prior therapies are defined as therapies that have been used within 30 days preceding the Screening visit or within the timelines specified in the Inclusion/Exclusion criteria, and then stopped prior to the Screening visit.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the Screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the study, or
- any new therapies received by the subject since the Screening visit.

4.6.2 Recording

Prior and concomitant therapies are to be recorded on the appropriate form in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis or dose modification for a chronic condition.

4.6.3 Authorized concomitant therapies

Unless listed in prohibited concomitant therapies (section 4.6.4), all therapies are authorized.

4.6.4 Prohibited concomitant therapies

The following therapies are prohibited during the study because they may interfere with the efficacy and/or safety assessment of the study product and/or injection procedure:

- Anticoagulants or inhibitors of platelet aggregation (e.g. aspirin, non-steroidal antiinflammatory drugs [NSAIDs]), Omega-3, or Vitamin E should not be used within 2 weeks (i.e. 14 days) before any treatment to avoid increased bruising or bleeding at injection sites. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.

- The study product contains lidocaine, but additional local anesthesia may be used. Lidocaine should, however, be used with caution in subjects receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g. certain antiarrhythmics, as the systemic toxic effects can be additive.
- Concomitant treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g. monoclonal antibodies, antiviral treatment for human immunodeficiency virus (HIV) or Hepatitis) is prohibited.
- Systemic steroids (except intranasal/inhaled steroids) or prescription topical steroids (below the level of the horizontal line from subnasale including the neck).
- Topical (facial) prescription retinoids below the level of the horizontal line from subnasale including the neck, or systemic retinoids.
- Energy-based aesthetic procedures (e.g. laser, intense pulsed light, radiofrequency and ultrasound) below the level of the horizontal line from subnasale including the neck.
- Mechanical (e.g. dermabrasion, needling) or chemical aesthetic procedures (e.g. chemical peel) below the level of the horizontal line from subnasale including the neck.
- Treatment with cryotherapy below the level of the horizontal line from subnasale including the neck.
- Lipolytic injections below the level of the horizontal line from subnasale including the neck.
- Neurotoxin treatment below the level of the horizontal line from subnasale including the neck.
- Treatments below the level of the horizontal line from subnasale including the neck with absorbable or temporary dermal fillers (e.g. collagen, hyaluronic acid products, Calcium Hydroxylapatite, poly L-lactic acid products, etc.).
- Treatments with any permanent filler or implant, lifting threads, or autologous fat in the face including the neck.
- Tattoo or piercing interfering with the study injections and/or study assessments.
- Planned aesthetic facial plastic surgery (e.g. surgery to either the upper or lower lip, facelift, rhinoplasty, facial liposuction etc.) or oral surgery including dental implants, tooth extractions, orthodontia are prohibited.
- Participation in any other clinical study during this study is prohibited.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, the Sponsor Medical Expert should be notified, time permitting, to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical study, the Sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical study.

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Table 1: Schedule of events

Procedure	Visit 1a	Visit 1b	Visit 2a ⁴	Visit 2b ⁴	Visit 3	Visit 3a ⁴	Visit 3b ⁴	Visit 3c ⁴	Visit 4	Visit 5	Visit 6	Visit 7	Visit 7a ⁴	Visit 7b ⁴	Visit 7c ⁴	Visit 8	Visit 9	Visit 10	Visit 11
	Visits may be combined if subject meets eligibility criteria		72 hrs after Tx (±24 hrs)	14 days after baseline (+7 days)	1 month ¹⁰ after baseline (+7 days)	72 hrs after optional TU (±24 hrs)	14 days after optional TU (+7 days)	1 month ¹⁰ after optional TU (+7 days)	3 months ¹⁰ after baseline (±7 days)	6 months ¹ after baseline (±7 days)	9 months ¹ after baseline (±7 days)	12 months ¹⁰ after baseline (±7 days)	72 hrs after optional Tx (±24 hrs)	14 days after optional Tx (+7 days)	1 month ¹⁰ after optional Tx (+7 days)	15 months ¹⁰ after baseline (±7 days)	18 months ¹⁰ after baseline (±7 days)	21 months ¹⁰ after baseline (±7 days)	24 months ¹⁰ after baseline (+7 days)
	Screening Day -30 to 1	Baseline/Tx Day 1	TC	Followup	Followup/Optional TU	TC	Followup	Follow-up	Followup	Followup	Followup	Followup/Optional Tx/ EOS ¹¹	TC	Followup	Followup	Followup	Followup	Followup	Followup/ EOS
Informed Consent	X																		
Med. Hx/prior therapies	X	X _{1,2}																	
Demographics	X																		
Height/Weight ⁶		X _{1,6}																	X ₆
Inclusion/Exclusion Criteria	X	X _{1,2}			X _{1,5,9}							X _{1,5}							
Urine pregnancy test ³	X	X _{1,2}			X _{1,5,9}							X _{1,5}							
Randomization		X																	
Treatment with study product		X ₉			X _{5,9}							X ₅							
Evaluate device deficiencies		X ₉			X _{5,9}							X ₅							

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Collect/Review Subject			X ₇	X	X ₉	X ₇	X	X					X ₇	X	X				
DiPhotographyary		X ₁		X	X ₁		X	X	X	X	X	X ₁		X	X	X	X	X	X
Concomitant therapies	X	X ₂	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments ⁶ : Jaw mobility and function test Jawline sensation Palpability Visual function assessments Facial nerve function test	X	X ₁		X	X ₁		X	X	X	X	X	X ₁		X	X	X	X	X	X
Evaluate change in facial hair				X	X ₁		X	X	X	X	X	X ₁		X	X	X	X	X	X
GrowthAssessment of AEs		X ₉	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treating Investigator Assessments																			
CCI					■				■	■	■	■				■	■	■	■
Galderma Jawline Scale	X	X _{1,2}			X ₁							X ₁							
Blinded Evaluator Assessments																			
Galderma Jawline Scale	X	X _{1,2}							X	X	X	X ₁				X	X	X	X

Effective

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	Visit 1a	Visit 1b	Visit 2a ⁴	Visit 2b ⁴	Visit 3	Visit 3a ⁴	Visit 3b ⁴	Visit 3c ⁴	Visit 4	Visit 5	Visit 6	Visit 7	Visit 7a ⁴	Visit 7b ⁴	Visit 7c ⁴	Visit 8	Visit 9	Visit 10	Visit 11
Subject Assessments																			
CCI CCI																			
¹ Prior to any planned treatment ² Omitted if the screening and baseline visits occur on Day 1. Screening visit and baseline visit can be combined if no drug washout is needed ³ For females of childbearing potential ⁴ Visit is scheduled only if initial treatment, optional touch-up or optional treatment has been performed ⁵ Omitted if optional touch-up or optional treatment is not performed ⁶ Subject self-reported. Height only needs to be collected at baseline CCI													ET = Early Termination EOS = End of Study GAIS = Global Aesthetic Improvement Scale TC= Telephone call TU = Touch-up Tx = Treatment						
⁸ As required at screening to confirm study eligibility. The safety assessments should be done prior to treatment. At the treatment visits the visual function assessment tests will be performed prior to and approximately 30 minutes post injection of the study product. ⁹ For subjects randomized to study treatment ¹⁰ One month is defined as 4 weeks in the study ¹¹ For subjects in the no treatment/control group if not receiving optional treatment																			

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4.7 Visits

4.7.1 Visit 1a: Screening (Day -30 to Day 1)

The following activities and screening assessments will be performed within 30 days prior to baseline/Day 1 visit:

- Obtain Informed Consent.
- Obtain demographic data: Date of birth, gender, ethnicity, race, and FST. For determination of the FST, see Table 2.
- Record the subject's medical history (including any prior dermatological procedures or implants) and prior or concomitant therapies.
- For all females of childbearing potential, perform urine pregnancy test (UPT) prior to treatment. Test result must be negative for the subject to be eligible for treatment.
- Assess GJS – Treating Investigator and Blinded Evaluator.
- Perform jaw function test.
- Perform jawline sensation assessment.
- Perform facial nerve function test.
- Perform palpability assessment.
- Perform visual function assessments.
- Assess eligibility (inclusion and exclusion criteria).
- Schedule the baseline/Day1 (initial treatment) visit or proceed to Day 1 activities if subject meets all eligibility criteria.

Table 2: Fitzpatrick Skin Type (FST)

Skin type	Skin color	Skin characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

FST is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet Light ⁷

4.7.2 Visit 1b: Baseline/Day 1 (Initial Treatment)

The screening visit and baseline visit (Day 1) may be performed on the same day if a subject is deemed eligible by the Treating Investigator.

If screening visit and baseline/Day 1 visit are not performed on the same day, the following procedures should be repeated at the baseline/Day 1 visit:

- Review for changes in medical history and concomitant therapies.

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- Re-confirm eligibility criteria.
- Perform jaw function test.
- Perform jawline sensation assessment.
- Perform facial nerve function test.
- Perform palpability assessment.
- Perform visual function assessments.
- Perform UPT for all females of childbearing potential (prior to treatment). Test result must be negative for the subject to be eligible for study treatment.
- Assess GJS – Treating Investigator and Blinded Evaluator.



Once the subject is deemed eligible for study participation by the Treating Investigator, the following procedures should be completed:

- Record subject's height and weight.
- Obtain pre-treatment photographs of the jawline.

Randomize the subject to treatment (using needle, cannula or both combined according to what is agreed per site) or to no treatment.

For subjects randomized to no treatment:

- Schedule Visit 3, 1 month (+7 days) post-baseline visit),

For subjects randomized to treatment:

- Subjects will be injected with the study product.
- Record all concomitant medications/procedures used prior, during, or after the injection session.
- Record the number of syringes used and the volume of study product injected per treatment area during the injection session. Record the injection details (i.e. injection method and depth of injection).
- Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in section 8.12.
- Perform visual function assessments approximately 30 minutes after injection.
- Evaluate post-injection AEs by Treating Investigator.



- Schedule the 72 hours (± 24 hours) follow-up phone call (Visit 2).
- Schedule Visit 2b, 14 days (+7 days) and Visit 3, 1 month (+7 days) after the baseline visit (Visit 1b).

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4.7.3 Visit 2a: Follow up 72-hour (± 24 hours) telephone call after initial treatment

Visit conducted for subjects randomized to treatment only.

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.



- Remind subject of the next scheduled on-site visit.

4.7.4 Visit 2b: Follow up visit 14 days (+ 7 days) after initial treatment *Visit*

conducted for subjects randomized to treatment only.

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.




- Perform visual function assessments.
- Perform jaw function test.
- Perform jawline sensation assessment.
- Perform facial nerve function test.
- Perform palpability assessment.
- Evaluate changes in facial hair growth in the treated area.
- Obtain photographs.
- Remind subject of the next scheduled on-site visit.

4.7.5 Visit 3: Follow-up visit 1 month (+ 7 days) after baseline/ Optional touch-up □


Interview the subject regarding concomitant therapies.

- Interview subject and evaluate any AEs that have occurred since the last visit.
- Obtain photographs (if treatment is given, ensure photos are taken prior to injection)

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- Assessments to be performed for all subjects (prior to optional touch-up if treatment will be given):
 - GJS - Treating Investigator ○ GAIS – Treating Investigator and Subject ○ Perform visual function assessments.
 - Perform jaw function test. ○ Perform facial nerve function test. ○ Perform palpability assessment
 - Evaluate changes in facial hair growth in the treated area
- Schedule Visit 4, 3 months (\pm 7 days) after the baseline visit (Visit 1b).

For subjects randomized to treatment

- 
- Assess whether optimal aesthetic result has been achieved by subjects randomized to treatment (as agreed by the Treating Investigator and subject) and determine whether optional touch-up is appropriate.
- Subject must meet eligibility criteria for touch-up to be provided.
- Touch-up should not be provided if the subject has a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a touch-up.

If touch-up is to be performed:

- Prior to any treatment, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive the touch-up treatment.
- Subjects will be injected with the study product.
- Record all concomitant medications/procedures used prior, during or after the injection session.
- Record the number of syringes used and the volume of study product injected per treatment area during the injection session. Record the injection details (i.e. injection method and depth of injection).
- Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in Section 8.12.
- Perform visual function assessments approximately 30 minutes after injection
- Evaluate post-injection AEs by Treating Investigator



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- Schedule the 72 hours (\pm 24 hours) follow-up phone call (Visit 3a), Visit 3b, 14 days (+7 days) after optional touch-up, and Visit 3c, 1 month (+ 7 days) after optional touchup.

4.7.6 Visit 3a: Follow-up 72-hour (\pm 24 hours) telephone call after optional touchup performed

This visit should only be conducted for subjects who received a touch-up treatment at Visit 3.

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.

- CCI

- Remind subject of the next scheduled on-site visit.

4.7.7 Visit 3b: Follow up visit 14 days (+ 7 days) after optional touch-up performed

This visit should only be conducted for subjects who received touch-up treatment at Visit 3.

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.

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- Perform visual function assessments.
- Perform jaw function test.
- Perform jawline sensation assessment.
- Perform facial nerve function test.
- Perform palpability assessment.
- Evaluate changes in facial hair growth in the treated area.
- Obtain photographs.
- Remind subject of the next scheduled on-site visit.

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4.7.8 Visit 3c: Follow up visit 1 month (+ 7 days) after optional touch-up performed

This visit should only be conducted for subjects who received a touch-up treatment at Visit 3.

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.



- Perform visual function assessments.
- Perform jaw function test.
- Perform jawline sensation assessment.
- Perform facial nerve function test.
- Perform palpability assessment.
- Evaluate changes in facial hair growth in the treated area.
- Obtain photographs.
- Remind subject of the next scheduled on-site visit.

4.7.9 Visits 4 to 6: Follow-up visits 3, 6, and 9 months (\pm 7 days) after baseline □

Interview subject regarding any concomitant therapies.

- Interview subject and evaluate any AEs that have occurred since the last visit.
- Obtain photographs.
- Assessments to be performed:

CCI [redacted] CCI [redacted]
CCI [redacted] [redacted] [redacted] [redacted]
[redacted] [redacted] [redacted]
[redacted] [redacted] [redacted]
[redacted]
CCI [redacted]
CCI [redacted]

- Schedule Visits 5, 6, and 7, for 6, 9, and 12 months \pm 7 days after baseline visit (Visit 1b).

4.7.10 Visit 7: Follow-up visit 12 months (\pm 7 days) after baseline / Optional treatment

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- Interview the subject regarding concomitant therapies.
 - Interview subject and evaluate any AEs that have occurred since the last visit.
 - Obtain photographs (if treatment is given, ensure photos are taken prior to injection) ☐
- Assessments to be performed, prior to optional treatment:



For subjects in the No Treatment (control) group NOT receiving optional treatment:

- If optional treatment is NOT performed for subjects in the No Treatment (control) group this is the last visit. Complete the End of Study form in the eCRF.

For subjects in the Treatment group NOT receiving optional retreatment:

- Schedule follow up Visit 8, (15 months (+ 7 days) after the baseline visit (Visit 1b).

For subjects in the Treatment group and No Treatment (control) group receiving optional treatment:

- Subject must meet eligibility criteria for treatment to be provided. Treatment should not be provided if the subject has a disease or condition described in the exclusion criteria or an ongoing treatment-related AE that in the opinion of the Treating Investigator would be worsened by a treatment.

If treatment is to be performed:

- Prior to any treatment, perform UPT for all females of childbearing potential. The test result must be negative for a subject to receive the optional treatment.
- Subjects will be injected with the study product.
- Record all concomitant medications/procedures used prior, during or after the injection session.
- Record the number of syringes used and the volume of study product injected per treatment area during the injection session. Record the injection details (i.e. injection method and depth of injection).
- Evaluate for device deficiencies. If deficiencies are noted, complete form as specified in Section 8.12.
- Perform visual function assessments approximately 30 minutes after injection.

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- Evaluate post-injection AEs by Treating Investigator



- Schedule the 72 hours (\pm 24 hours) follow-up phone call (Visit 7a), Visit 7b, 14 days (+7 days) after optional treatment, and Visit 7c 1 month (+ 7 days) after optional treatment (Visit 7).

4.7.11 Visit 7a: Follow-up 72-hour (\pm 24 hours) telephone call after optional treatment

This visit should only be conducted for subjects who received optional treatment at Visit 7.

- Interview subject regarding any concomitant therapies.
- Interview subject regarding any AEs that have occurred since receiving treatment. If AEs are reported, notify the Investigator immediately and determine whether subject should return to the site for an unscheduled visit. The Investigator should assess all reported AEs in a timely manner.



- Remind the subject of the next on-site visit.

4.7.12 Visit 7b: Follow up visit 14 days (+ 7 days) after optional treatment

This visit should only be conducted for subjects who received optional treatment at Visit 7.

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.



- Perform visual function assessments.
- Perform jaw function test.
- Perform jawline sensation assessment.
- Perform facial nerve function test.
- Perform palpability assessment.

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- Evaluate changes in facial hair growth in the treated area.
- Obtain photographs.
- Remind subject of the next scheduled on-site visit.

4.7.13 Visit 7c: Follow up visit 1 month (+7 days) after optional treatment

This visit should only be conducted for subjects who received optional treatment at Visit 7.

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.



- Obtain photographs.
- Assessments to be performed:
 - Visual function assessments ○ Jaw function test ○
 - Jawline sensation ○ Facial nerve function test ○
 - Palpability assessment ○ Evaluate changes in facial hair growth in the treated area.
- Schedule Visit 8, 15 months (± 7 days) after the baseline visit (Visit 1b).

4.7.14 Visits 8 to 10: Follow-up visits 15, 18, and 21 months (± 7 days) after baseline

- Interview subject regarding any concomitant therapies.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Obtain photographs.

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- Schedule Visits 9 and 10, for 18 and 21 months (+ 7 days) after the baseline visit (Visit 1b).

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4.7.15 Visit 11: Follow-up visit 24 months (+ 7 days) after baseline / End of Study ☐

Interview subject regarding any concomitant therapies.

- Record the subject's self-reported weight.
- Interview subject and evaluate any AEs that have occurred since the last visit.
- Obtain photographs

- CCI

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[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]
- Remind subjects to contact the study site if any new AE occurs after study exit. Subjects will be asked to return to the study site to be evaluated and receive treatment, if applicable.
- Complete Study Exit form in the eCRF.

5. Subjects

5.1 Subject information and informed consent

The PI or his/her authorized designee must always use the most recently IRB-approved subject information and Informed Consent Form (ICF). The ICF it must not be changed without prior discussion with the Sponsor and approval from the applicable IRB.

Prior to inclusion in the study, it is the responsibility of the PI or his/her authorized designee to give each subject full and adequate verbal and written information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the study (e.g. explanation of the purpose and procedures of the study, the duration and number of expected participants, possible risks involved, and the opinion of the IRB). The subject shall be informed that the participation is confidential and voluntary and that s/he has the right to withdraw from the study at any time, without any consequences to his/her future medical care, treatment, or benefits to which s/he is otherwise entitled. The information shall be provided in a language clearly and fully understandable to the subject. The subject shall be given sufficient time to read and understand the ICF and to consider participation in the study. The PI/designee should make sure the subject has understood the information. Before any study-related activities are performed, the ICF shall be personally signed and dated by the subject and the PI or his/her authorized designee responsible for conducting the informed consent process. The consent includes information that data will be collected, recorded, processed, and may be transferred to other countries. The data will not contain any information that can be used to identify any subject.

Photographs collected during the study will be analyzed and stored in a database by the Sponsor and its representatives in order to evaluate the effect of the treatment in the study. The subjects will be recognizable on the photographs, but their names will not be disclosed.


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All signed ICFs shall be filed in the Investigator file. The subject shall be provided with a copy of the signed and dated ICF and any other written information.

The Investigator shall ensure that important new information is provided to new and existing subjects throughout the study. The subject should be informed that a description of this study, as well as results of the study once completed and reported, will be available on <http://www.ClinicalTrials.gov>. This web site can be searched at any time. The web site will not include information that can identify the subject.

5.2 Inclusion criteria

The subjects must meet all the following criteria to be eligible for the study:

1. Subject is willing to comply with the requirements of the study, including being photographed, following post-treatment care instructions,  attending all study visits and providing a signed written informed consent.
2. Males or non-pregnant, non-breastfeeding females, over the age of 21.
3. Moderate to very severe (Grade 2 to 4) on the Galderma Jawline Scale with no more than one grade difference between the left and right side at baseline as assessed by the Blinded Evaluator.
4. Intent to receive bilateral jawline definition treatment.
5. Subject is willing to abstain from any other facial, submental, and/or neck aesthetic procedure(s) or implant for the duration of the study.

Inclusion criteria 6 - 7 apply to female subjects only

6. If the subject is a female of childbearing potential, she agrees to use an acceptable form of effective birth control for the duration of the study and is willing to take a urine pregnancy test (UPT) at the screening/enrollment visit and prior to treatment. Acceptable forms of effective birth control include:
 - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical caps) with spermicidal foam/gel/film/cream/suppository.
 - Bilateral tubal ligation.
 - Combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 28 days prior to Day 1.
 - Hormonal or copper intra uterine device (IUD) inserted at least 28 days prior to Day 1.
 - Vasectomized partner (in monogamous relationship) for at least 3 months prior to screening.
 - Strict abstinence (at least one month prior to baseline and agrees to continue for the duration of the study or use acceptable form of birth control).
7. Negative urine pregnancy test for females of childbearing potential at screening and all injection visits.

5.3 Exclusion criteria

The presence of any of the following exclusion criteria excludes a subject from enrollment in the study:

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1. Known/previous allergy or hypersensitivity to any injectable hyaluronic acid (HA) gel or to gram positive bacterial proteins.
2. Known/previous allergy or hypersensitivity to local anesthetics, e.g. lidocaine or other amide-type anesthetics.
3. Previous or present multiple allergies or severe allergies, such as manifested by anaphylaxis or angioedema, or family history of these conditions.
4. Prior surgery in the treatment area or neck surgery that in the Treating Investigator's opinion could interfere with the study safety and/or effectiveness assessments.
5. Any previous aesthetic procedures or implants:
 - Previous permanent filler or implant, lifting threads, or autologous fat in the face or neck regardless of time.
 - Previous Calcium Hydroxylapatite (CaHA), poly L-lactic acid (PLLA) below the level of the horizontal line from subnasale including the neck within 24 months.
 - Previous HA filler or collagen filler below the level of the horizontal line from subnasale including the neck within 12 months.
 - Previous botulinum toxin treatment below the level of the horizontal line from subnasale including the neck and in the masseter area within 6 months.
 - Previous energy based aesthetic procedures (e.g. laser, intense pulsed light, radiofrequency and ultrasound) below the level of the horizontal line from subnasale, in the submental area and neck within 6 months.
 - Previous mechanical (e.g. dermabrasion, needling) or chemical aesthetic procedures (e.g. chemical peel) below the level of the horizontal line from subnasale, in the submental area and neck within 6 months.
 - Previous treatment with cryotherapy below the level of the horizontal line from subnasale, in the submental area and neck within 6 months.
6. Deoxycholic acid treatment in the submental region within the last 6 months.
7. Presence of any disease or lesions near or on the area to be treated, e.g.:
 - Inflammation, active or chronic infection (e.g., in mouth, dentals, head and neck region);
 - Facial psoriasis, eczema, acne, rosacea, perioral dermatitis, herpes simplex or herpes zoster;
 - Scars or deformities;
 - Cancer, or precancer such as actinic keratosis or actinic cheilitis.
8. Evidence of scar-related disease or delayed healing activity within 12 months, or subjects susceptible to keloid formation, hyperpigmentation, or hypertrophic scarring.
9. History of cancer or previous radiation in the treatment area.
10. Subjects with temporomandibular joint dysfunction, jaw pain, chewing pain, muscular related pain in the treatment area, and pain from opening and closing the mouth.
11. Presence of a dental, oral, or facial condition which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment, e.g. has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities. Any planned procedure (e.g.

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dental implants, tooth extractions, orthodontia) during the study period, that would make the subject unsuitable for inclusion in the opinion of the Investigator.

12. Presence of abnormal rating in jaw mobility and function; jaw mobility restrictions or inability to pronounce at least 80% of the pre-selected words.
13. Presence of abnormal rating in jawline sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the jawline, or abnormal rating of facial nerve function.
14. Detection of any abnormal jawline structure, such as unexpected lump or non-uniform density
15. Any past or current history of severely impaired/absent eye function in 1 or both eyes and/or uncontrolled retinal disease, retinal vascular occlusion (e.g. vein or arterial occlusion), narrow angle glaucoma, neovascular eye disease, detached retina, or any other condition with the potential to cause a decline of visual acuity (e.g. uncontrolled diabetes).
16. Poor visual acuity; with an absolute score on the Snellen chart of 20/50 or worse in one or both eyes using the prescribed correction (e.g. contacts or eyeglasses) or the other visual function assessment tests with abnormal clinical findings according to Treating Investigator.
17. An underlying known disease, a surgical or medical condition that would expose the subject to undue risk, e.g. HIV, active hepatitis, autoimmune disease, history of bleeding disorders, connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, or scleroderma.
18. Use of concomitant medications that have the potential to prolong bleeding times, such as anticoagulants or inhibitors of platelet aggregation, e.g. aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), Omega 3, or Vitamin E within 2 weeks (i.e. 14 days) before treatment. Omega 3 and Vitamin E are acceptable only as part of a standard multivitamin formulation.
19. Treatment with chemotherapy, immunosuppressive agents, immunomodulatory therapy (e.g., immunosuppressive monoclonal antibodies, antiviral treatment for HIV or hepatitis) within 3 months.
20. Treatment with systemic corticosteroids within 3 months before treatment (inhaled corticoids are allowed).
21. Use of topical facial corticosteroids or prescription retinoids (below the level of the horizontal line from subnasale) within 1 month of the baseline visit or systemic retinoid treatment within 6 months of the baseline visit, or plan to receive such treatment during participation in the study.
22. Presence of tattoo, piercing, beard or facial hair, which, in the Treating Investigator's opinion, would interfere with the study injections and/or study assessment.
23. Presence of any condition which, in the opinion of the Treating Investigator, makes the subject unable to complete the study per protocol, e.g.:
 - Subject is not likely to avoid other prohibited facial cosmetic treatments
 - Subject is not likely to complete the study because of other commitments

- Subject is anticipated to be unavailable for visits, incapable of understanding the investigational assessments, or has unrealistic expectations of treatment result
- Subject who has a concomitant condition (e.g. acute viral or bacterial infection with fever) that might interfere with study treatments or assessments

24. Women who are pregnant or breast feeding, or women of childbearing potential who are not practicing adequate contraception or planning to become pregnant during the study period.
25. Study site personnel, close relatives of the study site personnel (e.g. parents, children, siblings, or spouse), employees, or close relatives of employees at the Sponsor Company.
26. Participation in any other interventional clinical study within 30 days before treatment.

5.4 Subject number

Prior to any study procedures being conducted, the subject must sign the ICF. Following this, a subject identification number will be assigned at the screening visit.

A screen failure is a subject who signed the informed consent but never enrolled (i.e. was randomized and/or received treatment) in the study. For screen failures, the subject source documents should indicate which assessments have been made and the reason why the subject was determined to be a screen failure. A screen failure should not be re-entered in the study. A subject is considered enrolled when they have signed the ICF, is randomized, and/or is treated.

For the duration of the clinical study, each subject will be identified using his/her subject number for all documentation and discussion. A subject identification log is required to be kept in the Investigator file.

5.5 Withdrawal of subjects


An investigator may decide to discontinue a subject from the clinical study for safety reasons.

Although the importance of completing the entire clinical study should be explained to the subject by the clinical study personnel, a subject is free to discontinue participation in this clinical study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and, when appropriate, a subject may be treated with other conventional therapy as clinically indicated.

When a subject does not complete the clinical study, s/he will be fully assessed, if such assessment is possible. The procedures designated for the Early Termination (ET) visit should be completed for all subjects discontinuing the clinical study and the appropriate eCRF should be completed.

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the Study Exit form.

For discontinuation due to an AE, the Adverse Event form is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

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A subject who has been randomized cannot be replaced by another subject if s/he discontinues the clinical study for any reason.

Pregnancies occurring during the screening period are considered screening failures; they should be recorded as such in the eCRF and no pregnancy form is to be completed.

In case of a pregnancy occurring after the baseline visit, the Investigator should follow the procedures described in section 8.11.13. The subject may remain in the study, but no invasive procedure should be conducted.

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical study.

Potential reasons for discontinuation are defined below:

The withdrawal criteria are:

- ☐ **Medical Reasons:** If the subject suffers from a medical condition and/or Adverse Event(s) that, in the judgment of the Investigator makes it medically necessary to withdraw the subject. The specific rationale for Investigator-initiated withdrawal of a subject for medical reasons should document the specific condition for withdrawing the subject.
- ☐ **Withdrawal by Subject:** Includes consent withdrawal, subject relocation, schedule conflicts. A subject can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorized representative at any time for any reason.
- ☐ **Lost to follow-up:** If a subject does not return for a scheduled visit, reasonable effort shall be made to contact that subject, i.e. confirmed with three documented phone calls and a certified letter (delivery receipt requested) without answer before declaring the subject lost to follow-up.
- ☐ **Other:** This category is to be used for a subject who discontinues due to a reason other than as specified in the pre-defined categories above. Explain the reason for discontinuation.

If reason for discontinuation is "withdrawal by subject" or "other," the subject will be followed up to rule out the possibility of an AE. If an AE led to discontinuation then "Adverse Event" should be chosen as the reason for discontinuation, rather than "withdrawal by subject" or "other."

If an AE, which, according to the Investigator's assessment, is related to the use of any of the study products and is still ongoing at the time of the withdrawal, the Investigator shall followup with the subject until the AE resolves, is assessed by the Investigator to be "chronic" or "stable," or subject is lost to follow up. Follow-up information shall be reported on the AE follow-up form.



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6. Study Product

The term “study product” refers to GP0109. The study product will be provided by the Sponsor.

6.1 Investigational product

The investigational device GP0109 (i.e. study product) is an injectable, sterile, transparent and biodegradable gel.

The sterilized gel contains 25mg/mL crosslinked HA, whereof   after crosslinking, and 3 mg/mL lidocaine hydrochloride in a physiological buffer. Each syringe contains 1 mL gel.

GP0109 is supplied sterile, 1 mL filled in a disposable glass syringe with a luer lock fitting.

6.2 Additional products and materials

The Sponsor will provide OraStrech scales, cotton wisps, monofilaments, Snellen charts, eye occluders, and pen lights to each study site. Urine pregnancy tests will also be provided to each site for testing of all females of childbearing potential, at screening, baseline, and prior to treatment.

Topical or local anesthesia may be used at the discretion of the Treating Investigator before the treatment. If used, the anesthesia shall be supplied by the study site. Type of anesthesia, administration route, product name, and quantity used must be recorded in the eCRF.

Commercially available needle TSK Steriject 27G x 3/4" (19 mm) and cannula TSK Steriglide 25G x 2" (50 mm) will be used in the study. The needle and cannula are approved for use in the US. The needle will be provided to sites.

6.3 Labelling and storage

Labelling will be performed according to United States Code of Federal Regulations (CFR) 21 CFR 812.5: Labelling of investigational devices. The syringes will be labelled with the lot number and manufacturing date. The carton will be labeled as below:

Clinical Trial Number: 43BBJ1911	
Injectable Gel Content: 1 syringe (1 mL): GP0109 Sodium hyaluronate, crosslinked 25 mg/mL Lidocaine hydrochloride 3 mg/mL For single use only. Do not use if package is damaged. Store up to 25°C (77°F). Protect from freezing and sunlight.	CAUTION - Investigational Device. Limited by US Law to Investigational Use. Manufactured by: Q-Med AB Seminariégatan 21 SE-752 28 Uppsala Sweden 90-33178-01

The syringes should be stored in their original packaging at a temperature up to 25°C (77°F), protected from sunlight and freezing. Opened packages or partially used devices should not be reused. Detailed product information is provided in the IFU.

6.4 Product accountability

The study products will be released to the Investigator or his/her authorized designee after study approvals have been received from the FDA and IRB and the CTA has been signed by all parties.

The Investigator must ensure that the study products are kept in a secure location, with access limited to those authorized by the Investigator.

The study products must be traceable from the manufacturer to their use in subjects until return or disposal. It is therefore important that the Investigator maintains accurate product accountability records, i.e. documentation of the physical location of all study products, deliveries, and return of study products between the Sponsor and the Investigator, and documentation of administration of product to the subject.

When the study is completed, all unused or expired study product at each study site should be returned to the Sponsor representative for destruction or be destroyed locally at the site if documented as agreed with Sponsor.

Any malfunctioning study products should be reported as described in section 8.12.

Products deliberately or accidentally destroyed during shipment or at a study site should be accounted for and documented. Used syringes, needles, and any unused material must be discarded immediately after the treatment session and must not be reused due to risk for contamination of the unused material and the associated risks including infections according to standard procedures at the site. Disposal of hazardous material, i.e. syringes and needles, must conform to applicable laws and regulations. The study products must not be used outside the study.

6.5 Treatment

The investigational product is reserved for use by Treating Investigators who are experienced in jawline injection procedures. Treating Investigators should be aware of important neurovascular and anatomical structures near injection sites, which include the facial artery and vein, mental nerve and artery, parotid gland, superficial temporal artery and vein, and marginal mandibular nerve. Treating Investigators will be trained on the use of GP0109. The Treating Investigator must be trained on, and have at hand, the relevant clinical practice guidelines¹ and the actions to be taken if visual disturbances occur. The Treating Investigator should also have reviewed the Intravascular Treatment Protocol supportive tool provided separately in the Investigator file.

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Detailed information regarding the injection procedure, pre- and post-treatment care, and patients' instructions are provided in the IFU.

6.5.1 Pre-Treatment procedure

A visual function assessment should be performed prior to injection of the investigational product, see section 8.8.

Any make up in the lower face should be removed. It is important to thoroughly cleanse the face with an antiseptic preparation that extends below and above the jawline.

The study product contains lidocaine hydrochloride to reduce pain, but additional topical or local anesthesia or ice pack may be used at the discretion of the Treating Investigator to enhance the experience of the subject. Any additional topical or local anesthesia used should be recorded in the source documentation and on the eCRFs.

6.5.2 Treatment Regimen (dose and interval)

Subjects in the treatment group will receive one GP0109 treatment at baseline (initial treatment) and one optional touch-up treatment 1 month after initial treatment, if deemed necessary by Treating Investigator and subject to obtain optimal aesthetic improvement. Subjects in the no treatment control group will be offered treatment at the 12 months followup visit. The subjects who received treatment at baseline will also be offered an optional retreatment at the month 12 visit, if aesthetic improvement is not maintained (as determined by the Treating Investigator and subject). Subjects will be treated to optimal jawline correction, which is defined as at least 1 GJS grade improvement from baseline and best correction that can be achieved as agreed upon by the Treating Investigator and the subject.

Sites will be selected to use either needle, cannula or a combination of both for injection of all subjects at their site. Injection technique is at the Treating Investigator's discretion in the deep subcutaneous tissue or supraperiosteal plane. Depending on the location and injection tool, serial puncture (needles), tunneling, and linear threading among other techniques can be used to safely and effectively enhance the contour, shape, and definition of this aesthetic region. The injection technique and the use of needle/cannula per treated area (i.e. left mandibular angle, post-jowl and pre-jowl area on each side of the face) will be recorded.

Allowed maximum injection volume is 4 mL per treatment session and side of face, with a total maximum of 8 mL per treatment session. Care should be taken to avoid excess deposition of material into treatment area. The injection can bridge all the way from the mandibular angle, post-jowl and to the pre-jowl area (from tip of ear to tip of chin). Treatment of chin area is allowed for achieving a smooth contour; however, treatment of chin retrusion is not within the scope of the study. The jawline should not be "overcorrected." If an overcorrection should occur, the area should be firmly massaged between fingers to obtain optimal results. Aspiration is recommended prior to each injection. Slow injection is recommended.

It is recommended to start injection with small aliquots at the edge of the angle of the mandible in the deep subcutaneous tissue or supraperiosteal to enhance the mandibular angle. Once the mandibular angle is defined, continue the correction with the mandible body with a threading technique medially and inferior to the masseter and the post-jowl sulcus using needle or cannula. The antegonial notch injection where facial artery is should be avoided; in this area, subcutaneous injection is recommended. The ascending mandibular ramus is recommended to be treated in the subcutaneous plane to avoid the parotid gland.

Injection into the masseter muscle should be avoided and attempts should be made to inject superficial to or deep below the masseter muscle. Care must be taken to avoid facial artery and vein, mental nerve and artery, parotid gland, superficial temporal artery and vein, marginal mandibular nerve.

6.5.3 Post-treatment care

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When the injection is completed, the treated area may be gently molded and massaged for any irregularities. Brisk molding or massaging should be avoided in order to prevent undue swelling of the region.

Post treatment procedures with ice pack is allowed as per the Treating Investigator's normal procedure. Ice pack can be applied for approximately 10 minutes if the treated area is swollen.

After the injection, some common injection-related reactions might occur. These reactions include erythema, swelling, pain, itching, bruising, or tenderness at the implant site. Typically, resolution is spontaneous within two weeks after injection into the skin.

Post-injection visual function assessment tests including the Snellen visual acuity test, Extraocular muscle function test, and Confrontation visual field test, by the Treating Investigator will be repeated approximately 30 minutes after injection, see section 8.8.

Any medication or therapy used by the subject must be recorded in the eCRF.

The subject must avoid exposing the treated area to excessive sun or ultraviolet radiation or extreme cold until any signs of initial swelling and redness have disappeared. The subject must also avoid touching or shaving the treated area before the skin has healed completely, in order to prevent infections or elicit an inflammatory reaction.

6.5.4 Post-trial provisions

In time, the implant will be degraded in the body and additional treatments will be necessary to maintain the aesthetic result.

After the final study visit, the Sponsor will not supply any more treatments to the subjects, even if the result does not persist.

6.5.5 Treatment compliance

Not applicable; the treatment will be administered by the injector at the investigational site.

7. Effectiveness Assessments

7.1 General information

The methods for collecting effectiveness data are described in the following sections. To minimize inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. Beard or facial hair, that could interfere with effective assessments should be removed prior to an applicable study visit (i.e. 3, 6, 9, 12, 15, 18, 21, and 24 months after baseline).

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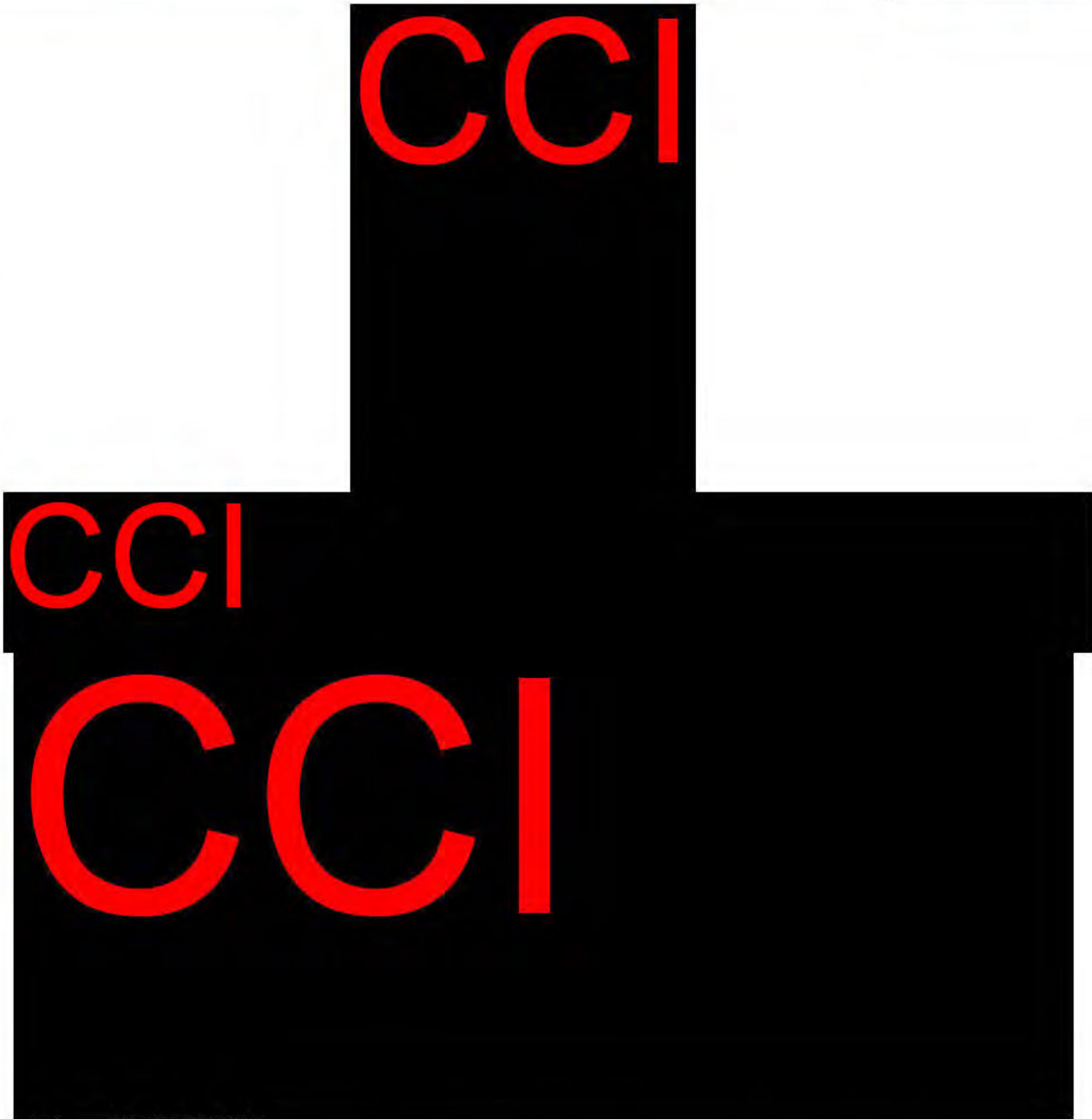
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7.1 Photography

In order to document treatment effect, photographs will be taken prior to treatments with study product and at every follow-up visit. Photographs will also be taken of subjects who are randomized to the No Treatment (control) group. Photographs may also be taken to document AEs at the Treating Investigator's discretion. Baseline photographs may be used as a reference in the  assessment by the Treating Investigator and subject. Site personnel will be thoroughly trained in the photographic equipment and techniques before study start.

Camera equipment will be provided by the Sponsor or their designee and standardized photographs should be achieved. Further details regarding photography procedure will be specified in a separate user guide.

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8. Safety Assessments

8.1 General information

The safety assessments described below are included specifically for the study.

8.2 Assessment of AEs by direct question to subject and evaluation of subject

Safety evaluations for this study include an interview of the subjects at each visit to obtain information about any medical occurrence that meets the definition of an Adverse Event (AE). Each subject should be questioned about AEs at each study visit following the baseline visit. The question should be asked: *“Since your last clinical visit have you had any health problems?”* Information on AEs can also be obtained from signs and symptoms detected during each examination by the Investigator or designee, which should include visual inspection of the treatment area or from a laboratory test, review of the subject diaries, or spontaneous reports from the subjects or their relatives.

AEs must be documented in the source document and eCRF without regard for cause or relation to investigational product and injection procedure. If, in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, it must be documented in the source document(s) and eCRF.

It is the responsibility of the Investigator to determine severity of the AE and relatedness of the event to the study product and injection procedure.

8.3 Jaw mobility and function assessment

A baseline value for jaw mobility and function will be obtained, and new assessments will be done at all physical visits thereafter. The Investigator will evaluate jaw mobility and function. Assessments will be reported as “normal” or “abnormal.” The Investigator should evaluate all “abnormal” findings for confirmation of any potential AE.

8.3.1 Jaw mobility

Each subject’s jaw function will assess for mobility restrictions for opening or closing the mouth and for restrictions moving the jaw from side to side.

OraStretch scales will be used to assess jaw function:

- rotational vertical maximum-interincisal opening
- lateral (side-to-side) measurement
- protrusion

8.3.2 Intra-oral exam

Intra-oral exams will be performed and reported as “normal” or “abnormal.” An abnormal or suspected lesion will be evaluated by the Investigator for a potential AE. The site, description and color for all abnormal or suspected lesions should be documented.

8.3.3 Pronunciation

The subject’s ability to effectively pronounce a series of 10 pre-selected words will be assessed. Each word pronounced correctly will score one point. A score of 8 words or more; pronounced correctly; will be considered a normal finding.

8.4 Evaluation of jawline sensation

Evaluation of jawline sensation (both jawlines) will be obtained at screening, baseline and all physical follow-up visits thereafter. Jawline sensation will be assessed as “Normal” or “Abnormal.” Inability to feel the monofilament or cotton wisp at any point will be considered abnormal. After receiving treatment, any subject with abnormal ratings should be assessed by the Investigator for confirmation of a potential AE. Jawline sensation will be tested using two methods:

- 1) Monofilament test - Assesses the subject’s ability to feel the sensation of a SemmesWeinstein 0.4G monofilament on 3 points on both the left and right mandibular angle, post jowl sulcus and pre jowl sulcus, and
- 2) Cotton Wisp test - assesses the subject’s ability to feel the sensation of a cotton wisp on 3 points on both the right and left mandibular angle, post jowl sulcus and pre jowl sulcus. The 3 different points on the jawline will be tested randomly. Subjects will be asked to close their eyes and to acknowledge sensation or lack of sensation at each point.

8.5 Palpability

The Investigator will palpate the jawline for detection of any unexpected feel such as nonuniform density or unexpected lumpiness at baseline and all physical follow-up visits thereafter. The study products are generally palpable (i.e. can be felt under the skin) and have uniform density. Any unexpected feel upon palpation will be assessed as “Abnormal” and should be reported as an AE by the Investigator, and should include a description of the localization, feel, and approximate size.

8.6 Facial nerve function test

The Investigator will assess changes of the facial nerve function compared to baseline prior to treatment.


The major extracranial facial branches of facial nerve will be evaluated at baseline and every physical visit thereafter. The subject’s face at rest will be evaluated for asymmetry, paying attention to forehead wrinkles, nasolabial folds, and angles of the mouth. In addition, facial movement will be evaluated by the subject’s ability to carry out a sequence of facial expressions while, again, observing for asymmetry; raised eyebrows, closed eyes, blown out cheeks, smiling, and pursed lips. The evaluation will be recorded as “normal” and “abnormal.” If evaluated as “abnormal” and considered clinically significant, the finding should be reported as an AE.

8.7 Changes in hair growth

The Treating Investigator will ask if the subject has noticed any changes in hair growth (e.g. loss or growth) in the treated area at physical follow-up visits after baseline. Clinically significant changes in hair growth, as determined by the Treating Investigator, will be reported as an AE.

8.8 Visual function assessment

Visual function assessments will be performed at screening, baseline and all following physical visits. At the treatment visits the visual function assessment tests will be performed prior to and

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approximately 30 minutes post injection of the study product. These assessments include Snellen visual acuity, extraocular muscle function, and confrontation visual field tests.

The subject is considered to have normal or acceptable visual acuity if the Investigator can adequately measure the quality of his/her eyesight using the Snellen Eye Chart. If the subject is found to have severely impaired/absent eye function (20/50 or worse) in one or both eyes, even with the use of prescribed corrective lenses, and/or any other condition with the potential to cause a decline of visual acuity, s/he will be considered to have abnormal vision and will not be eligible for enrollment.

All worsening in vision during the study (for visual acuity compared to baseline, and post injection compared to pre injection at treatment visits) **should be assessed by the Investigator as an AESI per section 8.11.3 and reported per section 8.11.8.** If the subject experiences clinically significant changes in vision, the Investigator should consider further assessment and treatment by an eye specialist (ophthalmologist or retinal specialist). The Investigator should conduct appropriate follow up with the subject to determine the cause, severity, seriousness, relationship to the study product or procedures, and outcome.

8.8.1 Snellen visual acuity test

A Snellen Eye Chart will be used to objectively assess visual acuity for distance vision. Visual acuity will be conducted using the subject's best distance correction (e.g. contacts or eyeglasses) at a distance of 6 feet from the chart. Each eye will be measured separately by either using an occluder or having the subject cover each eye. The subject will be asked to start reading the letters at the top of the chart working their way to the bottom. The smallest row of letters that the subject can read will indicate their visual acuity listed on the chart. Any subject requiring vision acuity correction must be assessed using the prescribed correction (e.g. contacts or eyeglasses). Unacceptable vision for a subject to be eligible for enrollment would be an absolute score on the Snellen chart 20/50 or worse in one or both eyes. Worsening in visual acuity (i.e. change of one line or greater from baseline, and post injection compared to pre injection at treatment visits) on the Snellen Chart during the course of study should be reviewed and assessed by the Investigator and reported as an AE. The Sponsor will evaluate all negative one line or greater changes in visual acuity on the Snellen exam and the need to refer for an ophthalmic evaluation.

8.8.2 Extraocular Muscle Function Test

Extraocular muscle function testing examines the function of the eye muscles. This test observes the movement of the eyes in six specific directions to evaluate weakness or other problem in the extraocular muscles. The subject will be asked to sit or stand with his/her head up and looking straight ahead. The assessor will hold a pen or other object approximately 16 inches in front of the subject's face. The assessor will then move the object in several directions and ask the subject to follow it with their eyes, without moving their head. The result shall be reported as "normal" or "abnormal" for each eye. Changes in movement of the eyes during the course of the study should be reviewed and assessed by the Investigator and reported as an AE. In the event of a change from baseline the Investigator should recommend the subject to receive an ophthalmic evaluation.

8.8.3 Confrontation Visual Field

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The Confrontation Visual Field Test will be used to assess the subject's peripheral vision. The examiner will sit facing the subject, about 3 to 4 feet away from the subject and ask the subject to fix their gaze on the examiner's eye. The examiner will hold their arms straight out to the side and bring their hands into the subject's visual field from the sides in each quadrant. The subject will signal as soon as the hand is seen. Each eye will be recorded as normal or abnormal. Changes in the visual field of the eyes during the course of the study should be reviewed and assessed the Investigator and reported as an AE. In the event of a change from baseline the Investigator should recommend the subject to receive an ophthalmic evaluation.

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8.10 Laboratory assessments

Pregnancy Test

For all women of childbearing potential, including those currently using contraception, a urine pregnancy test is required prior to receiving any study treatment (Day 1, optional touch-up, or optional treatment). **The test result must be negative for the subject to receive any**

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treatment with study product. The test result will be documented in the subject's file and eCRF.

8.11 Adverse Events

8.11.1 Definition of an Adverse Event

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons¹, whether or not related to the study product.

This definition includes:

- a) events related to the investigational product or the reference product
- b) events related to the procedures involved
- c) events that are anticipated as well as unanticipated

8.11.2 Definition of a Serious Adverse Event A

SAE is an AE that:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
 - a. a life-threatening² illness or injury, or
 - b. a permanent impairment of a body structure or body function, or
 - c. hospitalization or prolonged hospitalization³, or
 - d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
 - e. chronic disease
- c) led to fetal distress, fetal death, or a congenital physical or mental impairment or birth defect

In cases of doubt, whether an AE fulfils a serious criterion or not, there should be a predisposition to report as an SAE rather than not report as such (see section 8.11.7).


8.11.3 Definition of an Adverse Events of Special Interest

All incidences of visual disturbances, regardless of relationship to study product or seriousness, are considered Adverse Events of Special Interest (AESIs) and include, but are not limited to, the following:

¹ For users or other persons, this definition is restricted to events related to the investigational product.

² The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (Source: ICH-E2A clinical safety data management: definitions and standards for expedited reporting).

³ Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE. (Source: ISO14155:2011).

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- Loss of vision □ Blurry vision
- Double vision
- Pain in or around the eye
- Blind spot or shadow in the visual field
- Trouble moving eyes
- Any change to ocular motility, as determined by a worsening on the Extraocular Muscle Function Test
- Any change to peripheral vision, as determined by a worsening on the Confrontation Visual Field Test
- Any worsening in visual acuity (i.e., negative change of one line or greater on the Snellen Visual Acuity Test) indicating:
 - a worsening from the baseline value
 - a worsening post injection compared to pre injection at a treatment visit

8.11.4 Definition of an unanticipated adverse device effect

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the investigational product, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with a device that relates to the right, safety or welfare of the subject (see FDA regulation CFR 812.3 (s)).


8.11.5 Recording instructions

When an AE is related to a device deficiency (refer to section 8.12), including technical device malfunction, the AE shall be recorded on the AE form/module in the eCRF and the technical complaint shall be reported separately on the clinical study complaint form provided separately in the Investigator file.

Investigators, or other study site personnel, shall record all AEs in the eCRF, including:

- Event term (recorded in standard medical terminology and avoiding abbreviations)
- Affected area
- Start date (first day with symptoms)
- Stop date (last day with symptoms)
- Intensity (mild, moderate, or severe according to definition in section 8.11.5.1)
- Seriousness (serious or not serious, according to definition in section 8.11.5.2)
- Causal relationship to study product or study product injection procedure (yes or no)
- Action taken (none, medication treatment, non-pharmacological treatment, or other procedures/tests, subject withdrawn)
- Outcome of the AE (ongoing, recovered, recovered with sequelae, death, chronic/stable, not recovered at the end of the study)

The AE form/module in the eCRF must be signed and dated by the Investigator.

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8.11.5.1 Intensity

Intensity will be recorded for each reported AE. The following definitions of intensity are to be used:

Mild: Awareness of symptoms or signs, but easily tolerated (acceptable)

Moderate: Enough discomfort to interfere with usual activity (disturbing)

Severe: Incapacity to work or to do usual activity (unacceptable)

If the intensity changes within one day, the maximum intensity of the AE during that day shall be recorded.

8.11.5.2 Causal relationship and seriousness

Each AE shall be assessed by the Investigator for causal relationship with the study product and its use (the injection procedure) and for seriousness (Yes or No) of the event.

A two-point scale (Yes or No response) shall be used for the causality assessments. The Investigators shall be asked to indicate a response to each of the following questions in the eCRF:

- ☐ “Do you consider that there is a reasonable possibility that the event may have been caused by the study product?”, and

□

“Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?”

If any of these questions is answered Yes, the AE is considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfill regulatory requirements.

In addition, each SAE will be classified by both the Investigator and Sponsor separately, according to four different levels of causality:

1. **Not related** - Relationship to the device, comparator or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/ exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2. **Possible** - The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. **Probable** - The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. **Causal relationship** - the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

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- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
 - the investigational device or procedures are applied to;
 - the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/ exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

8.11.6 Reporting of Adverse Events

Adverse Event reporting on each subject shall start once a subject is enrolled (i.e., randomized to treatment or to no treatment) in the study. All other events that occur after the subject signs the ICF but before enrollment will be recorded in the subject's medical history. The reporting shall continue during each follow-up visit (including telephone contacts and extra visits between planned visits) until the last scheduled visit in the study.

All AEs, non-serious as well as serious, are to be reported as an AE in the eCRF. A request for additional information from the Sponsor/ CRO Medical Expert(s) for non-serious AEs, should be collected and answered using the Adverse Event Clarification Form.

8.11.7 Reporting of Serious Adverse Events

The Investigator shall report any **SAE** to the Sponsor **immediately but not later than 24 hours of awareness of the event**. This initial report can be made via e-mail or submitted via the eCRF.

In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted, with the following information as a minimum, irrespective of whether some of it is regarded as preliminary:

- Subject identification (age, gender, initials, subject number)

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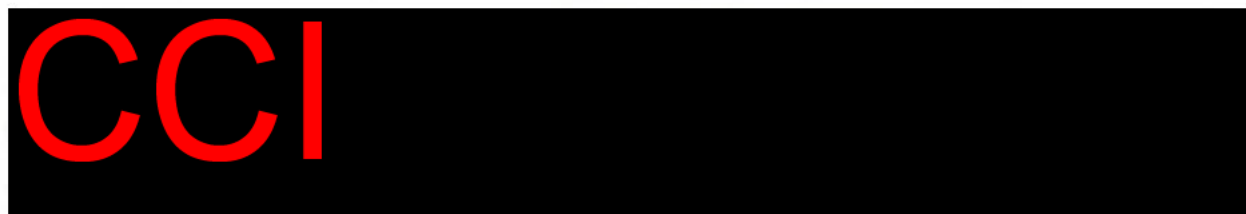
- Adverse Event description
- Date when AE occurred
- Name of PI

Name of study product

Follow-up information and data missing in the initial SAE reporting shall be gathered as soon as possible and reported to the Sponsor immediately but not later than 24 hours of awareness of the new data. Complete and adequate information on each SAE is required. All attempts to obtain this information, including dates for follow-up activities, must be documented by the Investigator.

Supporting documentation to be provided with the SAE report:

- Concomitant therapies form/list
- AE form/list
- Medical history form/list
- Any other relevant supporting documentation (e.g. hospital notes, death certificate, autopsy reports etc.)
- Study treatment records from eCRF pages including information for: time of injection, lot number, volume used, injection method and needle and/or cannula used.



The SAE form must be signed and dated by the Investigator. If the initial 24-hour SAE report does not contain full information or if it is made without using the SAE form the fully completed and signed SAE form shall be e-mailed or faxed to the Sponsor. A copy of the fully completed SAE form shall be kept at the site.

In addition, the PI shall report SAEs to the responsible IRB without undue delay. The PI is responsible for checking what reporting procedures are applicable for his/her IRB regarding SAEs and final report of the outcome of the study and to comply with such reporting procedures during the study period.

The Sponsor is responsible for reporting to the RA, if applicable and according to national regulations.

8.11.8 Reporting of Adverse Events of Special Interest (AESIs)

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In case of difficulty to obtain all the required information within 24 hours, an initial report can be submitted with follow up information provided within 24 hours of awareness of the new information.

The following information should be provided when reporting an AESI:

- Subject identification (subject number and initials)
- Event description including observed symptoms
- Medical history related to event
- Event onset date and time
- Depth of injections
- Interventions implemented to treat event
- Event outcome (with resolution date and time if applicable)
- Relatedness to study product or procedure
- Seriousness of event
- Study treatment information (number of injections, date of injections, name of product injected, volume injected, injection tool used etc.)

If the Investigator assesses an AESI to be serious, an SAE report should be submitted as specified in section 8.11.7.

Upon receipt of the AESI report, the Sponsor/CRO Medical Expert(s) will further evaluate and document the evaluation of the reported incident.

If any of the following events occur the Sponsor will expedite the report to FDA, within 10 days and to the IRB as applicable:

1. All incidences of visual disturbances (loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving the eyes), regardless of relationship to study product or seriousness;
2. Any worsening in visual acuity (i.e. negative change of one line or greater) related to the treatment procedure or study product;
3. Any abnormal results on extraocular muscle function test or confrontation visual field;
4. A medical concern that requires continued monitoring of the patient's condition in regard to an AESI or if additional examinations may be needed, as assessed by the Investigator (e.g. referral to an eye specialist).

8.11.9 Reporting of unanticipated adverse device effect

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An Investigator shall prepare and submit a complete and accurate report to the Sponsor/CRO, for contact details see section 8.11.7, and to the reviewing IRB on a suspected UADE as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect, in accordance with FDA regulation CFR 812.150.

8.11.10 Stopping rule

Enrollment and treatment in the study will be temporarily halted if a serious adverse event (SAE) occurs for the following:

any unanticipated SAE which is possibly related to the study device or procedure including but not limited to a vascular embolic event that leads to skin necrosis, vision loss or stroke, damage to facial nerves which may result in facial paralysis or injury to internal facial structures.

The SAE will be investigated by the Sponsor. If the Sponsor's investigation concludes the SAE:

- was unanticipated,
- directly related to the study product or device injection procedure,
- and presents an unreasonable risk to study subjects, the study will be terminated, and the Investigators will be notified. The IRB and RA will also be notified if the study is prematurely terminated due to safety concerns. If the SAE does not meet the above criteria, then enrollment in the study will continue.

8.11.11 Follow-up of unresolved events ongoing at termination of the study

All serious as well as non-serious AEs with a causal relationship to the study product or treatment procedure and ongoing at study end, shall be followed up after the subject's participation in the study is over. Such events shall be followed-up after the last study visit until resolved, assessed as chronic or stable, or subject is lost to follow up. Final outcome after the end of the study shall be reported on the AE Follow-up form.

8.11.12 Reporting and follow-up of events occurring after subject termination of the study

All Adverse Events with a causal relationship to the study products or treatment procedure that the Investigator becomes aware of, serious as well as non-serious, with onset after the study termination (subject's last study visit) shall be reported to the Sponsor by email to safety.qmed@galderma.com. The Investigator shall follow the subject until the event is resolved.

8.11.13 Pregnancy

Pregnancy itself is not regarded as an AE. If there is a pregnancy during the study period, the subject must be withdrawn from any following study treatment but should continue to be followed within the study and the outcome of pregnancy must be reported even if the delivery occurs after study completion.

A pregnancy confirmed during the study period must be reported by the Investigator on a pregnancy report form immediately upon acknowledge and be submitted to the Sponsor

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according to contact details specified in section 8.11.7. The report can be prospective or retrospective. Follow-up shall be conducted to obtain outcome information on all prospective reports.

Cases that led to fetal distress, fetal death or a congenital abnormality or birth defect are to be regarded as SAEs and shall be reported on the exposure *in utero* report form to the Sponsor immediately but no later than 24 hours after the Investigator's awareness. These events shall be handled as SAEs during data processing. Other complications during the pregnancy that are related to the pregnant woman and fulfils any serious criteria, such as pre-eclampsia requiring hospitalization, shall be reported, and handled as SAEs. Elective abortions without complications shall not be reported as AEs.

8.11.14 Anticipated Adverse Events

Information regarding anticipated AEs for GP0109 is included in the study specific IFU.

8.12 **Device deficiencies**

8.12.1 Definition of a device deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety⁴, or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

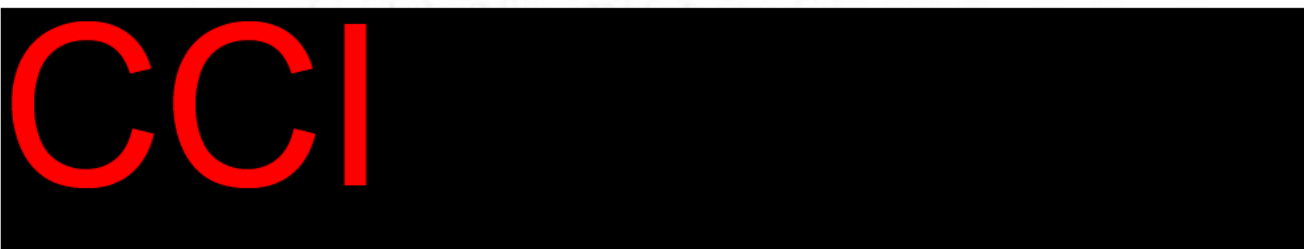
8.12.2 Recording instructions

When a device deficiency is discovered, Part A of the clinical study complaint form shall be completed by the Investigator. The type of complaint shall be described and injury to the subject or user or unintended exposure to study product shall be reported as applicable. If an injury has occurred, an AE or an SAE form shall be completed as applicable (refer to sections 8.11.6 and 8.11.7). If no SAE was experienced as a result of the device deficiency the Investigator shall assess whether or not the device deficiency *could have led* to an SAE if:

- Suitable action had not been taken, ☐ Intervention had not been made, or
- Circumstances had been less fortunate

In Part B of the clinical study complaint form, the Sponsor will make the same assessment.

8.12.3 Reporting of device deficiencies



⁴ Inadequacy of device safety refers to properties of the device which could have or have led to an AE.

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A device deficiency that led to an SAE and any device deficiency that could have led to an SAE shall be reported to the Sponsor within 24 hours after the Investigator's awareness (for contact information, see section 8.11.7).

If the Investigator or the Sponsor assesses that the device deficiency could have led to an SAE the Sponsor is responsible for reporting the device deficiency to RA and the PI is responsible for reporting it to the IRB.

The deficient study product shall be kept by the study site until the Sponsor has confirmed whether the product shall be returned to Sponsor for further study or if it can be destroyed at the study site.

9. Data Handling and Management

9.1 Data management

Data management based on GCP refers to the activities defined to achieve safe routines to enter clinical data information into a database, efficiently and avoiding errors. The data management routine includes procedures for database set-up and management, data entry and verification, data validation, and documentation of the performed activities including information of discrepancies in the process. The data management process will be described in detail in the data management plan (DMP).

The database, the data entry screens, and program will be designed in accordance with the CIP and the eCRF template. Data validation will be performed by computerized logical checks and manual review. Drugs and events will be coded in accordance with World Health Organization (WHO) Drug and Medical Dictionary for Regulatory Activities (MedDRA) dictionaries as specified in the DMP. Safety data (SAE and if applicable AE of special interest) in the clinical database will be reconciled against the data in the safety database.

When all efforts have been made to ensure that the data recorded in the eCRFs and entered in the database is as correct and complete as possible, the clinical database will be locked. Study data will be transferred to SAS datasets, which thereafter will be write-protected. Statistical analyses will be generated in SAS using data from the locked datasets.

9.2 Electronic Case Report Forms

A 21 Code of Federal Regulations Part 11-compliant electronic data capture application will be used to collect, modify, maintain, archive, retrieve, and transmit study data. An electronic Case Report Form (eCRF) is required and should be completed electronically for each screen failure as well as enrolled subjects.

The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data should be entered directly from the source documents, which are to be defined at each site before inclusion of the first subject.

Authorized study site personnel designated by the Investigator should complete data collection. Appropriate training and security measures should be completed with all authorized investigation site personnel prior to the study being initiated and any data being entered into the system for any subject.

The study data is the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate RA, without written permission from the Sponsor. At the end of the study, electronic data are kept at the Sponsor and a copy (provided by the vendor) at the study site as part of the Investigator file.

Any delegation of collection of data should be specified in a signature and delegation log.

9.2.1 Data entry

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during or after the subject's visit. The subject's identity must always remain confidential, i.e. the name and address of the subjects must not be registered in the eCRFs or

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in the database. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator shall indicate this in the eCRF. The Investigator shall electronically sign off the study data. By signing, the Investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

9.2.2 The query process

The monitor shall review the eCRFs and evaluate them for completeness and consistency. Each eCRF shall be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations shall be made by the PI or his/her authorized designee. The monitor cannot enter data in the eCRFs. Once study data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering study data into the eCRF shall be determined in advance. If discrepant data is detected during review of the data, either by the Sponsor or by its representatives, the responsible data manager or monitor shall raise a query in the electronic data capture application. The query shall state the question or data to be changed and shall be resolved in the system by the PI or his/her authorized designee. The appropriate study site personnel shall answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of study site personnel, time, and date is logged.

9.2.3 User identification

The eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records shall be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction shall be made in accordance with the relevant software procedures.

9.2.4 Audit trail

All changes will be fully recorded in a protected audit trail and a reason for the change shall be stated. Once all data have been entered, verified, and validated, the database will be locked.

9.3 **Source documents**

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These should be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject for whom signed informed consent has been collected. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the CTN and subject number. Any personal information, including name, should be removed or rendered illegible to preserve individual confidentiality.

9.4 Record keeping and access to source data

The Investigator/Institution should permit study-related monitoring, audits, IRB review, and RA inspections and should provide direct access to the source data/medical record including the identity of all participating subjects (sufficient information to link records, i.e. eCRF, medical records, original signed ICFs and detailed records of study product accountability). The records should be retained by the Investigator as required by local legislation and international guidelines. Any transfer of responsibility for storage of the records should be documented and the Sponsor should be informed in writing.

The Sponsor should verify that each subject has consented in writing to direct access to the original medical record/source data (by the use of written subject information and signed informed consent). The data recorded in the eCRFs will be checked for consistency with the source documents/medical record by the monitor during monitoring (source data verification; SDV). In order to be able to perform SDV, information about each subject's participation in the study has to be detailed in the medical record.

9.5 Document and data retention

All records pertaining to the conduct of the study, including signed eCRFs, ICFs study product accountability records, source documents, and other study documentation must be retained for as long as is specified in the CTA. Measures should be taken to prevent accidental or premature destruction of these documents (e.g. protection against damage and unauthorized access, preferably by storage in a fire-proof cabinet).

It is the Investigator's responsibility to inform the Sponsor in writing if the Investigator file is moved or if the responsibility for the documents is transferred to someone else.

9.6 Clinical Study Report

Two Clinical Study Reports (CSRs) will be compiled; an interim CSR, see section 10.8 and a CSR after completion of the whole study. A summary of the study results will be published on a public database, <http://www.ClinicalTrials.gov>.

10. Statistical Methods

10.1 General

A comprehensive Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be developed before database lock.

All study data will be listed in subject data listings.

All statistical analyses, including summary tables and data listings, will be performed using SAS. Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be twosided, unless otherwise specified.

Continuous endpoints will be summarized using descriptive statistics, e.g. number of subjects (n), mean, median, standard deviation, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

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10.2 Analysis populations

The following populations will be defined:

- Intention-to-treat (ITT) Includes all subjects who are randomized and will be analyzed according to the randomization scheme
- Per protocol (PP) Includes all subjects in ITT who complete the 3 months after baseline visit, without any deviations considered to have substantial impact on the primary effectiveness outcome
- Safety Includes all subjects who were treated with GP0109 or randomized to the control group, and will be analyzed according to as-treated principle

Intention-to-treat is the primary population for all efficacy analyses. If the PP population contains less than 90% of the subjects in the ITT, a sensitivity analysis of the primary efficacy endpoint will be performed based on the PP population. Safety analysis is performed based on the safety population set.

The disposition of subjects will be presented in tables and/or figures as appropriate. The number of screened, randomized, treated, completed, and withdrawn subjects will be presented, as well as number of subjects in each analysis population set.

10.3 Demographics, baseline assessments, and subject characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the ITT analysis set using descriptive statistics by treatment, as appropriate.

10.4 Effectiveness analysis

10.4.1 Primary effectiveness analysis

Responder rate based on the GJS, as assessed live by the Blinded Evaluator at Month 3 after baseline, will be the primary effectiveness endpoint. A responder will be defined as a subject with at least 1 grade improvement from baseline on both sides of the face concurrently.

The null hypothesis will be that there is no relationship between responder rate and treatment group (i.e. the responder rate is the same in treated and untreated subjects). The alternative hypothesis will be that there is a relationship between responder rate and treatment group (i.e. the responder rate is different in treated subjects compared to untreated subjects).

The estimates of the responder rate in each treatment group will be presented as well as the difference in responder rates. Corresponding confidence intervals for responder rates and the difference in responder rates along with the p-value for the difference will also be presented.

First, the Breslow-Day test for homogeneity of odds ratios will be used to assess consistency of GJS odds ratios across all strata (the needle-treated group, the cannula-treated group, and the combination group). A significance level of 0.05 will be used to determine if the responder rates are non-homogenous. If the Breslow-Day p-value is less than or equal to 0.05, the primary analysis will be stratified (i.e. conducted separately) for the needle treated group, the cannula-treated group, and the combination group, using a significance level of 1.7% to account for multiplicity. If the Breslow-Day p-value is greater than 0.05, the analysis will be carried out on

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pooled groups, using a significance level of 5%. Regardless of whether the primary analysis will be based on pooled injection tool groups, or done separately, the no treatment control subjects will be pooled across all study sites. Fisher’s exact test will be used to compare the responder rates between the treated and untreated subjects at Month 3.

In order to assess the poolability of study sites, a Breslow-Day test for homogeneity of odds ratios across sites will be performed. If the p-value of the sites test is <0.05, then subgroup analysis by study sites will be done.

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10.5 Safety analysis



All AEs will be coded according to MedDRA and summarized by system organ class (SOC), preferred term (PT) and treatment (no treatment, 1st treatment including touch-up if applicable, and 2nd treatment).

A summary of all AEs will be provided, which will include:

- number of subjects with at least one AE and number of events (in total as well as serious AEs)
- number of subjects with at least one related AE and number of events (in total as well as serious AEs)
- number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs)
- number of subjects who did not have an AE

The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT and maximum severity. In addition, for related AEs the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median. Action taken for related AEs will also be summarized. Serious AEs, and AEs with onset >21 days after most recent treatment will be listed.

Non-related AEs will be summarized by SOC, PT and intensity.

To evaluate consistency of AEs across different subgroups, AEs will also be summarized by subgroups defined as described below.

Safety analysis will be descriptive only.

10.6 Subgroup analyses

10.6.1 Effectiveness

In order to investigate the homogeneity of the results of the analyses of the primary endpoint, as well as the first secondary endpoint, across different subgroups, the following factors will be used for definition of subgroups, respectively:

- Injection tool (needle, cannula, and combination)
- Study site
- Fitzpatrick skin types (I-III and IV-VI)
- Race
- Ethnicity
- Gender
- Age (\leq median age vs $>$ median age)
- Injection volume (\leq median total injection volume vs $>$ median total injection volume)

Fisher's exact tests will be used for comparison of responder rates, as well as confidence intervals of the differences in responder rates within each subgroup. These will be displayed in graphs.

10.6.2 Safety

The consistency of AE data across different subgroups will also be evaluated. The following subgroup factors will be used:

- Injection tool (needle, cannula, and combination)
- Study site
- FST group (I-III, and IV-VI)
- Injection volume (\leq median total injection volume vs $>$ median total injection volume)
- Gender
- Age (\leq median age vs $>$ median age).



10.7 Handling of drop-outs and missing data

Number of missing values will be summarized and reported as appropriate.



All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases in the Safety population.

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10.8 Interim analysis

An interim analysis based on 12 months data from baseline is planned for this study. This includes data for all subjects (both Stage 1 and Stage 2) up to this timepoint. All data collected up to the interim analysis will be verified and may be updated, if applicable, until final closure of the study database.

10.9 Data monitoring committee

Not applicable

10.10 Withdrawals and deviations

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Subjects with CIP deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to database lock.

Deviations from the statistical plan will be documented in the Clinical Study Report.

10.11 Sample size

10.11.1 Sample size

A total sample size of approximately 224 subjects will be included in this study.

Approximately 168 subjects will be randomized to treatment with GP0109 (~56 will be injected using needle, ~56 will be injected using cannula, and ~56 will be injected using both combined) and approximately 56 will be randomized to no treatment. Sample size justifications are given below.

10.11.2 Previous data

Since the primary endpoint will be based on a new scale, no existing data is available. Similarly,



10.11.3 Assumptions

Based on results in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a responder rate of at least 70% in the GP0109 treatment group at 3 months after baseline. For the no treatment control group, responder rates up to almost 30% have been observed in the data on file. Based on this, it is assumed that the response rate will be maximum 32% in the no treatment control group at 3 months after baseline.



10.11.4 Calculations

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Using a two-sided test at the 5% significance level will have more than 99% power to demonstrate difference between a responder rate of 70% in the GP0109 group and a responder rate of 32% in the no treatment control group when the sample sizes are 150 and 50, respectively.

Performing the same test, but in needle, cannula, and combination subjects separately (at the 1.7% level of significance for each test to account for multiplicity), the power will be approximately 90% (assuming the same responder rate of 70% in all GP0109 groups (needle, cannula, and combination). All no treatment subjects will be included in each of the by strata tests.

Accounting for approximately 10% dropouts at 3 months after baseline, approximately 224 subjects need to be randomized in a 3:1 ratio (GP0109 to no treatment).



10.11.5 Safety considerations

With 168 treated subjects, there will be a probability of approximately 80% for the study to detect at least one subject having an adverse event with an assumed population incidence of 1%.

11. Protection of personal data

All processing of personal data must be carried out in accordance with national legislation concerning the protection of personal data. The Institution and the Investigator are responsible for complying with all requirements pursuant to national legislation in which the Institution and the Investigator are located. The Sponsor will ensure that all requirements for data processing are fulfilled.

The Investigator understands that clinical studies conducted under an IDE are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and the study subject should be made aware of this exception in the informed consent. The Institution and Investigator are jointly responsible for providing sufficient information to all subjects to enable them to give their informed consent not only to the participation in the investigation, but also to the processing of Personal Data. Such information includes information regarding the purposes of the processing, the length of time during which Personal Data will be stored, the right of access to stored Personal Data and the right to correction or purging of incorrect or obsolete Personal Data. A subject may also withdraw his or her consent at any time.

A subject who withdraws his or her consent to the processing of Personal Data must be considered to have withdrawn from the investigation but the data collected until the consent was withdrawn may be used in the statistical analyses.

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Authorized representatives from the Sponsor, CRO, or a RA may visit the study site to perform audits/inspections, including SDV, i.e. comparing data in the subjects' medical records and the eCRF. Data and information shall be handled strictly confidential.

The study shall include collection and processing of personal data as specified in the Regulation European Union (EU) 2016/679 (General Data Protection Regulation, GDPR) and the regulation EU 2017/745 (Medical Devices Regulation; MDR) on the protection of individuals with regard to the processing of personal data and. For the purposes of the study, the Sponsor will be considered the data controller, and Institution and PI will both be considered data processors.

12. Quality Control and Quality Assurance

12.1 Quality control

On-site monitoring of the study will be arranged by the Sponsor according to GCP guidelines to verify that the rights and well-being of the subjects are protected, the reported data are accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved CIP, subsequent amendment(s), GCP and the applicable regulatory requirements. Specific details about monitoring in the study will be outlined in a separate Monitoring Plan.

Any CIP deviation shall be documented appropriately, verified, discussed, and collected by the monitor and appropriate actions will be taken. The PI is responsible for promptly reporting any deviations from the CIP that affects the rights, safety or well-being of the subject or the scientific integrity of the study, including those that occur under emergency circumstances, to the Sponsor as well as the IRB if required by national regulations. Deviations will be reviewed to determine the need to amend the CIP or to terminate the study.

12.2 Quality assurance

The study site may be subject to quality assurance audit by the Sponsor as well as inspection by appropriate RA. It is important that the PI and other relevant study site personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study site team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study.

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the signature and delegation log.

12.3 Changes to the clinical study protocol

The PI and other site personnel involved in the study must not implement any changes to the CIP without agreement with the Sponsor and prior review and documented approval from the IRB and RA, if applicable, except where necessary to eliminate an immediate hazard to the subjects. All changes to the final CIP must be documented in a dated and version-controlled written protocol amendment.

12.3.1 Amendments

Protocol version 3.0 is the first version approved by the RA.

12.3.2 Protocol amendment history

Summary of Changes in Clinical Investigation Plan from Version 3.0 to Version 4.0

Section in the clinical investigation plan	Rational for changes	Description of changes
Abbreviation and Definitions of Terms	Clarification of childbearing potential	A female that had surgical sterilization procedure is not considered of childbearing potential.
Synopsis, sections 5.2 and 5.2 Inclusion and exclusion criteria	Clarification of visual function	Visual function requirement was moved from inclusion criterium #5 and further clarified in exclusion criterium #16
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Section 7.1 General information	Clarification for beard or facial hair during the study.	Beard or facial hair, that could interfere with effective assessments should be removed.
Section 8.2.1, 8.11.3 and 8.11.8 definition and reporting of Adverse Events of Special Interest	Clarification of reporting	Section 8.2.1 moved to new section 8.11.2 for definition of AESI. All reporting instructions included in section 8.11.6. Clarification for which visual disturbances or worsening in vision will be reported to FDA.
Section 8.8, 8.8.1, 8.8.2, 8.8.3 Visual function assessment	Clarification of worsening visual acuity	Correction to worsening of vision. Clarification for visual acuity, worsening compared to baseline, and post injection compared to pre injection at treatment visits should be reported as AESI. Clarification for referral/recommendation for an ophthalmic evaluation
Section 8.11.6 Reporting of adverse event	Added form for collection of information	The Adverse Event Clarification Form should be used for collection of additional information for non-serious AEs
Section 8.11.9 Reporting of UADE	Section was missing	Addition of unanticipated adverse device effect reporting

Section in the clinical investigation plan	Rational for changes	Description of changes
Sections 12.3.1 and 12.3.2 Amendments and protocol amendment history	New sections	New sections to track protocol amendment changes.
Subject information and informed consent form		Updates required: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
Investigator's Brochure (IB)		Updates required: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Study Specific IFU		Updates required: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Electronic case report form (eCRF)		Updates required: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>

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13. Financing, Indemnification, and Insurance

This study is fully sponsored by Galderma. The Clinical Trial Agreement (CTA) between Sponsor and Investigational sites outlines the compensation and payment terms of the study. The CTA must be signed before the first subject is screened in the study. If there are differences between the CTA and the CIP regarding certain rights and obligations, the CTA is the prevailing document.

The Sponsor's obligations in this clinical study are covered by Galderma's global general liability program. An insurance certificate will be provided upon request. The Institution/PI is obligated to maintain insurance coverage for their obligations in the clinical study according to the CTA.

14. Publication Policy

The PI's, Institution's, and Q-Med AB's obligations regarding intellectual property rights, confidentiality, and publications are described in detail in the CTA.

The aim is to submit the results of this study for publication in the public database www.ClinicalTrials.gov and to a medical journal for a first joint publication of the results. Everyone who is to be listed as an author of the results of this multicenter study shall have made a substantial, direct, intellectual contribution to the work. Authorship will be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (2) drafting the work or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the

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accuracy or integrity of any part of the work are appropriately investigated and resolved⁵. Conditions 1, 2, 3, and 4 must all be met in order to be designated as author. Those who do not meet all four criteria will be acknowledged. Among the authors that fulfil the above-mentioned criteria, one author will be appointed by Q-Med AB to take primary responsibility for the overall work as primary author.

15. Suspension or Premature Termination

The Sponsor will suspend or terminate the study when so instructed by the IRB or RA, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons, or for business reasons.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrollment or non-compliance with the CIP, GCP, or applicable regulatory requirements.

In the event of premature termination, Q-Med AB will provide information on the handling of currently enrolled subjects who have not completed the study.

⁵ Defining the role of authors and contributors, compiled by the International Committee of Medical Journal Editors (ICMJE) (<http://www.icmje.org>).

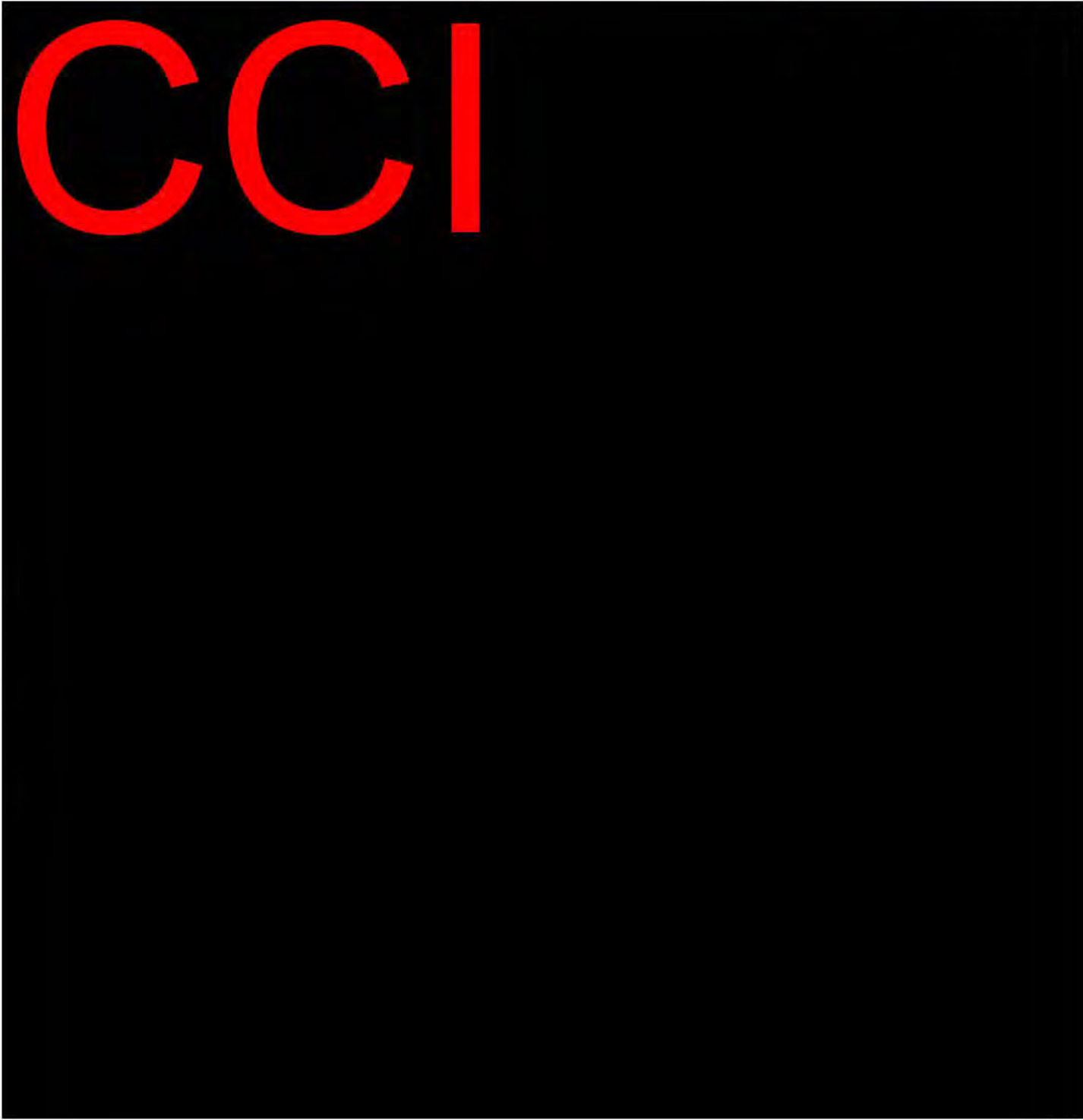
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6. Wat H, Wu DC, Goldman MP. Noninvasive Body Contouring: A Male Perspective. *Dermatol Clin.* 2018;36(1):49-55.
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Effective

Version: 4.0

Effective date: 2022-06-29 10:00

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