GALDERMA	Title **SAP, 43CH1626, Restylane Volyme Midface**	Doc id **MA-35135**

Effective date: 2017-11-03 11:43
Effective
Version: 1.0

Statistical Analysis Plan

Clinical Trial Number: 43CH1626

A randomized, multi-center, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Restylane Volyme for correction of Midface Volume Deficit and/or Midface Contour Deficiency

Effective date: 2017-11-03 11:43
Effective
Version: 1.0

Table of Contents

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

1 Study Information

1.1.1 Study design

This is a randomized, evaluator-blinded, no-treatment controlled study to evaluate the effectiveness and safety of Restylane Volyme for correction of Midface Volume Deficit and/or Midface Contour Deficiency in subjects of Chinese origin, men or women aged 18 years or older.

The study will be conducted at approximately 5 sites located in China, and subjects with a Medicis Midface Volume Scale (MMVS) score of 2, 3 or 4 on each side of the face, as assessed by the Blinded Evaluator, will be enrolled. The subjects will be followed for approximately 14 months.

Only the Evaluator will be blinded, both Treating Investigator and subjects will be aware of the treatment. To avoid 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.

For more details regarding the study, and references, please see the Clinical Study Protocol (CSP), MA-33281.

1.1.2 Number of subjects and randomization

A total of approximately 168 subjects will be enrolled.

Up to 20 subjects (2 first treated subjects per Treating Investigator, with maximum 2 treating investigators per site) will be enrolled as group A and all subjects in this group will receive treatment with Restylane Volyme. In group B, approximately 148 subjects will be randomized in a CCI ratio to treatment with Restylane Volyme or no treatment. The randomization will be stratified by site.

1.2 Study Objectives

The study objectives are:

- To evaluate the effectiveness of Restylane Volyme in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.

- To evaluate the safety of Restylane Volyme in the treatment of Midface Volume Deficit and/or Midface Contour Deficiency.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

1.3 Effectiveness Assessments

1.3.1 Medicis Midface Volume Scale (MMVS)

MMVS is a four-point photographic scale that assesses the fullness of the midface from 'Fairly full' (1) to 'Substantial loss of fullness' (4) as described below, see Table 1-1.

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The Blinded Evaluator will rate the subject's right and left midface for severity of volume deficiency using the MMVS at screening, baseline, CCI, 6, CCI months after last treatment in Group A and Treatment Group; and at screening, baseline, CCI and 6 months after randomization, as well as CCI and 6 months after last treatment in Control Group. CCI

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Effective date: 2017-11-03 11:43

Effective

Version: 1.0

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1.4 Effectiveness Endpoints

1.4.1 Primary effectiveness endpoint

The primary effectiveness endpoint is the percentage of responders, defined by at least 1 point improvement from baseline on the MMVS on both sides of the face concurrently, as measured by the Blinded Evaluator at 6 months after last treatment in Treatment Group and 6 months after randomization in Control Group.

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Effective date: 2017-11-03 11:43

Effective

Version: 1.0

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1.5 Safety Assessments

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A two-point scale ('*Yes*' or '*No*') will be used to assess causality of AEs, serious as well as non-serious. The Investigator shall be asked to indicate a response to each of the following questions in the electronic case report form (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 are answered with a '*Yes*', the AE will be considered related.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfill regulatory requirements. In case of a disagreement, the AE will be considered '*Related*'.

Any device deficiencies discovered in relation to treatment at baseline and 4-week follow-up visits for the Treatment Group and treatment at 6 months after randomization and 4-week follow-up after 6-moth treatment for the Control Group will be recorded.

1.6 Safety Endpoints

Safety endpoints include:

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(ii) Incidence, intensity, duration, and onset of adverse events (AEs) collected throughout the study.

2 Statistical Methods

2.1 General Methods

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Effective date: 2017-11-03 11:43

Effective

Version: 1.0

2.2 Analysis Populations

The following populations for Group B will be defined:

- Safety — Includes all subjects in Group B who were treated with Restylane Volyme or randomized to no-treatment group. Subjects are analyzed based on the as treated principle.
- Full Analysis Set (FAS) — Includes all subjects in Group B who were treated with Restylane Volyme or randomized to no-treatment group. Subjects are analyzed according to the randomization assignment.
- Per Protocol (PP) — Includes all subjects in FAS that comply to the protocol procedures with no deviations that can affect the evaluation of the primary variable.

The FAS population is the primary population for all effectiveness analyses. All safety analyses will be based on the Safety population.

Group A will be followed for safety evaluation throughout the whole study.

2.3 Study Subjects

2.3.1 Subject disposition

The number and percentage of subjects in each study population (FAS, PP, and Safety) will be summarized by site (including subject number) and in total (Table 4-1). Study population variables will also be presented in a data listing.

The disposition of subjects, including reason for withdrawals, will be presented by site and in total (Table 4-4). Number of completed, missed, and withdrawn subjects, as well as subjects continuing in the study will be accounted for by visit and treatment group (Table 4-5 and Table 4-6). Subject accountability will also be presented in a flowchart (Figure 4-1 and Figure 4-2).

All withdrawn subjects will be listed individually, including site number, subject number, treatment group, date of treatment and withdrawal, reason for withdrawal and last visit performed (Table 4-7 and Table 4-8).

Reasons for screening failures will be summarized (Table 4-9).

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

2.3.2 Protocol deviations

Subjects with CSP deviations will be presented by observed protocol deviation, number of subjects and number of deviations (Table 4-3). Depending on the seriousness of the deviation, the subject might be excluded from the PP population (Table 4-2), which shall be documented prior to database lock (DBL).

Definition of protocol deviations that will exclude subjects from the PP are defined (but not limited to) in Table 2-1 below.

Table 2-1: Protocol deviations

	Deviation
GENERAL	
	Visit out-of-window
	* Follow-up at 6 months after last treatment performed earlier than 1 week before the scheduled visit or later than 2 weeks after the scheduled visit in Treatment Group.
	* Follow-up at 6 months after randomization performed earlier than 1 week before the scheduled visit or later than 2 weeks after the scheduled visit in Control Group.
EFFECTIVENESS	
	MMVS assessed by Blinded Evaluator
	* Not done for both sides of the face at 6 months after last treatment in Treatment Group, or at 6 months after randomization in Control Group.
	* Pre-treatment MMVS not available for both sides of the face.
	* More than 1 grade difference in baseline MMVS score between the two sides of the face.
OTHER	
	Inclusion/exclusion criteria
	* Any inclusion criteria affecting primary effectiveness evaluation not met.
	* Any exclusion criteria affecting primary effectiveness evaluation met.

2.3.3 Demographics and Baseline characteristics

Demographic endpoints and subject baseline characteristics will be presented by treatment group (Table 5-1) using descriptive statistics. Gender, ethnic origin, and baseline MMVS score (assessed by Blinded Evaluator and CCI [redacted]) will be summarized as categorical end points using number and percentage of subjects. Age and baseline BMI will be summarized by number of subjects, mean, standard deviation, minimum, median, and maximum values.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

2.3.4 Medical history, and concomitant medication and procedures

All summaries will be based on the Safety population. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Medical history will be coded according to medical dictionary for regulatory activities (MedDRA).

Medical history/concurrent disease

The number and percentage of subjects reporting medical history/concurrent diseases and the number of conditions will be summarized by System Organ Class (SOC) and in total, for all medical history during the whole study and ongoing at study start (Table 5-2 and Table 5-3).

Prior use of facial fillers or implants will be summarized by type of fillers/implants using number and percentage of subjects and number of events (Table 5-4). Prior use of other facial dermatological procedures will be summarized by type of procedure using number and percentage of subjects and number of events (Table 5-5).

Concomitant medication and procedures

The number and percentage of subjects reporting concomitant medication ongoing at study start, initiated during study and in total (Table 6-1) will be summarized. In addition, the number and percentage of subjects reporting concomitant medication, and the number of medications will be summarized by reason and in total (Table 6-2). Also, the number and percentage of subjects, and the number of medications, will be summarized by ATC code and in total, along with an ATC text description (Table 6-3).

Concomitant medication taken due to an AE will be summarized by ATC code (along with an ATC text description) and in total using number and percentage of subjects and number of medications, and by MedDRA coded AE and whether the AE is related or not (Table 6-4 and Table 6-5).

Concomitant procedures will be presented by reason and in total (Table 6-6), as well as by type of procedure (Table 6-7), using number and percentage of subjects and number of procedures.

2.3.5 Extent of exposure

Volume injected (mL), for each treatment visit and in total will be presented by treatment group (Table 7-1) using number of subjects, mean, standard deviation, minimum, median, and maximum values. Depth of injection and injection method for each treatment visit will be summarized by treatment group using number and percentage of subjects (Table 7-1).

Local anaesthesia used and post-treatment care for each treatment visit will be summarized by treatment group using number and percentage of subjects (Table 7-2).

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

2.3.6 Post-treatment examinations

Change from baseline in post-treatment BMI will be presented for subjects with a change in BMI ≥ 2 units, if applicable (Table 8-1).

2.4 Effectiveness Analysis

2.4.1 Data sets analyzed

All effectiveness variables will be analyzed using the FAS population. The primary analysis will be repeated using the PP population. If it is deemed necessary, other analyses will be repeated using the PP population.

2.4.2 Handling of missing data

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

Different assumptions regarding the missing data will be used. For the primary effectiveness analysis, missing values in the FAS will be assumed to be missing due to lack of effect. Therefore missing data up to the Month 6 visit will be imputed using the baseline observation carried forward (BOCF) method. As an alternative approach, missing data will be assumed to be unrelated to treatment effect. To impute data under this assumption, missing data up to the Month 6 visit will be imputed using the hot deck method (Table 9-2). Both of these alternatives will estimate the effectiveness of the treatment policy (irrespective of use of disallowed treatments, procedures, or medications) rather than the true, clinical treatment effect.

To obtain an estimate of the true, clinical treatment effect, the primary effectiveness analysis will be performed using the PP population.

All other endpoints will be analyzed on available data, i.e. no imputations will be done.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

2.4.3 Primary analysis

The percentage of responders (a responder will be defined as a subject with at least 1 point improvement from baseline MMVS on both sides of the face concurrently) will be calculated for each group at Month 6 (after last treatment for Treatment group, and after randomization for Control group) based on the Blinded Evaluator's assessment. CCI

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Effective date: 2017-11-03 11:43

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2.5 Safety Analysis

All safety variables will be summarized descriptively based on the Safety population.

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2.5.2 Adverse Events

All AEs will be coded according to MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). All AE summaries defined below will be presented by treatment, i.e. no treatment at baseline vs. all treated subjects (at baseline and Month 6).

An overall summary of number and percentage of subjects with any AEs, including related/unrelated and serious AEs, and the number of events will be compiled (Table 10-5).

For related AEs, maximum intensity of the AE will be summarized (Table 10-6). The duration (Table 10-7) and time to onset (Table 10-8) of event will be summarized by SOC and PT using number of events, mean, standard deviation, minimum, median, and maximum statistics. Action taken due to a related AE will be summarized by SOC, and PT (Table 10-9) using number of events.

Number and percentage of subjects with unrelated AEs and number of events will be presented by SOC, PT and maximum intensity (Table 10-10).

Time to onset of an AE will be derived as the start date minus the date of the most recent treatment. If the start date is missing, it will be assumed that the AE started on the date of the most recent treatment.

Duration of an AE will be derived as the stop date minus the start date +1. If the start date is missing, it will be assumed that the AE started on the date of the most recent treatment. Missing stop date will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of AEs that were ongoing at the end of the study will be given.

Effective

Version: 1.0

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

2.6 Interim Analysis

No interim analysis is planned.

2.7 Determination of Sample Size

There are no available clinical data for Restylane Volyme studied under conditions similar to the current study. However, based on what is seen in clinical studies of injectable fillers in the facial areas, it is reasonable to assume a response rate of at least 70% in the Restylane Volyme treatment group at Month 6. For the no treatment control group, response rates as high as 35% have been observed in Glogau et al[1]. Based on this, it was assumed that the response rate will be maximum 35% in the no-treatment control group at Month 6.

2.8 Changes in the Analysis Planned in the Protocol

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

3 Reference List

1 Glogau RG et al. A randomized, evaluator-blinded, controlled study of the efficacy and safety of small gel particle hyaluronic acid for lip augmentation. Dermatol Surg. 2012 Jul; 38(7 Pt 2):1180-92.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

4 Appendix A1: Study Subjects

4.1 Analysis Populations

Table 4-1: Analysis populations

Site	Group	Subject number	Safety		FAS		PP	
			n	%	n	%	n	%
Site 1	A	1xx-1xx						
	B	1xx-1xx						
Site 2	A	2xx-2xx						
	B	2xx-2xx						
Site 3	A	3xx-3xx						
	B	3xx-3xx						
Site 4	A	4xx-4xx						
	B	4xx-4xx						
Site 5	A	5xx-5xx						
	B	5xx-5xx						
Total (N)								

% = n/N*100

4.2 Protocol Deviations

Table 4-2: Protocol deviations excluding subjects from PP population, Group B

Protocol deviation	Number of subjects[1)]	Subject numbers
Total		

1) The same subject may have been excluded from PP for more than one reason.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Table 4-3: Protocol deviations not excluding subjects from PP population, Group A and B

Protocol deviation	Group A		Group B		Total
	Number of subjects[1)]	Subject numbers	Number of subjects[1)]	Subject numbers	Number of deviations
Total					

1) A single subject may have reported several protocol deviations.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

4.3 Subject disposition

Table 4-4: Disposition of all subjects

Site	Group	Screened subjects		Enrolled subjects		Subject numbers	Treated subjects		Completed subjects		Withdrawn subjects	
		n	%	n	%		n	%	n	%	n	%
Site 1	A					1xx-1xx						
	B					1xx-1xx						
Site 2	A					2xx-2xx						
	B					2xx-2xx						
Site 3	A					3xx-3xx						
	B					3xx-3xx						
Site 4	A					4xx-4xx						
	B					4xx-4xx						
Site 5	A					5xx-5xx						
	B					5xx-5xx						
Total (N)												

% = n/N*100

Table 4-5: Subject accountability by visit: subjects randomized to treatment with Restylane Volyme, Group B

Visit	Number of subjects			
	Completed	Missed	Withdrawals	Continuing in study
Baseline/initial treatment				
4W follow-up/optional touch-up				
4W follow-up after last treatment				
3M after last treatment				
6M after last treatment				
9M after last treatment				
12M after last treatment				

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Table 4-6: Subject accountability by visit: subjects randomized to no-treatment control, group B

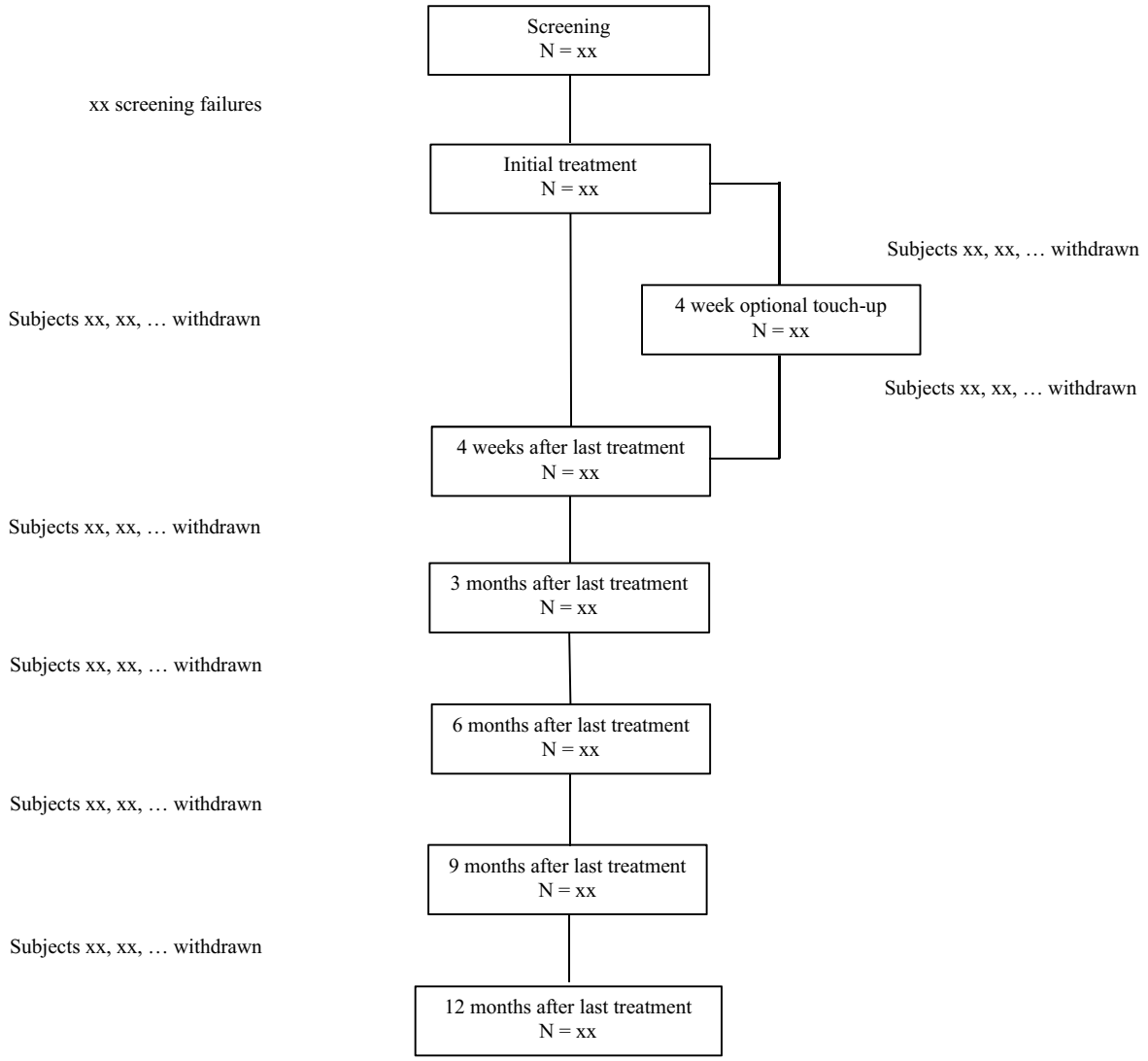
Visit	Number of subjects			
	Completed	Missed	Withdrawals	Continuing in study
Baseline				
4W follow-up				
3M follow-up				
6M follow-up/treatment				
4W follow-up/optional touch-up				
4W follow-up after last treatment				
3M after last treatment				
6M after last treatment				

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Figure 4-1: Subject accountability by visit in Group A



Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Figure 4-2: Subject accountability by visit in Group B

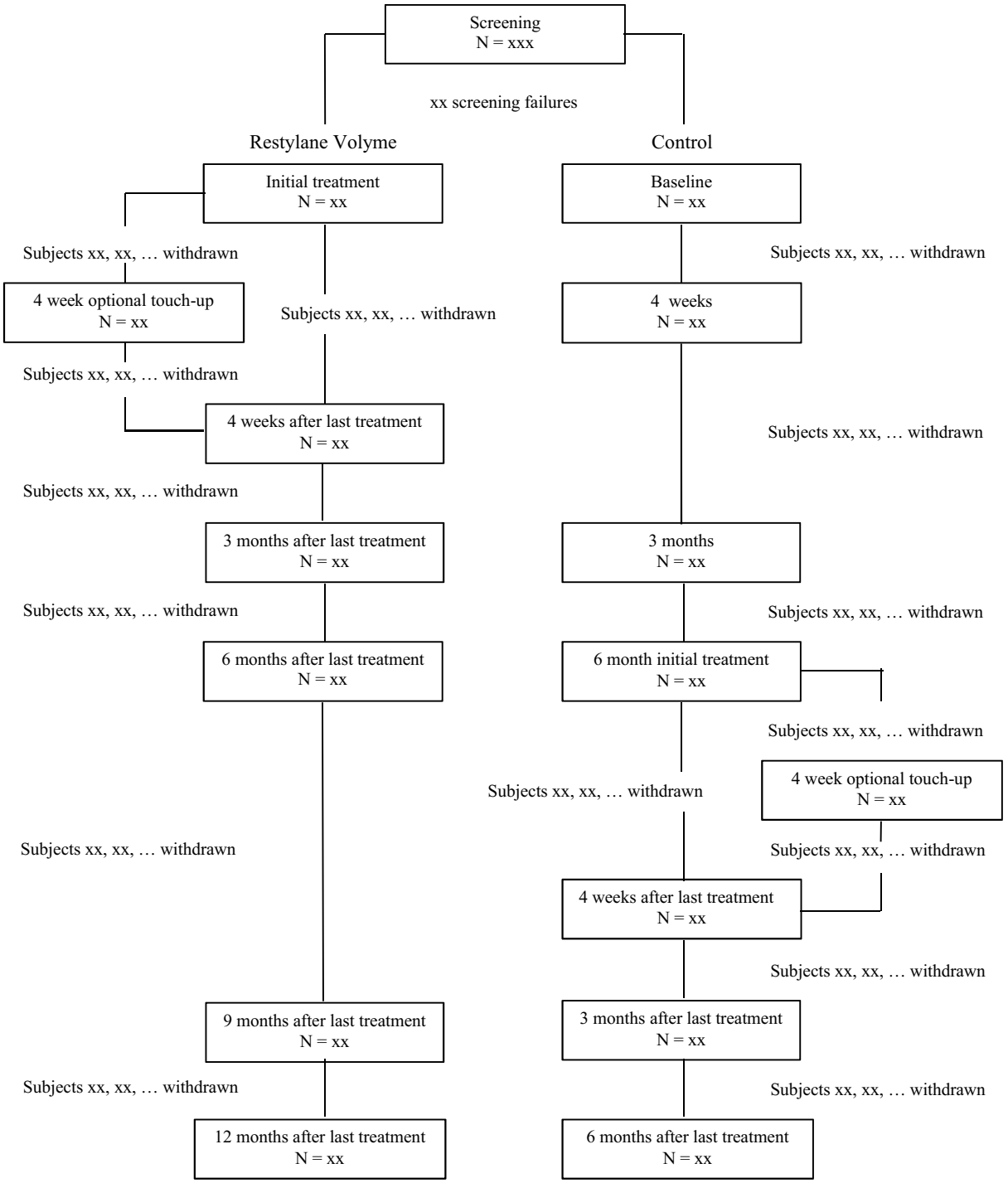


Table 4-7: Withdrawn subjects, Group A

Site	Subject number	Date of treatment		Last visit performed	Date of withdrawal	Reason for withdrawal
		Initial treatment	Optional touch-up treatment			

Table 4-8: Withdrawn subjects, Group B

Treatment group	Site	Subject number	Date of treatment		Last visit performed	Date of withdrawal	Reason for withdrawal
			Initial treatment	Optional touch-up treatment			
Restylane Volyme							
Control							

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Table 4-9: Screening failures

Reason for screening failure	Group A		Group B		Total
	Screening number	Number of subjects	Screening number	Number of subjects	Number of subjects

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

5 Appendix A2: Demographics

5.1 Demographics and baseline characteristics

Table 5-1: Summary of demographics and baseline characteristics, Safety population

Characteristics	Parameter	Group A N = xx	Group B		
			Restylane Volyme N = xxx	Control N = xx	Total N = xxx
Age (years)	N				
	Mean				
	SD				
	Median				
	Minimum				
	Maximum				
Gender					
Female	n (%)				
Male	n (%)				
Ethnic origin					
Han Chinese	n (%)				
Other[1)]	n (%)				
Baseline BMI	N				
	Mean				
	SD				
	Median				
	Minimum				
	Maximum				
Baseline MMVS score, Blinded Evaluator					
right side					
Score 2	n (%)				
Score 3	n (%)				
Score 4	n (%)				

% = n/N*100 1) Specification of Other: …, …, …..

Effective date: 2017-11-03 11:43
Effective
Version: 1.0

Characteristics	Parameter	Group A N = xx	Group B		
			Restylane Volyme N = xxx	Control N = xx	Total N = xxx
left side					
Score 2	n (%)				
Score 3	n (%)				
Score 4	n (%)				
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% = n/N*100

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

5.2 Medical history

Table 5-2: Subjects reporting medical history/concurrent diseases and number of conditions by MedDRA System Organ Class (SOC) in Group A, Safety population

Primary SOC	Total			Ongoing at study start		
	Subjects		Conditions	Subjects		Conditions
	n	%	n	n	%	n
Total (N)[1)]						

% = n/N*100

1) A single subject may have reported medical history/concurrent diseases by more than one primary SOC category.

Table 5-3: Subjects reporting medical history/concurrent diseases and number of conditions by MedDRA System Organ Class (SOC) in Group B, Safety population

Primary SOC	Restylane Volyme N = xxx						Control N = xx					
	Total			Ongoing at study start			Total			Ongoing at study start		
	Subjects		Conditions	Subjects		Conditions	Subjects		Conditions	Subjects		Conditions
	n	%	n	n	%	n	n	%	n	n	%	n
Total (N)[1)]												

% = n/N*100

1) A single subject may have reported medical history/concurrent diseases by more than one primary SOC category.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Table 5-4: Prior use of facial fillers or implants, Safety population

Fillers/implants	Group A N = xx			Group B					
				Restylane Volyme N = xxx			Control N = xx		
	Subjects		Filers/implants	Subjects		Fillers/implants	Subjects		Fillers/implants
	n	%	n	n	%	n	n	%	n
Hyaluronic Acid (HA)									
Permanent implant									
Semi-permanent implant									
Collagen									
Other[1)]									
Total[2)]									

% = n/N*100

1) Specification of Other: …, …, …..

2) A single subject may have had several fillers of implants.

Table 5-5: Prior use of other facial dermatological procedures, Safety population

Procedure	Group A N = xx			Group B					
				Restylane Volyme N = xxx			Control N = xx		
	Subjects		Procedures	Subjects		Procedures	Subjects		Procedures
	n	%	n	n	%	n	n	%	n
Botulinum toxin injection									
Resurfacing									
Mesotherapy									
Face-lift									
Autologous Fat transplantation									
Other[1)]									
Total[2)]									

% = n/N*100

1) Specification of Other: …, …, …..

2) A single subject may have had several facial dermatological procedures.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

6 Appendix A3: Concomitant medication and procedures

6.1 Concomitant medication

Table 6-1: Subjects reporting concomitant medication, Safety population

Concomitant medication	Any concomitant medication											
	Group A N = xx				Group B							
					Restylane Volyme N = xxx				Control N = xx			
	No		Yes		No		Yes		No		Yes	
	n	%	n	%	n	%	n	%	n	%	n	%
Ongoing at study start												
Initiated during study												
Total[1)]												

% = n/N*100

1) A single subject might have had concomitant medication ongoing at study start and initiated during study.

Table 6-2: Subjects reporting concomitant medication and number of medications by reason, Safety population

Reason for concomitant medication	Group A N = xx				Group B							
					Restylane Volyme N = xxx				Control N = xx			
	Subjects		Number of medications		Subjects		Number of medications		Subjects		Number of medications	
	n	%	Total	Ongoing at study end	n	%	Total	Ongoing at study end	n	%	Total	Ongoing at study end
Related Adverse Event												
Unrelated Adverse Event												
Medical History												
Other												
Total[1)]												

% = n/N*100

1) A single subject may have reported concomitant medication for several reasons.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Table 6-3: Subjects reporting concomitant medication and number of medications by ATC code, Safety population

ATC code	ATC text	Group A N = xx			Group B					
					Restylane Volyme N = xxx			Control N = xx		
		Subjects		Medications	Subjects		Medications	Subjects		Medications
		n	%	n	n	%	n	n	%	n
Total[1)]										

% = n/N*100

1) A single subject may have reported several types of concomitant medication.

Table 6-4: Subjects reporting concomitant medication taken due to an AE by ATC cod in Group A, Safety population

Concomitant medication				Adverse Event	
ATC code	ATC text	Subjects	Medications	PT	Related AE
		n	n		
					Yes/No
					Yes/No
					Yes/No
					Yes/No
Total[1)]					

% = n/N*100

1) A single subject may have reported several types of concomitant medication.

Note: if too much data for unrelated AEs then update this and the next table for related AEs only.

Table 6-5: Subjects reporting concomitant medication taken due to an AE by ATC code in Group B, Safety population

Concomitant medication				Adverse Event	
ATC code	ATC text	Subjects	Medications	PT	Related AE
		n	n		
					Yes/No
					Yes/No
					Yes/No
					Yes/No
Total[1)]					

% = n/N*100

1) A single subject may have reported several types of concomitant medication.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

6.2 Concomitant procedures

Table 6-6: Subjects reporting concomitant procedures and number of procedures by reason, Safety population

Reason for concomitant procedure	Group A N = xx			Group B					
				Restylane Volyme N = xxx			Control N = xx		
	Subjects		Procedures	Subjects		Procedures	Subjects		Procedures
	n	%	n	n	%	n	n	%	n
Adverse Event									
Medical History									
Other									
Total[1)]									

% = n/N*100

1) A single subject may have reported procedures for several reasons.

Please consider to add a table regarding “Concomitant procedures due to a related AE”.

Table 6-7: Subjects reporting concomitant procedures and number of procedures, Safety population

Concomitant procedure	Group A N = xx			Group B					
				Restylane Volyme N = xxx			Control N = xx		
	Subjects		Procedures	Subjects		Procedures	Subjects		Procedures
	n	%	n	n	%	n	n	%	n
Total[1)]									

% = n/N*100

1) A single subject may have reported several concomitant procedures.

Note: if too much data for unrelated AEs then update this table for related AEs only.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

7 Appendix A4: Treatment procedure

Table 7-1: Exposure to study treatment, Safety population

Assessment (right and left midface combined)	Parameter	Group A N = xx	Group B	
			Restylane Volyme N = xxx	Control N = xx
Volume injected (mL) at initial treatment	N			
	Mean (SD)			
	Median			
	Minimum, Maximum			
Volume injected (mL) at touch-up	N			
	Mean (SD)			
	Median			
	Minimum, Maximum			
Total volume injected (mL) at initial treatment and touch-up	N			
	Mean (SD)			
	Median			
	Minimum, Maximum			
Depth of injection at initial treatment				
Subcutaneous	n (%)			
Supraperiosteal	n (%)			
Other[1)]	n (%)			
Depth of injection at touch-up				
Subcutaneous	n (%)			
Supraperiosteal	n (%)			
Other[2)]	n (%)			
Injection method at initial treatment				
Linear retrograde	n (%)			
Small aliquots	n (%)			
Fanning injection technique	n (%)			
Other[3)]	n (%)			

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Assessment (right and left midface combined)	Parameter	Group A N = xx	Group B	
			Restylane Volyme N = xxx	Control N = xx
Injection method at touch-up				
Linear retrograde	n (%)			
Small aliquots	n (%)			
Fanning injection technique	n (%)			
Other4)	n (%)			

% = n/N*100
1) Specification of Other: …, …, ….
2) Specification of Other: …, …, ….
3) Specification of Other: …, …, ….
4) Specification of Other: …, …, ….

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

Table 7-2: Treatment procedure, Safety population

Time Point	Assessment (right and left midface combined)	Category	Group A N = xx	Group B	
				Restylane Volyme N = xxx n (%)	Control N = xx n (%)
Initial treatment	Local anaesthesia used?	No			
		Yes			
		Whereof topical cream			
		Whereof local infiltration			
Touch-up	Local anaesthesia used?	No			
		Yes			
		Whereof topical cream			
		Whereof local infiltration			
Initial treatment	Post-treatment care	None			
		Massage			
		Ice pack			
		Other[1)]			
Touch-up	Post-treatment care	None			
		Massage			
		Ice pack			
		Other[1)]			

% = n/N*100
1) Specification of Other: …, …, ….
2) Specification of Other: …, …, ….

Any device deficiencies will be listed in text or in a separate table, as appropriate.

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Version: 1.0

8 Appendix A5: Post-treatment examinations

Table 8-1: Subjects with change from baseline in post-treatment BMI ≥ 2 units, Safety population

Group A		Group B	
Number of subjects	Subject numbers	Number of subjects	Subject numbers

9 Appendix A6: Effectiveness Evaluation for Group B

9.1 Primary analysis

9.1.1 MMVS responder rate at Month 6

Table 9-1: MMVS responder rate at Month 6 by treatment, Blinded Evaluator

Population	Assessment/Time Point	Treatment group	Subjects in population	Responders		95% Confidence Interval	P-value
			N	n	%		
FAS[1)]	Right and left midface combined at Month 6	Restylane Volyme					
		Control					
		Difference					
PP[2)]	Right and left midface combined at Month 6	Restylane Volyme					
		Control					
		Difference					

1) Subjects with a missing MMVS score have their values imputed using BOCF up to Month 6.
2) No imputation is used for PP analysis. Only subjects with complete data are included.
Note: Responder is defined as a subject with an improvement of at least one grade on the MMVS from baseline.
Note: Responder rate (%) = n/N*100

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Version: 1.0

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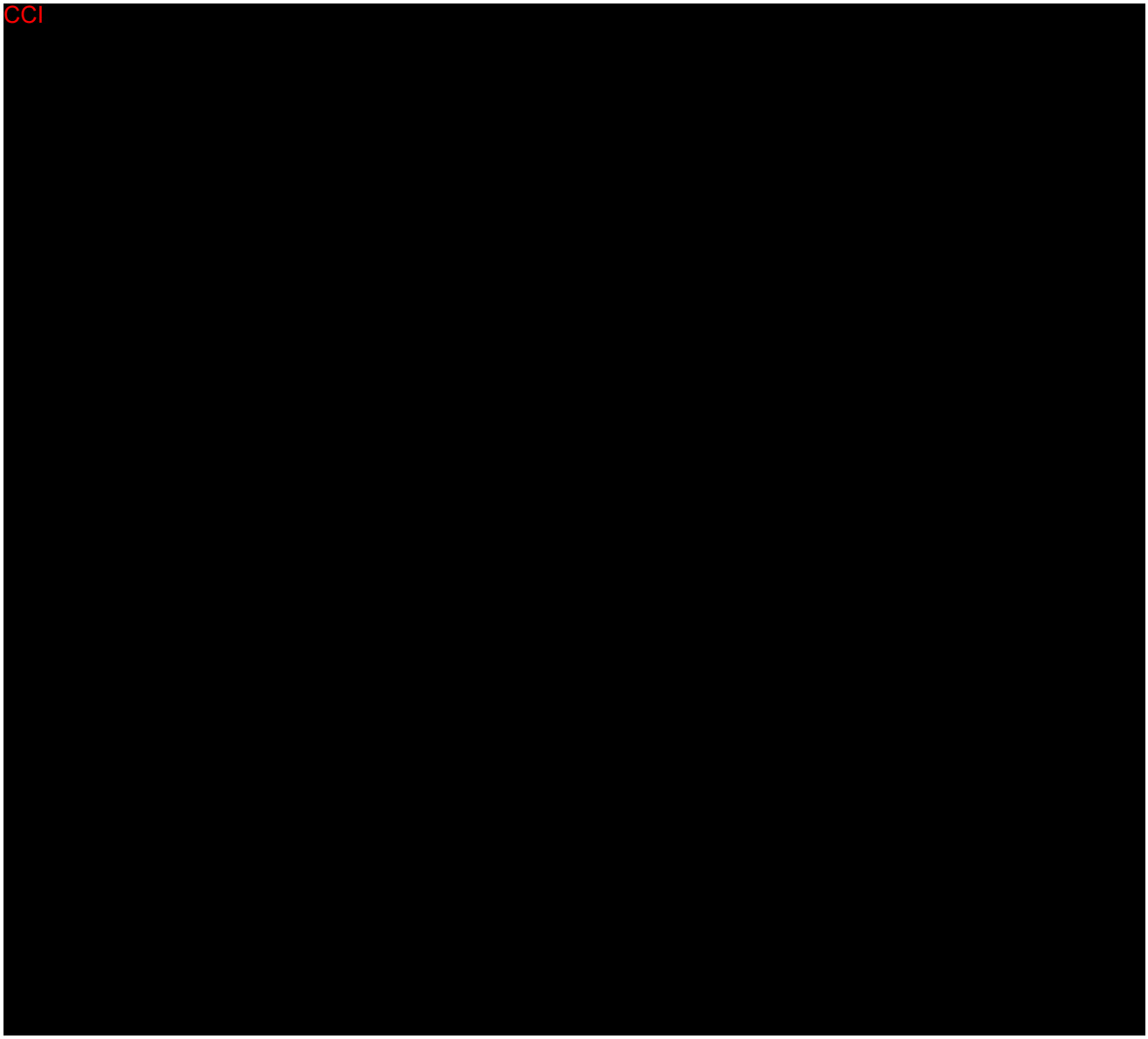

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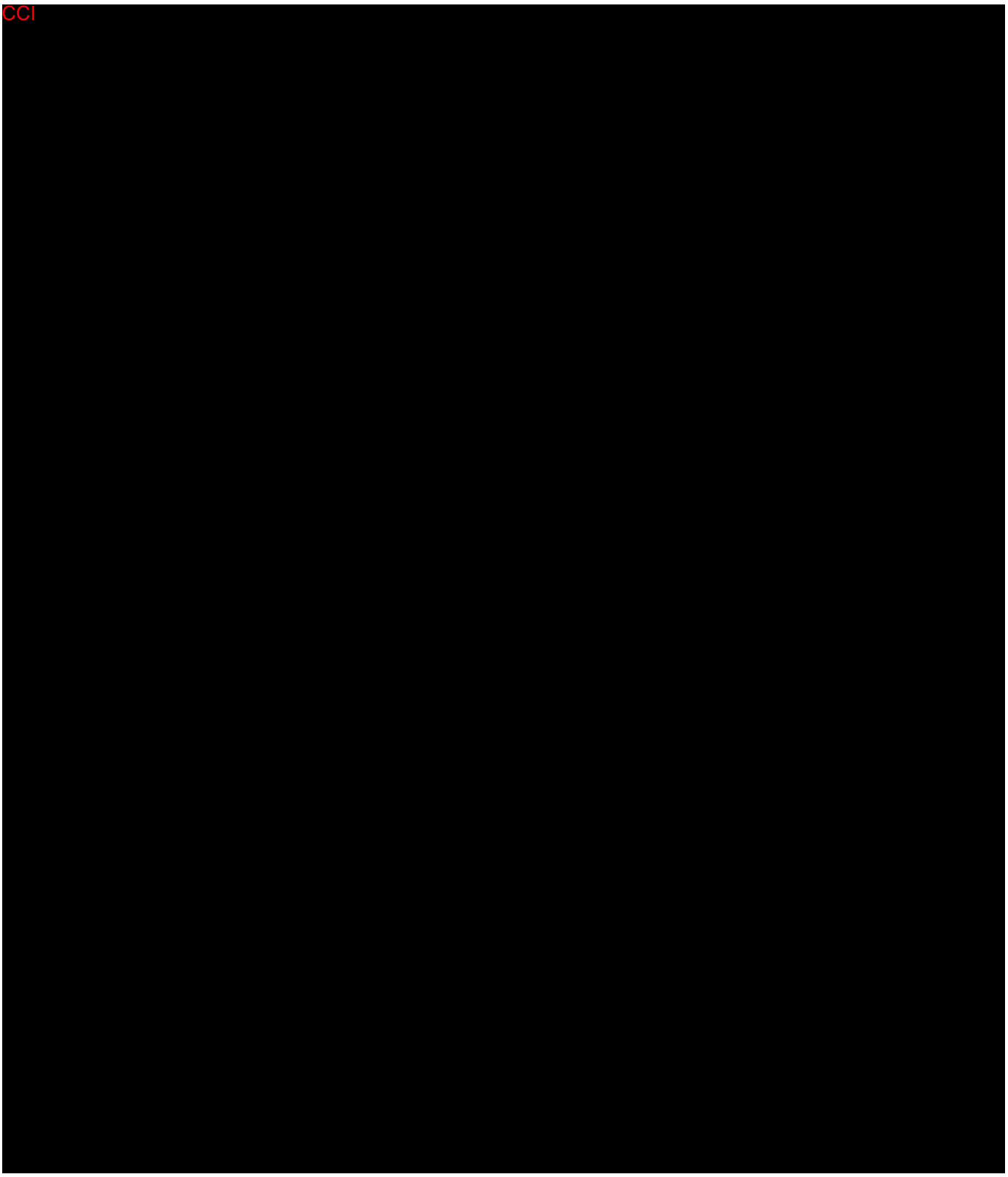

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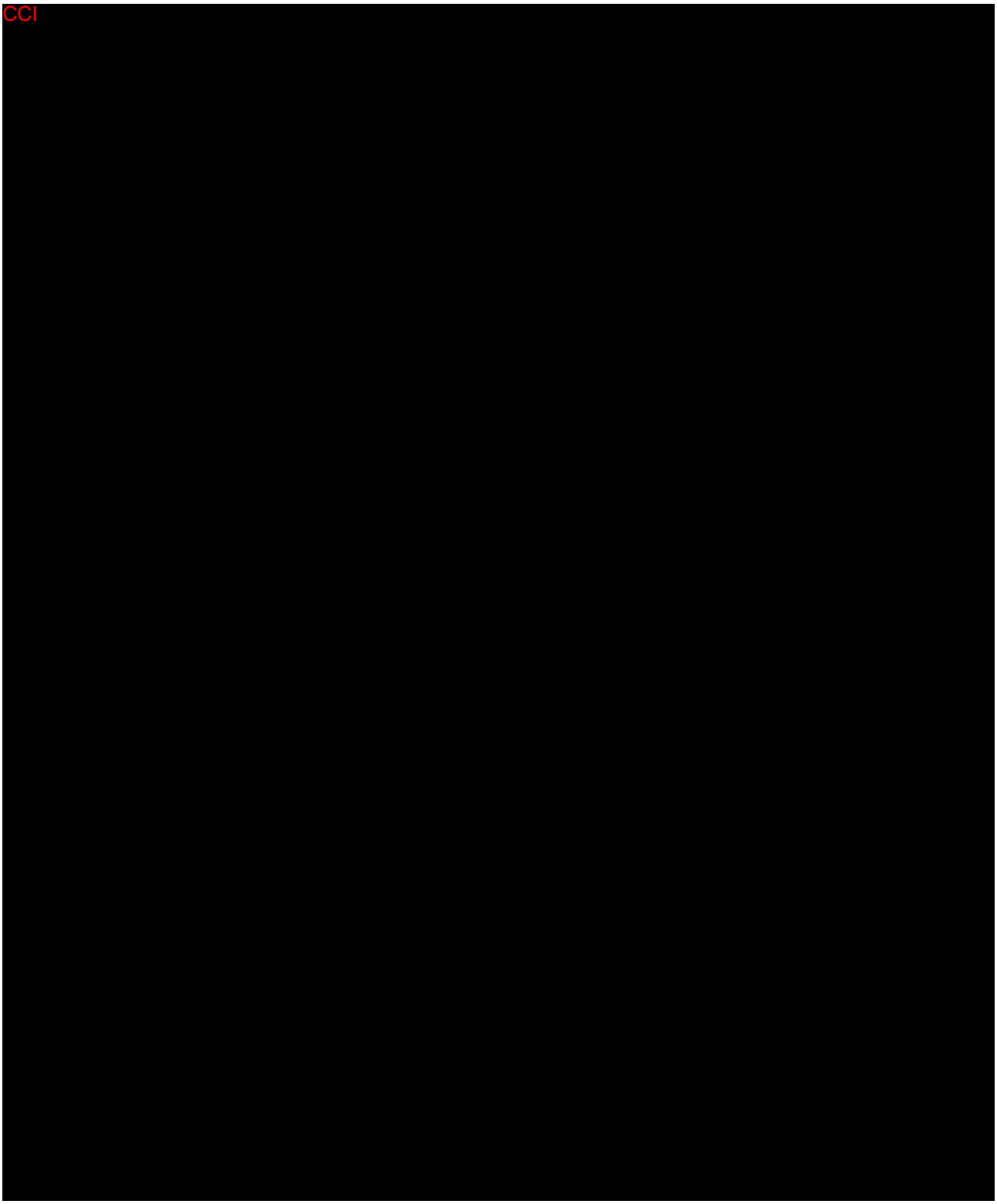

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Effective
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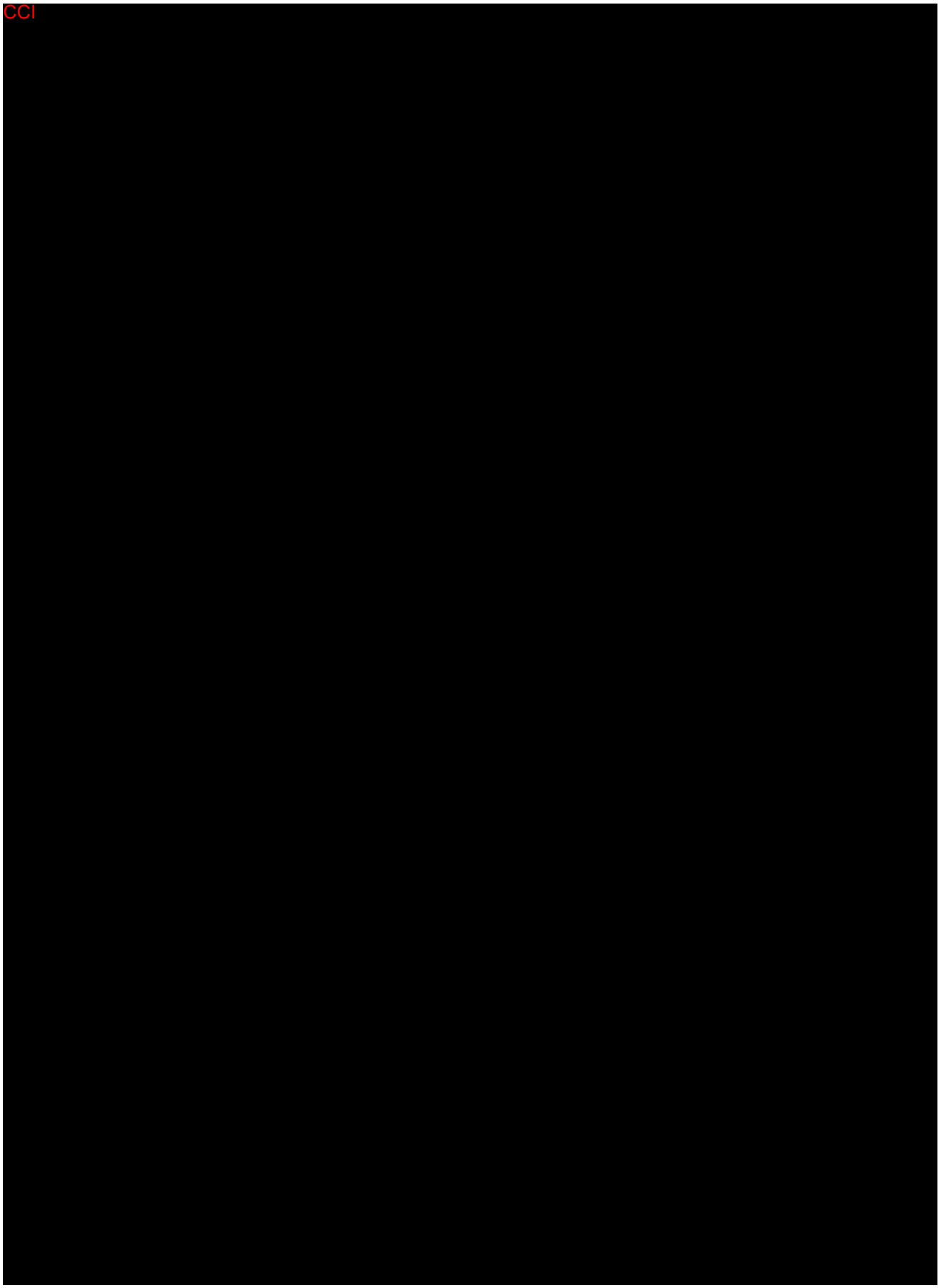

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Effective date: 2017-11-03 11:43

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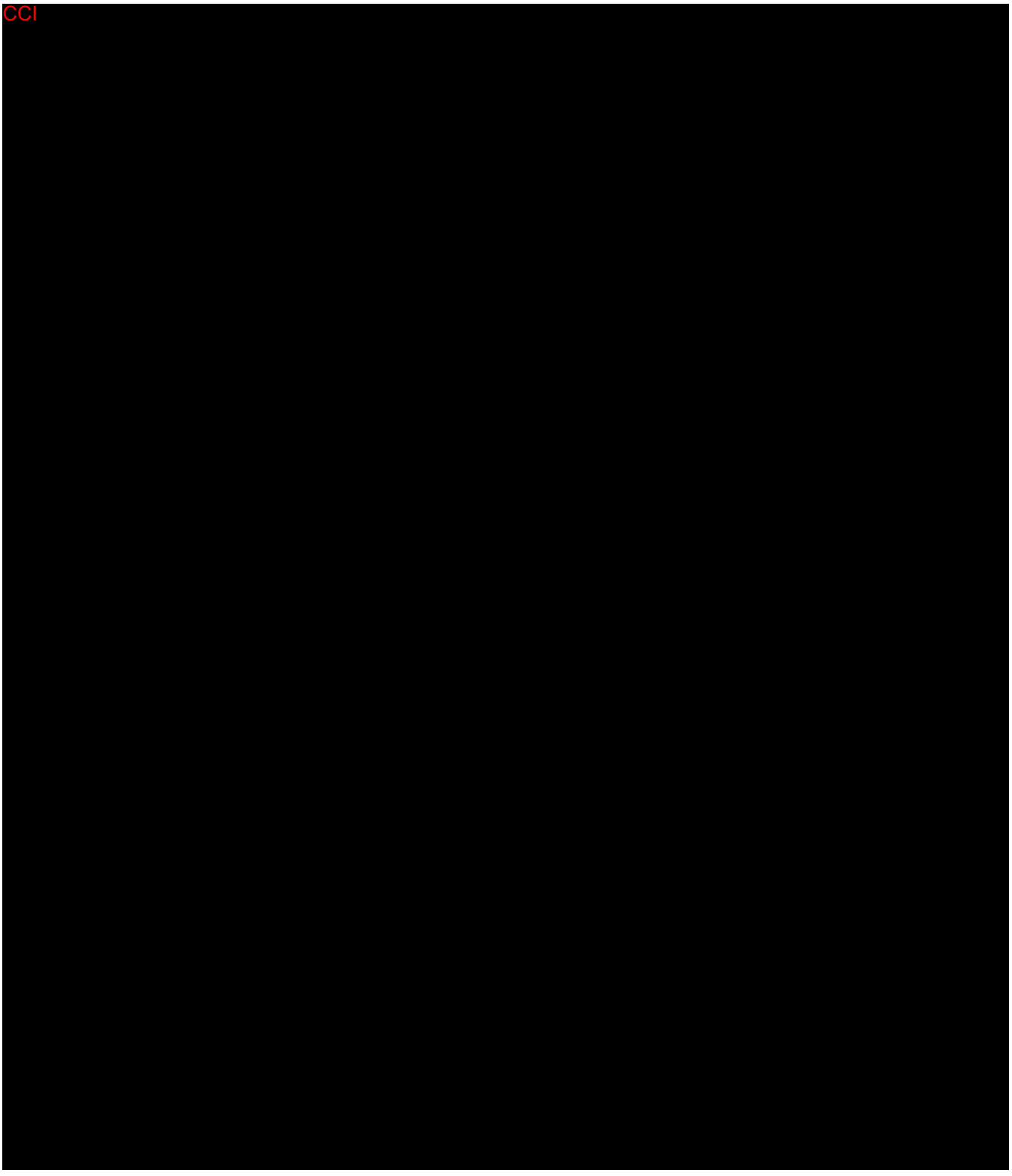

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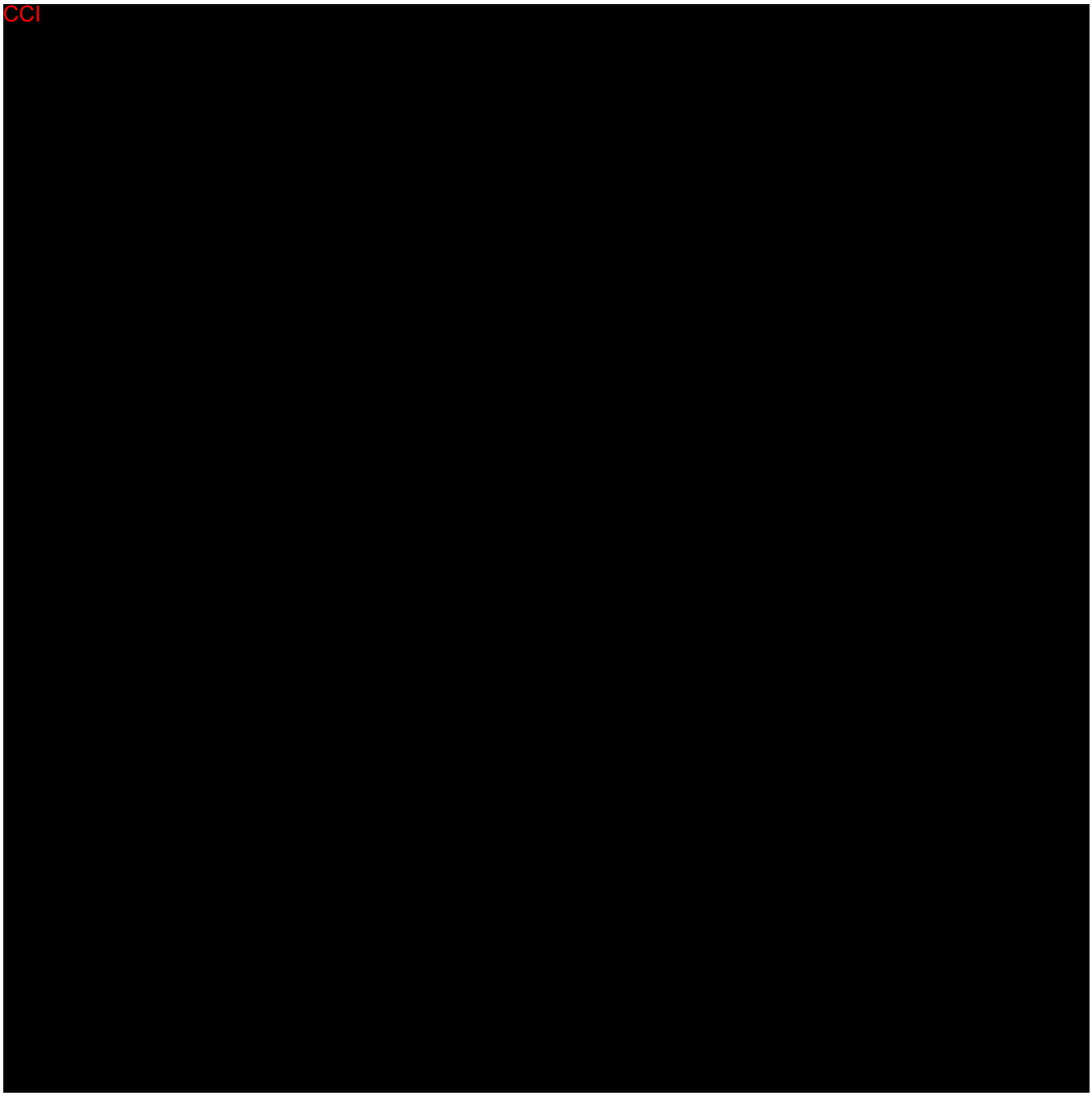

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Version: 1.0

10 Appendix A7: Safety evaluation

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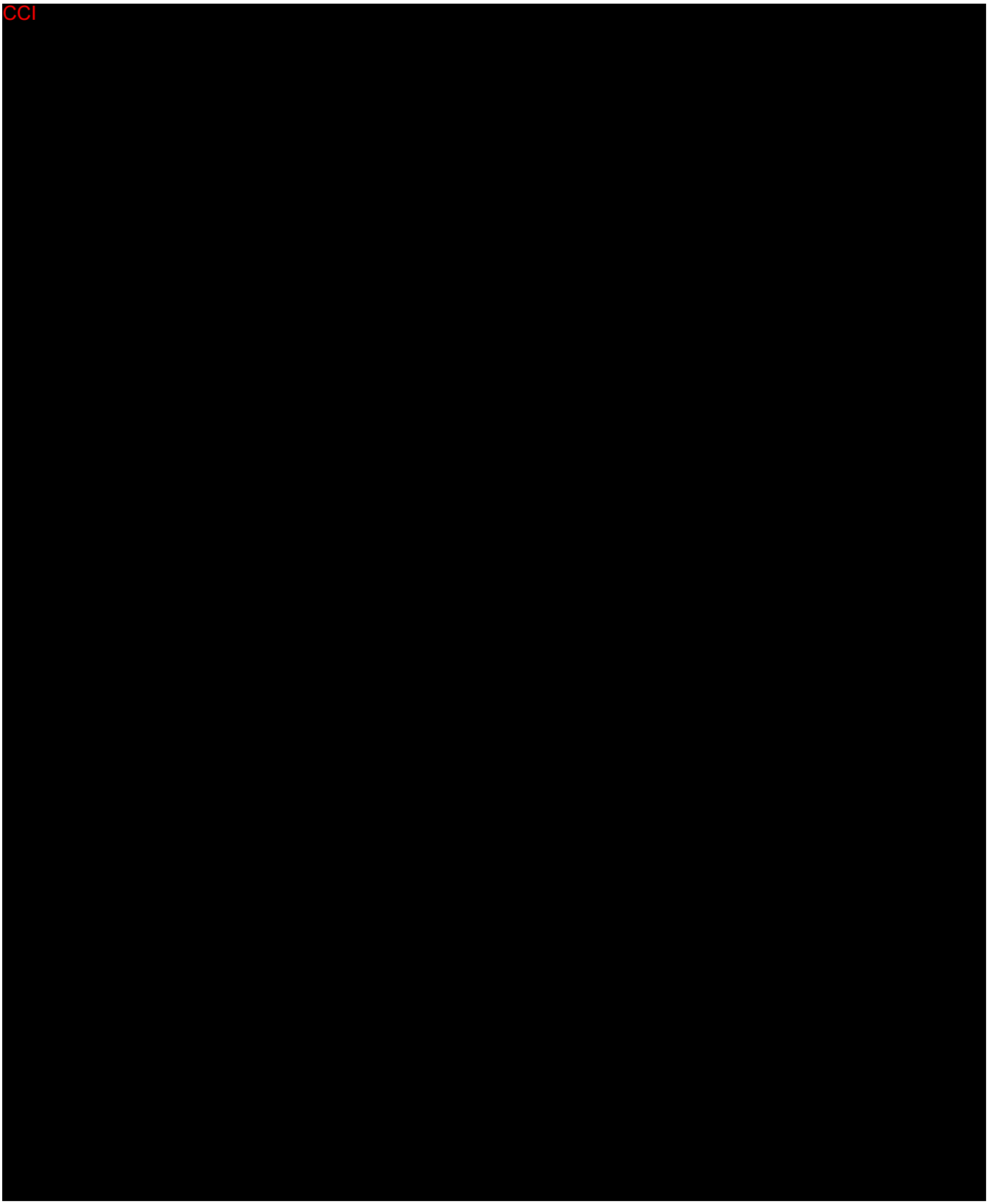

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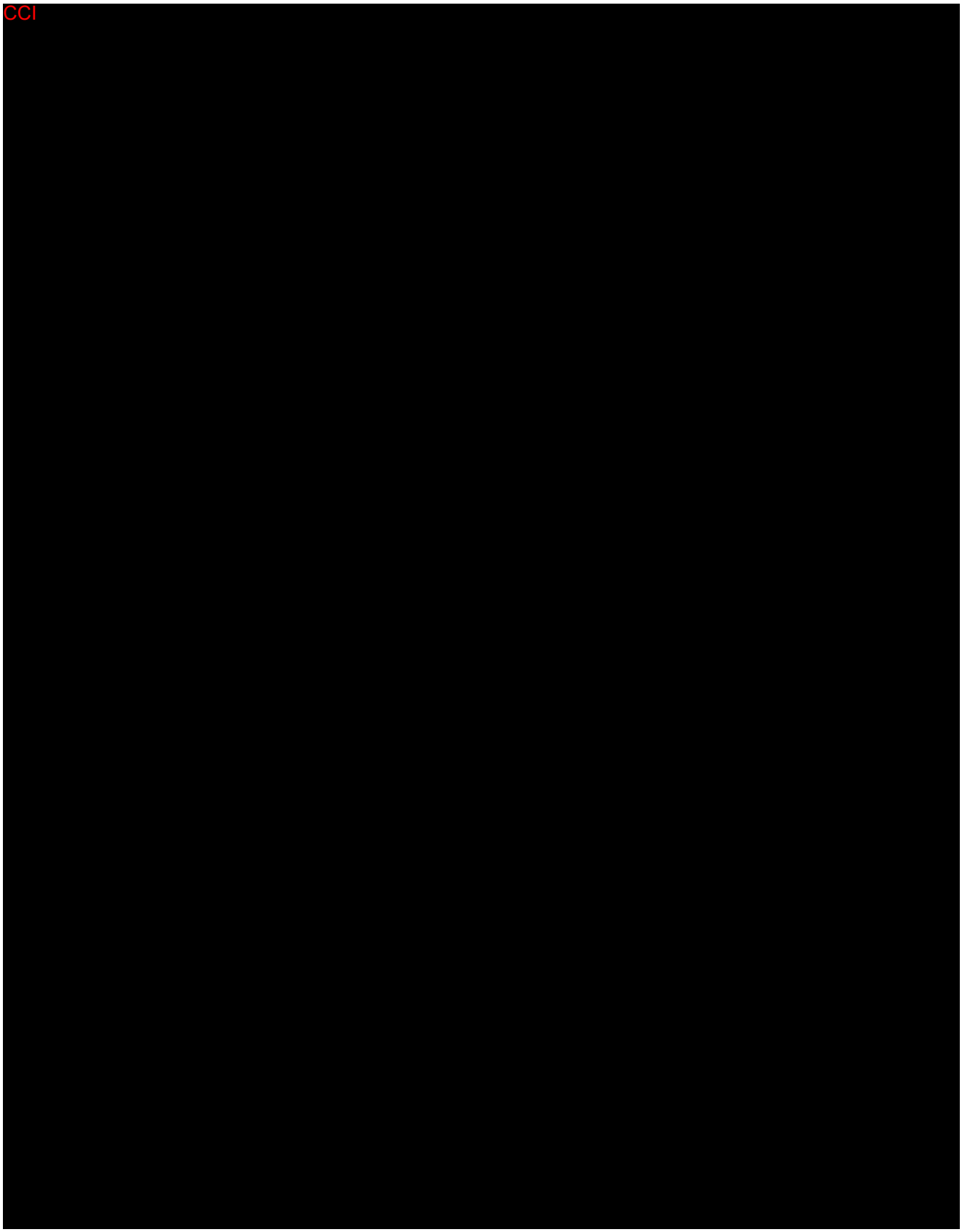

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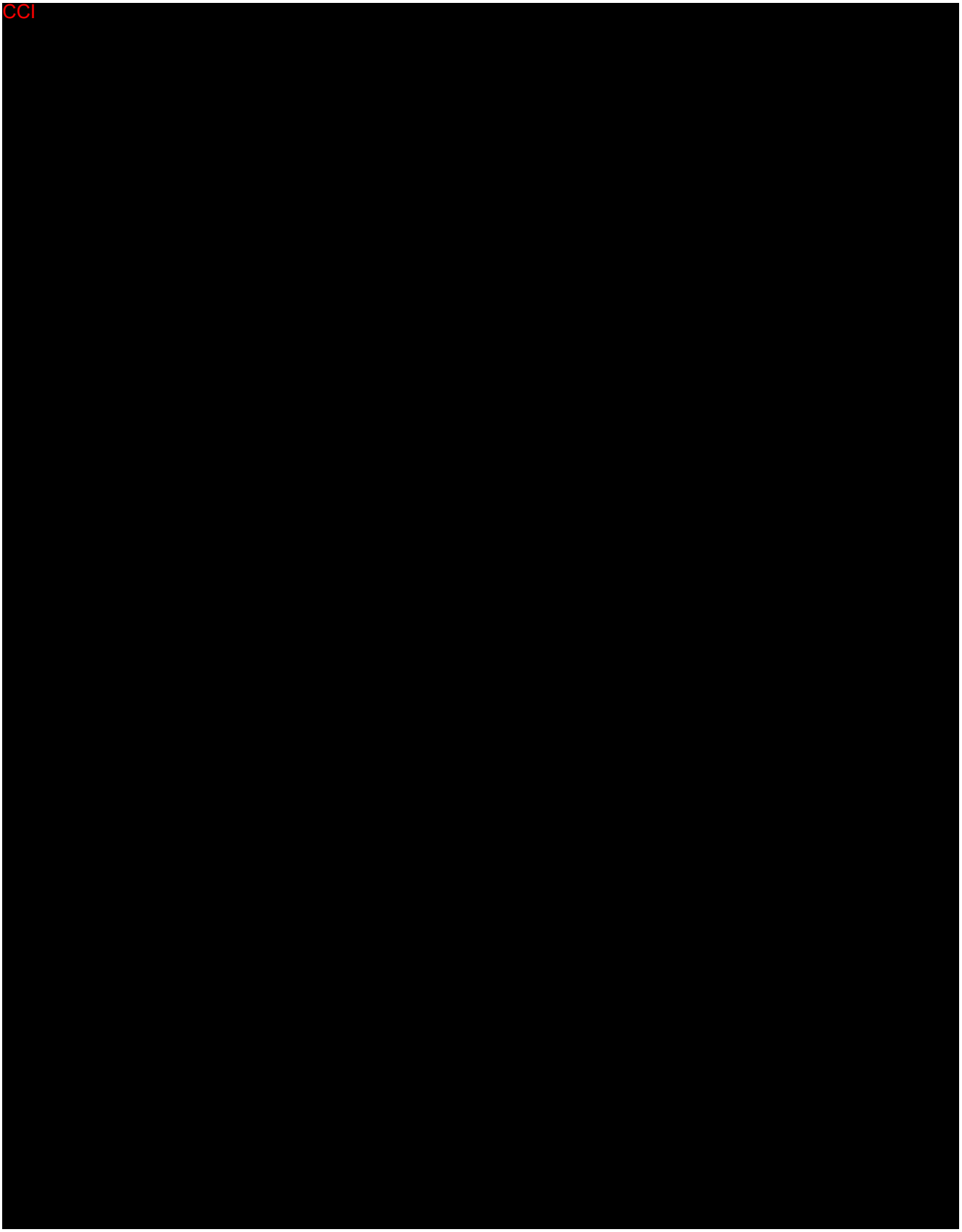

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Version: 1.0

10.2 Adverse Events

10.2.1 Summary of Adverse Events (AEs)

Table 10-5: Brief summary of all AEs, Safety population

	Group A N = xx			Group B					
				No treatment at baseline N = xx			Treatment with Restylane Volyme N = xxx		
	Subjects		Events	Subjects		Events	Subjects		Events
	n	%	n	n	%	n	n	%	n
Any AEs reported, total									
AEs related to product and/or injection procedure									
Of which were serious									
AEs unrelated to product and/or injection procedure									
of which were serious									
Subjects with no AE reported									

% = n/N*100

Note: Treatment with Restylane Volyme columns include data from subjects in the Restylane Volyme group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

10.2.2 Related AEs

Table 10-6: Related AEs occurring throughout the whole study period by MedDRA System Organ Class, Preferred Term, and maximum intensity, Safety population, Group B

Primary System Organ Class *Preferred Term*	Maximum intensity	No treatment at baseline N = xx		Treatment with Restylane Volyme N = xxx		Total N = xx	
		Subjects	Events	Subjects	Events	Subjects	Events
		n (%)	n	n (%)	n	n (%)	n
Any related AE	Total						
	Mild						
	Moderate						
	Severe						
SOC1	Total						
	Mild						
	Moderate						
	Severe						
PT11	Total						
	Mild						
	Moderate						
	Severe						
PT12	Total						
	Mild						
	Moderate						
	Severe						
SOC2	Total						
	Mild						
	Moderate						
	Severe						
PT21	Total						
	Mild						
	Moderate						
	Severe						

% = n/N*100

Note: Treatment with Restylane Volyme columns include data from subjects in the Restylane Volyme group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6.

Table 10-7: Duration (number of days days) of related AEs occurred throughout the whole study period by MedDRA System Organ Class and Preferred Term, Safety population, Group B

Primary System Organ Class *Preferred Term*	No treatment at baseline N = xx					Treatment with Restylane Volyme N = xxx					Total N = xxx				
	N (events)	Duration missing	Mean (SD)	Median	Min-Max	N (events)	Duration missing	Mean (SD)	Median	Min-Max	N (events)	Duration missing	Mean (SD)	Median	Min-Max
SOC1															
PT11															
PT12															
Total															

Note: Treatment with Restylane Volyme columns include data from subjects in the Restylane Volyme group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6.

Table 10-8: Time to onset (days) since most recent treatment of related AEs by MedDRA System Organ Class and Preferred Term, Safety population, Group B

Primary System Organ Class *Preferred Term*	No treatment at baseline N = xx				Treatment with Restylane Volyme N = xxx				Total N = xxx			
	N (events)	Mean (SD)	Median	Min-Max	N (events)	Mean (SD)	Median	Min-Max	N (events)	Mean (SD)	Median	Min-Max
SOC1												
PT11												
PT12												
Total												

Note: Treatment with Restylane Volyme columns include data from subjects in the Restylane Volyme group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6.

Table 10-9: Action taken due to related AEs by MedDRA System Organ Class and Preferred Term, Safety population

System Organ Class Preferred Term	Action Taken											
	No treatment at baseline N = xx				Treatment with Restylane Volyme N = xxx				Total N = xxx			
	None	Medication treatment	Non-pharmacological treatment or other procedures/tests	Subject withdrawn	None	Medication treatment	Non-pharmacological treatment or other procedures/tests	Subject withdrawn	None	Medication treatment	Non-pharmacological treatment or other procedures/tests	Subject withdrawn
SOC 1												
PT11												
PT12												
SOC 2												
PT21												
PT22												
All												

Note: Treatment with Restylane Volyme columns include data from subjects in the Restylane Volyme group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6.

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

10.2.3 Unrelated AEs

Table 10-10: Unrelated AEs by MedDRA System Organ Class, Preferred Term, and maximum intensity, Safety population

Primary System Organ Class *Preferred Term*	Maximum intensity	No treatment at baseline N = xx		Treatment with Restylane Volyme N = xxx		Total N = xx	
		Subjects	Events	Subjects	Events	Subjects	Events
		n (%)	n	n (%)	n	n (%)	n
Any related AE	Total						
	Mild						
	Moderate						
	Severe						
SOC1	Total						
	Mild						
	Moderate						
	Severe						
PT11	Total						
	Mild						
	Moderate						
	Severe						
PT12	Total						
	Mild						
	Moderate						
	Severe						
SOC2	Total						
	Mild						
	Moderate						
	Severe						
PT21	Total						
	Mild						
	Moderate						
	Severe						

% = n/N*100

Note: Treatment with Restylane Volyme columns include data from subjects in the Restylane Volyme group after their initial treatment at baseline, as well as data from subjects in the Control group after their initial treatment at Month 6.

GALDERMA	Title **SAP, 43CH1626, Restylane Volyme Midface**	Doc id **MA-35135**

Effective date: 2017-11-03 11:43

Effective

Version: 1.0

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Justification	Approved by Technical Expert
2017-11-02 08:19	PPD
Justification	Approved by Technical Expert
2017-11-02 14:06	PPD
Justification	Approved by Technical Expert
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Justification	Approved by Technical Expert
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