



Statistical Analysis Plan

‘Clinical analyses for Protexo’

Pr. Mondher TOUMI

MD, PhD, Msc

☎ +33 (0)4 72 43 16 54

mondher.toumi@univ-lyon1.fr

Pr. Michel LAMURE

MD, PhD, Msc

☎ + (33) 4 72 43 16 54

lamure@univ-lyon1.fr

Date: 19/04/2010

Update 1 : 06/08/2010

Update 2 : 06/10/2010

Université Claude Bernard Lyon 1 - Bât. Nautibus

Laboratoire ERIC - Equipe MA2D

43, boulevard du 11 Novembre 1918

69622 Villeurbanne Cedex - France

Preamble

First update contains rational for the choice of LOCF and adjustment on countries. No change was made on statistic analyses planned between this update and the original version.

Second update contains a clarification for the subgroup analysis. No change was made on statistic analyses planned between this update and the original version.

1. CONTENTS

1. Contents	3
2. Introduction.....	5
2.1 Trial design	5
2.2 Visits	5
3. Analysis populations and data definitions.....	6
3.1 GINA classification.....	6
3.2 Analysis populations.....	6
4. Statistical conventions	9
5. Baseline description.....	10
5.1 Demographical characteristics	10
5.2 Medical History.....	10
5.3 Physical Examination	11
5.4 Clinical assessment	11
6. Efficacy analysis	11
6.1 Responder rate	11
6.1.1 Primary endpoint.....	11
6.1.2 Sensitivity analysis on primary endpoint.....	12
6.2 AQLQ score.....	12
6.2.1 AQLQ score change	12
6.3 AQLQ subscores	12
6.4 AQLQ sleep items.....	13
6.4.1 AQLQ sleep items scores.....	13
6.4.2 AQLQ sleep items responders	14

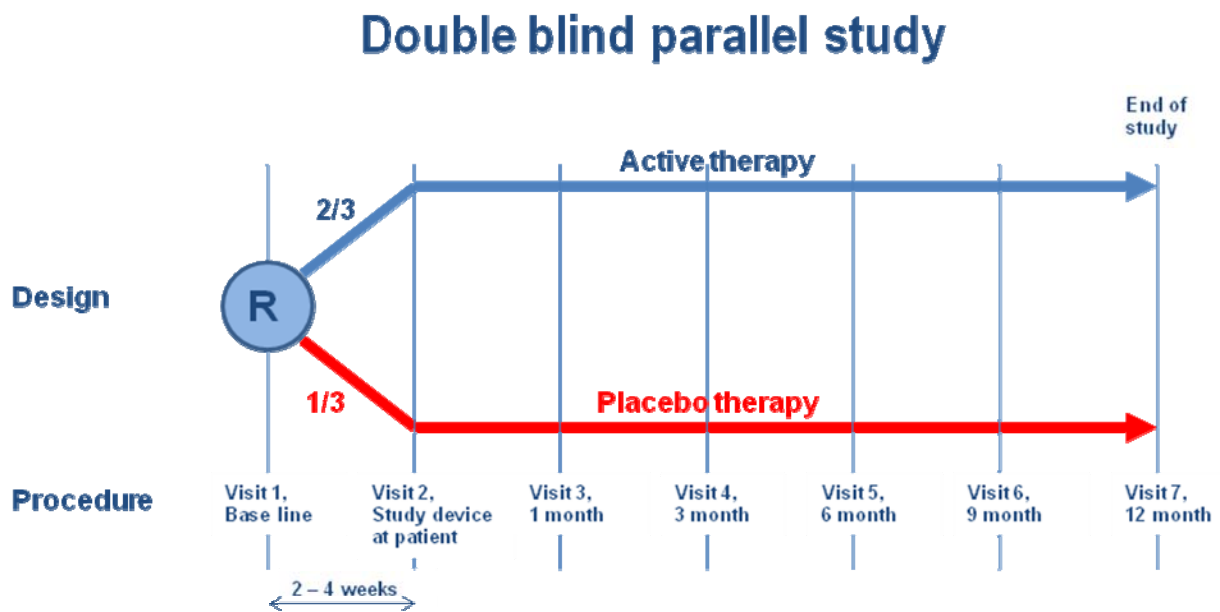
6.5	ACT scale.....	14
6.5.1	ACT scale scores.....	14
6.5.2	ACT scale responders.....	14
6.5.3	ACT classification.....	15
6.6	Specific allergens.....	15
6.6.1	Total IgE.....	15
6.6.2	Specific IgE.....	16
6.7	FENO and Spirometry.....	16
6.7.1	FENO and Spirometry.....	16
6.7.2	FENO classification.....	16
6.8	Rhinitis scale.....	17
6.8.1	Rhinitis scale score.....	17
6.8.2	Rhinitis scale items.....	17
6.9	Exacerbations.....	18
6.10	Eosinophils.....	18
7.	Medication.....	20
8.	Rationale for adjustment on country rather than on centre.....	20
9.	Appendix.....	21
9.1	Appendix 1.....	21

2. INTRODUCTION

2.1 Trial design

This was a multiple independent, double blind, randomized 52 weeks parallel trial comparing active and placebo treatment with Airsonett Airshower (AA). For ethical reasons the randomization was 2 to 1 for active and placebo treatment, respectively. At visit 1, patients were evaluated against the inclusion and exclusion criteria, randomized and all baseline measures taken. The Airsonett Airshower was installed in the patient’s home within 4 weeks after inclusion, during this time the patient got familiar with the use of the patient asthma diary and adhered to the requirements of the study participation. The first 3 months an unchanged maintenance medication was kept and month 4 - 12 medication was based on control (GINA 2006).

Figure 1. Study design



2.2 Visits

In this statistical analysis plan, we will assume that:

- Visit 1 = baseline
- Visit 2 = 2 weeks visit
- Visit 3 = 6 weeks visit
- Visit 4 = 14 weeks visit
- Visit 5 = 28 weeks visit

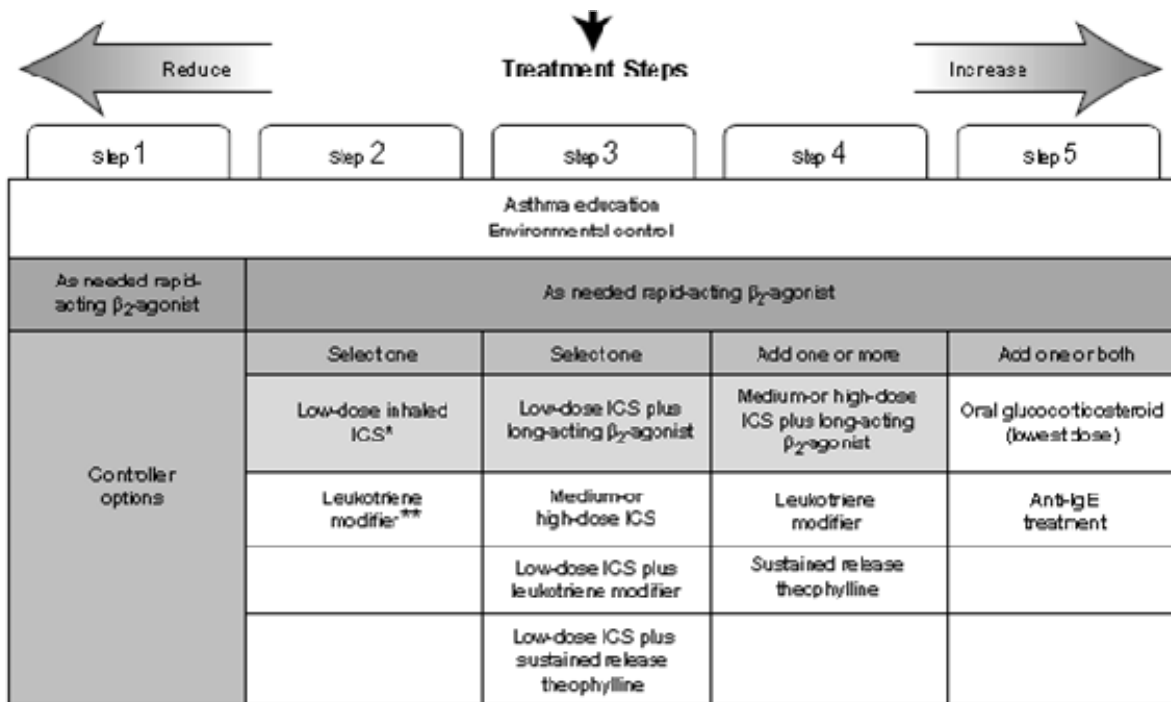
Visit 6 = 41 weeks visit

Visit 7 = 54 weeks visit

3. ANALYSIS POPULATIONS AND DATA DEFINITIONS

3.1 GINA¹ classification

GINA classification is based on treatment intensity, and will be used in adjustment as a proxy of treatment in analysis.



^{*} ICS=inhaled glucocorticosteroids
^{**}-Receptor antagonist or synthesis inhibitor

3.2 Analysis populations

The **Full Analysis Set (FAS)** contains all patients.

The **Intention-To-Treat (ITT) analysis set** consists of all randomized patients who have had at least one treatment day with the Airshower. 9 subsets are derived from ITT set:

¹ Pocket guide for asthma management and prevention, A Pocket Guide for Physicians and Nurses Revised 2006

- × **ITT**: all ITT population
- × **ITT-P12**: Pediatric ITT population (<12 years)
- × **ITT-A12**: Adults ITT population (≥ 12 years)
- × **ITT-P18**: Pediatric ITT population (<18 years)
- × **ITT-A18**: Adults ITT population (≥ 18 years)
- × **ITT-R**: ITT patients with rhinitis at baseline
- × **ITT-STB**: ITT stable² patients
- × **ITT-M-GINA**: ITT patients in step 3 or step 4 according to GINA classification
- × **ITT-S-GINA**: ITT patients in step 4 according to GINA classification

Patients, who drop out after randomization and before the first use of the Airshower, will be excluded from the intention-to-treat analysis.

The **Per Protocol-52 (PP52) analysis set** consists of all randomized patients who have used the Airshower minimum 80% of the 52 week trial period, as recorded on a data chip in the machine and 80% of the last 3 weeks prior to visit month 3 and 12. In the same way that for ITT, 9 subsets are derived from PP set:

- × **PP52**: all PP52 population
- × **PP52-P12**: Pediatric PP52 population (<12 years)
- × **PP52-A12**: Adults PP52 population (≥ 12 years)
- × **PP52-P18**: Pediatric PP52 population (<18 years)
- × **PP52-A18**: Adults PP52 population (≥ 18 years)
- × **PP52-R**: PP52 patients with rhinitis at baseline
- × **PP52-STB**: PP52 stable patients
- × **PP52-M-GINA**: PP52 patients in step 3 or step 4 according to GINA classification
- × **PP52-S-GINA**: PP52 patients in step 4 according to GINA classification

The **Per Protocol-12 (PP12) analysis set** consists of all randomized patients who have used the Airshower minimum 80% of the 12 week trial period, as recorded on a data chip in the machine

² A patient is considered stable if absolute difference between AQLQ score at V2 and AQLQ score at V1 is <0.5.

and 80% of the last 3 weeks prior to visit month 3 and 12. In the same way that for ITT, 9 subsets are derived from PP set:

- × **PP12:** all PP12 population
- × **PP12-P12:** Pediatric PP12 population (<12 years)
- × **PP12-A12:** Adults PP12 population (≥ 12 years)
- × **PP12-P18:** Pediatric PP12 population (<18 years)
- × **PP12-A18:** Adults PP12 population (≥ 18 years)
- × **PP12-R:** PP12 patients with rhinitis at baseline
- × **PP12-STB:** PP12 stable patients
- × **PP12-M-GINA:** PP12 patients in step 3 or step 4 according to GINA classification
- × **PP12-S-GINA:** PP12 patients in step 4 according to GINA classification

All analyses will be run on each of the 27 populations.

Further, analyses will be run on asthma severity defined as the intensity of treatment required to control the patient's asthma. Sub-group of treatment intensity (GINA) in combination with the activity of the underlying disease (ACT) according to the definition of asthma severity in ATS/ERS statement^{3,4} will be created.

The FAS contains 312 patients, the ITT set contains 282 patients, the PP52 set contains 205 patients and the PP12 set contains 230 patients.

	Nb of patients (TLA + placebo)		Nb of patients (TLA + placebo)		Nb of patients (TLA + placebo)
ITT	282 (189 + 93)	PP12	230 (157 + 73)	PP52	205 (139 + 66)
ITT-P12	68 (46 + 22)	PP12-P12	61 (41 + 20)	PP52-P12	58 (39 + 19)
ITT-A12	214 (143 + 71)	PP12-A12	169 (116 + 53)	PP52-A12	147 (100 + 47)
ITT-P18	152 (104 + 48)	PP12-P18	129 (90 + 39)	PP52-P18	119 (80 + 39)
ITT-A18	130 (85 + 45)	PP12-A18	101 (67 + 34)	PP52-A18	86 (59 + 27)
ITT-R	268 (180 + 88)	PP12-R	220 (151 + 69)	PP52-R	197 (134 + 63)
ITT-STB	129 (87 + 42)	PP12-STB	105 (74 + 31)	PP52-STB	96 (65 + 31)
ITT-M-GINA	228 (153 + 75)	PP12-M-GINA	187 (127 + 60)	PP52-M-GINA	166 (113 + 53)
ITT-S-GINA	129 (82 + 47)	PP12-S-GINA	111 (70 + 41)	PP52-S-GINA	96 (58 + 38)

ITT- UnC*	183 (125 + 58)	PP12- ACT<18	149 (103 + 46)	PP52- ACT<18	129 (89 + 40)
ITT-M- GINA- UnC*	153 (103 + 50)	PP12-M- GINA- UnC*	126 (85 + 41)	PP52-M- GINA- UnC*	109 (74 + 35)
ITT-S- GINA- UnC*	87 (57 + 30)	PP12-S- GINA- UnC*	74 (47 + 27)	PP52-S- GINA- UnC*	62 (37 + 25)

*UnC: Uncontrolled asthma according to section 5.4 clinical assessments

³ Reddel HK et al, An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations. American Journal of Respiratory and Critical Care Medicine Vol 180. pp. 59-99, (2009)

⁴ Taylor DR et al. A new perspective on concepts of asthma severity and control. Eur Respir J 2008,;32: 545-554.

4. STATISTICAL CONVENTIONS

ITT populations will be analyzed using the LOCF (Last Observation Carried Forward) technique. PP12 and PP52 populations will be described using OC (Observed Case) technique.

All continuous variables will be described using number of valid values, number of missing values, mean, standard deviation, 95%CI, min-max, median, and Q1-Q3.

All categorical variables will be described using number of valid values, number of missing values and percentages.

When provided, graphs will show the evolution of the considered outcome, from V1 to V7. SD of means will be provided on the graph.

Rationale for using LOCF method

How to integrate missing data, and in particular drop outs in an analysis, has always been a significant issue.

The Last Observation Carried Forward (LOCF) imputation method can be used when data are longitudinal (i.e. repeated measures have been taken per subject by time point). The last observed non-missing value is used to fill in missing values at a later point in the study. Therefore one makes the assumption that the response remains constant at the last observed value. (LOCF Method and Application in Clinical Data Analysis Huijuan Xu, Biogenidec, Inc., 2009]

The FDA has traditionally viewed LOCF as the preferred method of analysis, considering it likely (but not certain) to be conservative and clearly better than using observed cases (OC).

There is no perfect method to handle missing data. Nevertheless it is important to define it in the SAP, a priori. It is also important to choose one accepted by authorities (FDA and EMEA). Here are other considerations:

One must be sure that the method used does not penalize the product which shows less drop outs. If ever the product is not so efficient, or not well tolerated, there might be lots of drops outs in the active group.

There are 2 situations in clinical trials:

- If the disease is progressive, and if the treatment of interest aims at slowing the progression of the disease, OC (Observed Case) should be chosen. With LOCF, the treatment with the more drops out would be favored.
- If the treatment aims at improving any outcome, it is the contrary. LOCF should be chosen.

The alternative to LOCF is MMRM (which integrates use of all points, and then gives more power). But LOCF is the method the most frequently used in all clinical trials that are done for registering, and completely accepted by authorities.

Due to the relatively high patient dropout rate of this study, analysis will be conducted on two different datasets: one on ITT with an imputation of missing values according to the LOCF methodology and the other on PP in the absence of data imputation (that is, using OC method). It is common in clinical trials to analyze ITT population using the LOCF method, and to make a sensibility analysis working on PP population, using OC method.

5. BASELINE DESCRIPTION

5.1 Demographical characteristics

Sex, age, ethnic origin, weight, height, BMI, country and site at baseline will be described.

5.2 Medical History

Types of allergen at baseline will be described using the following variables:

- Dust mites
- Cat
- Other allergens
- No. of Perenn
- Pollen
- Perenn and Pollen

- Total number of allergens (as continuous and categorical variable)
- 1, 2 or more than 3 allergens

Presence of any significant medical history at baseline will be described.

5.3 Physical Examination

Presence of nasal polyps, septum deviation and rhinitis at baseline will be described.

5.4 Clinical assessment

ACT groups at baseline will be described. It was defined as follows:

- 0-17: Uncontrolled
- 18-19: Partially controlled
- ≥ 20 : Controlled

FENO groups at baseline will be described. It was defined as follows:

- 5-25: Normal
- 26-45: Increased risk
- > 45 : High risk

GINA groups at baseline will be described. Please refer to 3.1 for definition.

6. EFFICACY ANALYSIS

6.1 Responder rate

6.1.1 Primary endpoint

A short version of the AQLQ (Asthma Quality of Life Questionnaire), the mini-AQLQ, has been developed and fully validated. This instrument has 15 items and each item has the same 7 severity levels as the original (1 = severe impairment to 7 = no impairment). It consists of 5 items on symptoms, 4 items on activity limitations, 3 items on emotional function, and 3 items concerning environmental stimuli. For children under the age of 12 the P-AQLQ was used.

The primary endpoint, **responder rate**, is defined as follows: a patient will be considered as a responder if the increase at V7 compared to baseline in mean total AQLQ (mini-AQLQ or P-AQLQ) score is at least 0.5 units. Otherwise the patients are categorized as non responder.

The population considered for the primary endpoint will be the ITT population.

Responder rate at V7 will be compared between the treatment groups, using 3 tests:

- Chi2 test
- Adjusted test: logistic regression, adjusting on treatment, baseline AQLQ score, time since disease onset, GINA classification at baseline, and stratified on country
- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs (same adjustment will be used)

Note: some patient has been using both mini-AQLQ and P-AQLQ, the list describing if it is AQLQ or PAQLQ that should be used is in appendix 9.1.

Responder rates will also be described at each visit.

6.1.2 Sensitivity analysis on primary endpoint

Responder rate at V4 and sustained responders rate (responders at V4, who remain responders at V5, V6 and V7) will also be described and compared in the same way as primary endpoint as a sensitivity analysis.

6.2 AQLQ score

6.2.1 AQLQ score change

AQLQ (mini-AQLQ and P-AQLQ) scores will be described at each visit. Evolution graphs will be provided.

Change from baseline in AQLQ (mini-AQLQ and P-AQLQ) score between will be described in the same way. Comparison between treatment groups will be provided using 3 tests:

- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline AQLQ score, time since disease onset, GINA classification at baseline, and country
- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs (same adjustment will be used)

AQLQ change V4-V1 will also be analyzed.

6.3 AQLQ subscores

Mini-AQLQ can be assessed using 4 subscales scores:

- Symptoms subscore: mean of items 1, 4, 6, 8 and 10
- Emotions subscore: mean of items 3, 5 and 9

- Activities subscore: mean of items 12, 13, 14 and 15
- Environment subscore: mean of items 2, 7 and 11

In the same way, P-AQLQ can be assessed using 3 subscales scores:

- Symptoms subscore: mean of items 4, 6, 8, 10, 12, 14, 16, 18, 20 and 23
- Emotions subscore: mean of items 5, 7, 9, 11, 13, 15, 17 and 21
- Activities subscore: mean of items 1, 2, 3, 19 and 22

These subscores will be described at each visit. Evolution graphs will be provided.

Change from baseline in subscores will be described in the same way. Comparison between treatment groups will be provided using 3 tests:

- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline subscore, time since disease onset, GINA classification at baseline, and country
- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs (same adjustment will be used)

6.4 AQLQ sleep items

6.4.1 AQLQ sleep items scores

Items concerning quality of sleep of the patient will be analyzed.

One item is referring to the quality of sleep in the mini-AQLQ: item 8 “Have difficulty getting a good night’s sleep as a result of asthma? ».

Two items are referring to the quality of sleep in the P-AQLQ: item 16 “Wake-up during the night because of asthma? », and item 20 “Have trouble sleeping at night because of your asthma? »

These items will be described at each visit. Evolution graphs will be provided.

Change from baseline in scores will be described in the same way. Comparison between treatment groups will be provided using 3 tests:

- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline score, time since disease onset, GINA classification at baseline, and country
- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs. Same adjustment will be used.

6.4.2 AQLQ sleep items responders

A responder patient is defined as follows: a patient will be considered as a responder if the increase at V7 compared to baseline in AQLQ sleep item score is at least 0.5 units. Otherwise the patients are categorized as non responder.

Responder rate at V7 will be compared between the treatment groups, using 3 tests:

- Chi2 test
- Adjusted test: logistic regression, adjusting on treatment, baseline ACT score, time since disease onset, GINA classification at baseline and stratified on country
- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs. Same adjustment will be used.

Responder rates will also be described at each visit.

6.5 ACT scale

6.5.1 ACT scale scores

ACT scores will be described at each visit. Evolution graphs will be provided.

Change from baseline in ACT score will be described in the same way. Comparison between treatment groups will be provided using 3 tests:

- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline ACT score, time since disease onset, GINA classification at baseline, and country
- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs. Same adjustment will be used.

ACT change V4-V1 will also be analyzed.

6.5.2 ACT scale responders

A responder patient is defined as follows: a patient will be considered as a responder if the increase at V7 compared to baseline in mean total ACT score is at least 3 units. Otherwise the patients are categorized as non responder.

Responder rate at V7 will be compared between the treatment groups, using 3 tests:

- Chi2 test
- Adjusted test: logistic regression, adjusting on treatment, baseline ACT score, time since disease onset, GINA classification at baseline and stratified on country

- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs. Same adjustment will be used.

Responder rates will also be described at each visit.

Responder rate at V4 will also be compared in the same way.

6.5.3 ACT classification

ACT scores will be categorized into 3 classes for each visit, defined as follows:

- 0-17: Uncontrolled
- 18-19: Partially controlled
- ≥ 20 : Controlled

ACT classes will be provided at each visit (except V3 as assessment was not done).

Change in classes will be described at each visit, using 3 classes:

- worse
- no change
- improvement

Change in classes at V7 will be compared between the treatment groups using 2 tests:

- Chi2 test
- Adjusted test: logistic regression, adjusting on treatment, baseline ACT score, time since disease onset, GINA classification at baseline and country

ACT change group V4-V1 will also be analyzed.

6.6 Specific allergens

Specific groups will be analyzed for this outcome: patients cat allergic at baseline, and patients dust mites allergic at baseline.

6.6.1 Total IgE

Total IgE will be described at V1 and V7. Evolution graphs will be provided.

Relative change³ from baseline in IgE will be described in the same way. Comparison between treatment groups will be provided using 2 tests:

- Ttest

³ Relative change = $(V7-V1)/V1$

- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline value, time since disease onset, GINA classification at baseline and country

6.6.2 Specific IgE

Specific IgE (d1, d2, e1, e5, max(d1,d2), and max(d1,d2)+e1+e5) will be described as specific IgE at V1 and V7. Evolution graphs will be provided.

Relative change from baseline in specific IgE will be described in the same way. Comparison between treatment groups will be provided using 2 tests:

- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline value, time since disease onset, GINA classification at baseline and country

Specific IgE will also be analyzed as percentage of total IgE in the same way.

6.7 FENO and Spirometry

6.7.1 FENO and Spirometry

FENO and all spirometry variables (FEV1, PEF and FEF50, as percentages of reference) will be described at each visit. Evolution graphs will be provided.

Change from baseline in FENO and all spirometry variables (FEV1, PEF and FEF50) score will be described in the same way. Comparison between treatment groups will be provided using 3 tests:

- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline score, time since disease onset, sever GINA classification at baseline, and country
- Repeated observations model will be also used to account for heterogeneity between individuals and correct for potential bias associated with drop-outs. Same adjustment will be used.

FENO and all spirometry variables change V4-V1 will also be analyzed.

6.7.2 FENO classification

FENO quantitative variable will be categorized into 3 classes for each visit, defined as follows:

- 5-25: Normal
- 26-45: Increased risk
- > 45: High risk

FENO classes will be provided at each visit.

Change in classes will be described at each visit, using 3 classes:

- worse
- no change
- improvement

Change in classes at V7 will be compared between the treatment groups using 2 tests:

- Chi2 test
- Adjusted test: logistic regression, adjusting on treatment, baseline ACT score, time since disease onset, GINA classification at baseline and country

6.8 Rhinitis scale

6.8.1 Rhinitis scale score

Rhinitis scale score will be described at each visit. Evolution graphs will be provided.

Change from baseline in rhinitis scale score will be described in the same way. Comparison between treatment groups will be provided using 2 tests:

- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline rhinitis scale score, time since disease onset, GINA classification at baseline and country

6.8.2 Rhinitis scale items

Rhinitis is composed of 5 questions:

Question 1: Has the patient had rhinitis problem at any time yes/no.

Comparison between groups of amount of problems at V1 and V7 will be provided using 3 classes:

- worse
- no change
- improvement

Question 2: Has the patient had a rhinitis problem during the past year yes/no

Comparison between groups of amount of problems at V1 and V7 will be provided using 3 classes:

- worse

- no change
- improvement

Question 3: Has the patient had any problems with running/itching eyes in connection with rhinitis during the past year yes/no.

Comparison between groups of amount of problems at V1 and V7 will be provided using 3 classes:

- worse
- no change
- improvement

Question 4: Amount of months during the last year the patient has had with Rhinitis problem during the last year score 0-12.

Comparison of change in amount of months will be provided, using a ttest.

Question 5: During the last year, how much has rhinitis problems affected the patients daily activity: 0=not at all, 1=a bit (mild), 2=moderate, 3=a lot (severe).

Comparison between groups of amount of problems at V1 and V7 will be provided using 3 classes:

- worse
- no change
- improvement

6.9 Exacerbations

Analysis of systemic corticosteroids, and HCRU used will be used as a proxy for exacerbations.

Use of systemic corticocterooids, hospital day, emergency department visit and unscheduled visits at least once during the whole study will be described and analyzed. Comparison between treatment groups will be provided using 2 tests:

- Ttest
- Adjusted test: logistic regression, adjusting on treatment, time since disease onset, GINA classification at baseline and stratified on country

6.10 Eosinophils

Eosinophils will be described at V1 and V7.

Change from baseline in eosinophils will be described in the same way. Comparison between treatment groups will be provided using 2 tests:



- Ttest
- Adjusted test: analysis of covariance regression (ANCOVA), adjusting on treatment, baseline eosinophils, time since disease onset, GINA classification at baseline and country

7. MEDICATION

Assuming dates of start and stop of treatment are available and usable, medication will be categorized using 5 classes:

- ICS (inhaled corticosteroids)
- OCS (oral corticosteroids)
- LABA (long acting β -agonist)
- SABA (short acting β -agonist)
- LTRA (leukotriene receptor antagonist)
- Other

For each class, use of medication will be described using the following variables:

- Use of medication at each visit
- If use of medication, daily dose at each visit
- If use of medication, number of days under medication class between previous visit and current visit, starting from V2
- If use of medication at the previous visit, stopping of medication at the current visit
- Change in the GINA treatment steps V7-V1

8. RATIONALE FOR ADJUSTMENT ON COUNTRY RATHER THAN ON CENTRE

Using center for adjustment is the most appropriate method in multicentric studies. However the low number of patients by centers and the large number of center and disparity across center suggested that center adjustment might not be feasible. This is why the original version of the SAP proposed to adjust on countries rather than centers.

This was confirmed during the analysis. Further analysis showed that there were too many centers ($n=20$) and not enough patients per centers for sub-analysis (please refer to 3.2). Adjusting on centers would have caused a significant loss of power. Moreover, some models did not converge using this adjustment and a pooling of centers was necessary. This was linked to the large number of centers, and the disparity of number of patients per center. Most of sub-analysis would have not been possible (those where only a small selection of population was analyzed).

That is why we anticipated to chose country as alternative adjustment. This was shown in the analysis to be relevant.

9. APPENDIX

9.1 Appendix 1

Site	Pat No	Initials	PAQLQ=P	MAQLQ=A
1	1	WHG	x	
1	3	ABL		x
1	4	VMP	x	
1	5	PAK	x	
1	6	SLS		x
1	7	AVA	x	
1	8	ETS		x
1	9	HIH	x	
1	39	NAT		x
1	40	TKH		x
1	41	KEL		x
1	42	AWV		x
1	43	SNM	x	
1	44	CSE		x
1	145	NLA	x	
1	146	AFW		x
1	149	RMG		x
1	150	FRL		x
1	152	JBj		x
1	153	MGW		x
1	163	SCB	x	
1	164	FMM		x
1	165	SMW		x
1	166	MMN	x	

Site	Pat No	Initials	PAQLQ=P	MAQLQ=A
1	168	ETA	x	
1	169	IJW	x	
1	170	AAV		x
1	171	CEL		x
1	316	JCP		x
1	320	SHK		x
1	321	OG		x
1	322	AHT		x
1	323	GLF		x
1	324	AGA		x
1	370	TVM	x	
1	371	KLN		x
1	372	KAM	x	
1	373	OJW	x	
1	374	ZIZ		x
14	46	ROS		x
14	47	SAJ	x	
14	49	KLC		x
14	51	JOJ		x
14	53	SRO	x	
14	103	LOU		x
14	106	ROC		x
14	108	RCS		x
14	181	HAS	x	