STATISTICAL ANALYSIS PLAN

Non-Interventional Study (NIS) Protocol	
NIS Name/Code	ESMAA/
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Date	30 June 2016

ESMAA

Evaluation of Asthma Management in Middle EAst North Africa Adult population

Descriptive study on the management of asthma in asthmatic Middle East Africa adult population

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1. SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN APPROVAL
Version 3.0, 30 June 2016

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1. SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN APPROVAL
Version 3.0, 30 June 2016

Version history

Version	Date	Main changes/Justification
V1.0	2 March 2016	Initial version
V2.0	29 April 2016	Modifiee following Data Review Meeting on April 27th 2016
V3.0	30 June 2016	Final version before DB lock and after answers from Astra Zeneca

	Name	Signature	Date
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3. PROTOCOL SYNOPSIS

ESMAA

Evaluation of Asthma Management in Middle EAst North Africa Adult population

Descriptive study on the management of asthma in asthmatic Middle East Africa adult population

National Co-ordinating Investigator of the Non-Interventional Study

According to the local regulation, each country could have a local national coordinator.

Steering Committee of the Non-Interventional Study

In each participating country, AstraZeneca team or representative could constitute a local steering committee

Study Site(s), number of subjects and countries planned

- Patients' / sites number :

The calculation of the minimum sample size is based on the principal objective of the study.

The frequency of patients who have an optimal asthma control according to the GINA 2012 classification is not well known in each country, even if some pilot studies were performed

Regarding each country data, based on asthma control rate, the sample size will be calculated for each country based on accuracy degree between 2% and 5% and a type I risk $\alpha = 5\%$.

The percentage of unemployable data and non-response to patient's auto-questionnaire is estimated at 15%; therefore the estimate of the minimal sample size of patients should consider this parameter for each country.

Physicians' sample:
The investigators list will be drawn from the sample of doctors who manage asthmatic patients (general practitioner and specialist (pulmonologist and/or allergologist) of the public and private sector. The physicians' number will be proportional to the sample size.
Each generalist or specialist investigator (pneumologist and/or allergologist) of the public or private sector should include an average of 10 patients meeting the eligibility criteria.

- Countries planned :

Emirates, Kuwait, Qatar, Lybia, Saudi Arabia, Egypt, Tunisia, Iraq, Turkey, Lebanon, Jordan, Iran, Algeria.

Total planned Study period	
Estimated date of first subject in	Q1 2014
Estimated date of last subject in	Q4 2014
Estimated date of last subject last visit	Q4 2014
Estimated date of data base lock	Q2 2015

Medicinal Products (type, dose, mode of administration) and concomitant medication

It is a non-interventional epidemiological study, no medical product is required.

Rationale for this Non-Interventional Study (NIS)

Asthma is a chronic disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person.

Symptoms may occur several times in a day or a week in asthma patients, and for some people become worse during physical activity or at night.

Asthma, because of its intensity of symptoms, frequency, lethality, the economic burden generated and its impact on quality of life, is a real public health problem in many countries(1).

According to estimates of the World Health Organization (WHO), there are currently 300 million asthmatic patients worldwide (2).

In Europe, where 30 million asthmatics are recorded, the prevalence rates are highly variable with extremes ranging from 2.3% in Switzerland to 18.4% in Scotland (3). In France, this rate is estimated at 6.7% of the general population (4)

According to the study carried out in France in 2006 in asthmatic patients followed-up in general medical consultation, only 21% of patients had an optimal control of their asthma and 7% an acceptable control (5).

A more recent study (AIR MAG study) conducted in the three Maghreb countries, on the general population (children and adults), finds comparable figures , the sex and age adjusted prevalence, is estimated at 3.45% in Algeria , 3.89% in Morocco, and 3.53% in Tunisia, with higher rates in extreme ages (children and adults) (6) .

The annual incidence, according to the same study, was estimated at 4.6 ‰ in Algeria and 2.8‰ in Tunisia.

Objectives of this Non-Interventional Study

Primary objective

- Assess the asthma control level in patients treated in public or private consultations according to the GINA 2012 classification.

Main secondary objectives

- Describe the general and sociodemographic patient's characteristics at enrolment: sex, age, BMI, educational level, occupation, comorbidities, smoking status, and social security coverage.

- Describe the characteristics of the disease at enrolment.

- Assess the asthma control level with the ACT questionnaire.

- Describe the therapeutics used in the basic asthma treatment during the six months prior to inclusion.

- The average frequency of reliever use in previous week.

- Identify predictive factors of asthma control, such as age, sex, BMI, smoking status, adherence to treatment, asthma history, and comorbidity.

- Evaluate the patient's quality of life.

- Assess patient's compliance to treatment.

Study design

Descriptive, epidemiological, multicentre study, conducted in a random sample of general practitioners and specialists (pulmonologists and/or allergologists) from the public and the private sector.

General practitioners and specialists in the public and the private sector are drawn from a database of physicians managing asthma patients, and will recruit patients meeting the eligibility criteria. The physicians' number will be proportional to the patients sample size.

The time needed to fill in patient questionnaires is long, that is why only the first patient of each physician consultation will be recruited in the study.

Target subject population

Patients included in the study will be mainly adult with asthma for at least one year prior to enrolment, and not associated with any chronic respiratory disease.

At each public or private site represented by a general practitioner or a medical specialist, patients meeting the eligibility criteria will be enrolled in the study.

The medical investigator before inclusion should ensure that the patient has the inclusion criteria targeted. Also ensures that the patient is voluntary to participate in this study. Once done, the patient will be enrolled in the study and the physician may then give him the questionnaires at this unique consultation.

Inclusion criteria

The subject population that will be included must fulfil all of the following criteria:

- Provision of subject informed consent
- Female and/or male aged 18 years and over

- Asthmatic diagnosed patient for at least 12 months

Non-inclusion criteria

- If participating in any interventional clinical trial, should be adapted to each country local regulation,

- Patients with any other chronic respiratory diseases; which are a group of chronic diseases affecting the airways and the other structures of the lungs, whom definition [7]:

    - Bronchiectasis
    - Chronic obstructive lung disease, including chronic obstructive pulmonary disease, bronchitis and emphysema
    - Chronic rhino sinusitis
    - Hypersensitivity pneumonitis
    - Lung cancer and neoplasms of respiratory and intrathoracic organs
    - Lung fibrosis
    - Chronic pleural diseases
    - Pneumoconiosis
    - Pulmonary eosinophilia
    - Pulmonary heart disease and diseases of pulmonary circulation including pulmonary
    - embolism, pulmonary hypertension and corpulmonale
    - Rhinitis
    - Sarcoidosis
    - Sleep apnea syndrome

- Patients consulting for asthma attack (defined as asthma symptom deterioration resulting in oral/rectal/parenteral Glasgow Coma Scale (GCS) medication or emergency room treatment or hospitalisation) within 4 weeks before enrolled
- Patients with any psychotic disorders.

- Pregnancy

- Patients who did not signed the consent form.

Study variable(s):

Primary variable

- Rate of asthma control according to GINA 2012 classification: controlled, partly controlled, and uncontrolled.

Other Variables

-Level of control during the last four weeks prior to inclusion in the ACT questionnaire (first 4 questions), and concordance with the assessment of the patient (fifth question).

- Risk associated with each factor studied in a non-optimal asthma control, as measured by the odds ratio (OR)

- The score of the quality of life using the SF-8 questionnaire (cf. Table 5)

- The score of treatment compliance with the Morisky survey (cf. Table 6).

Statistical methods:

1. Descriptive analysis of the sample

- For quantitative variables, note the number of missing data, extreme values, estimate the mean, median, standard deviation and quartiles,

- For qualitative variables, estimate the frequencies of different modalities with their confidence interval 95%.

2. Identification of predictive factors of asthma control, such as age, sex, BMI, smoking status, adherence to treatment, asthma history, comorbidity,

- Univariate analysis

Link between each factor studied and asthma control using the χ^2 test and the estimation of the OR with its confidence interval 95%,

- Multivariate analysis

- Dichotomous logistic regression model: factors included in the model are those found significant or borderline significance ($p < 0.10$) in the univariate analysis,

- Ordinal logistic regression model: the variable to be explained is the control of asthma (with its three terms), the explanatory variables are the factors found significant or borderline significance ($p < 0.10$) in the univariate analysis.

3. Quality of life analysis

- Descriptive analysis of different items involved in assessing the quality of life (SF-8 questionnaire),

- Link between quality of life and asthma control using the χ^2 test,

- Comparison of different scores of quality of life according to the three levels of asthma control using an ANOVA test.

4. Treatment compliance assessment

- Descriptive analysis of different items involved to assess treatment compliance (Morisky questionnaire),

- Correlation between compliance score assessed by the patient and the doctor’s opinion on compliance, using the Pearson correlation coefficient.

4. ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ADR	Adverse Drug Reaction
Asthma	Asthma is a chronic disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. Symptoms may occur several times in a day or week in affected individuals, and for some people become worse during physical activity or at night.
Assessment	An observation made on a variable involving a subjective judgement (assessment)
AZ	AstraZeneca
BMI	Body Mass Index
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
COPD	Chronic Obstructive Pulmonary Disease is not one single disease but an umbrella term used to describe chronic lung diseases that cause limitations in lung airflow. The more familiar terms 'chronic bronchitis' and 'emphysema' are no longer used, but are now included within the COPD diagnosis. The most common symptoms of COPD are breathlessness, or a 'need for air', excessive sputum production, and a chronic cough. However, COPD is not just simply a "smoker's cough", but an under-diagnosed, life threatening lung disease that may progressively lead to death.
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ePRO	Electronic Patient Reported Outcome
FEV	Forced Expiratory Volume
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GINA	Global Initiative for Asthma
GSP	Global Safety Physician
ICH	International Conference on Harmonisation
National Coordinator	The National Coordinator is the main line of contact to coordinate the submissions and responses of the Leading Ethics Committee and of the Ethics Committees related to the other participating sites (Non-Leading Ethics Committees).
NIS	Non-Interventional Study
NISA	Non-Interventional Study Agreement
NISP	Non-Interventional Study Protocol
NISR	Non Interventional Study Report
OR	Odds Ratio
PEF	Peak Expiratory Flow
PI	Principal Investigator responsible for the conduct of a NIS at a site

Abbreviation or special term	Explanation
PRO	Patient Reported Outcomes
SF-36	Short Form 36
SF-8	Short Form 8
Variable	A characteristic of a property of a subject that may vary eg, from time to time or between subjects
WHO	World Health Organization

5. STUDY CONDUCT

At the time of preparation of this statistical analysis plan (SAP), 7245 patients have been recruited and are almost entered in database.

6. STATISTICAL METHODOLOGY

6.1 GENERAL CONSIDERATIONS

A Non-Interventional Study is a study in which epidemiological methods including other methods that can be used to analyse human population health data.

The statistical analysis will be performed by Clinica Group, under the responsibility of the Sponsor Astra Zeneca, on the basis of the present document.

The statistical analysis will be performed using SAS® software, version 9.4 in a Windows XP operating system environment.

Following analyses will be performed for overall and according to country (Algeria, Egypt, Iraq, Iran, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, Tunisia, and UAE).

Statistical tables will also be generated for each participating country.

- For quantitative variables, descriptive statistics will include: number of missing values, number of observed values, minimum, maximum, median, quartiles, mean and standard deviation.

- For qualitative variables, descriptive statistics will include: number of missing values, number of observed values, frequencies and percentages per modality.

Except for logistic models, no statistical tests will be performed due to the descriptive nature of this analysis.

No replacement of missing values is planned, other than those noted in Section 6.2. Thus the number of patients included in the analyses may vary depending on availability of the considered parameter.

6.2 HANDLING OF MISSING AND INCOMPLETE DATA

Listings were edited for the Data Review meeting in order to make general decisions in terms of missing data, particularly for the primary endpoint assessment. Primary endpoint assessment if they are missing values was updated (section 11.1) following the Data Review meeting.

For the questionnaires (ACT, Morisky, SF-8), handling of missing data will be described in each questionnaire analysis section.

7. NUMBER OF PATIENTS

The main objective of this study is to estimate the frequency of asthma control in asthmatic patients treated and followed-up in public or private centers, according to the GINA 2012 classification.

The calculation of the minimum sample size based on the need to ensure that the frequency of asthmatic patients with an optimal asthma control according to the GINA 2012 classification can be estimated with a sufficient accuracy.

Regarding to the 2006 French survey with general practitioner (Asthma de l'adulte Item 226;College des enseignants en Pneumologie (CEP)- Referentiel pour la preparation de l'ECN, mise a jour Decembre 2010), 21% of patients have an optimal control of their asthma.

The calculation of the minimum sample size will be done with an accuracy degree varying between 2-5 %, to be adapted for each country, and each one will have a calculating sample size using its' local or regional data.

The sample size calculating will be done using the application:

$N = (1.96)^2 \, p_0 \, q_0 \, / i^2$

Where : p_0 : percentage of patients with a good control of their asthma ; q_0: 1- p_0 ; i: Accuracy degree

The percentage of unexploitable data and non-response to patient's auto-questionnaire is estimated at 10%.

The sample size for this study will be per country:

- Algeria 1000 patients
- Egypt 1000 patients
- Iran 1000 patients
- Iraq 700 patients
- Jordan 450 patients
- Kuwait 370 patients
- Lebanon 385 patients
- Qatar 200 patients
- Saudia Arabia 1000 patients
- Tunisia 600 patients
- United Arab Emirates 540 patients

The sample size should be adapted if needed regarding the local / international published data.

8. POPULATIONS

8.1 DATA SETS ANALYSED

Two populations will be defined for this study:

Enrolled Population: all patients who signed an Informed Consent Form.

Analysed Population: all patients from the enrolled population without major protocol deviations

8.2 PROTOCOL DEVIATIONS

Protocol deviations are defined as deviations liable to prevent or change the interpretation of the results of the study.

Before locking the database, the precise reasons for excluding patients from the analysed population were fully defined and documented during the Data Review Meeting (April 27th, 2016).

Protocol deviations were defined as:

- inclusion and exclusion criteria not met:
  - IC1: patient aged 18 years and over, IC2: patient asthmatic since 12 months before inclusion, IC3: informed consent form signed,
  - EC4: patient participating in any interventional clinical trial,
  - EC5: patient with any other chronic respiratory diseases except rhinitis,
  - EC6: patient with any psychotic disorders,
  - EC7: pregnancy,
  - EC8: patients consulting for asthma attack within 4 weeks before enrolled.

The Data Review committee identified all the deviations of the study prior to locking the database.

9. PATIENT DISPOSITION AND PROTOCOL DEVIATIONS

9.1 PROTOCOL DISPOSITION

The number of patients for enrolled and analysed populations will be described overall, by country.

Number of patients and sites per country (as qualitative), and number of patients per site (as quantitative) in each country will be provided.

9.2 PROTOCOL DEVIATIONS

Number of patients excluded from analysed population will be described overall and by country with the frequency of reasons of exclusion.

A listing of patients presenting at least one protocol deviation (i.e. patients excluded from analysed population) will be produced.

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

10.1 DEMOGRAPHICS

- Age (years; by class: 18-35; 35-55; above 55 years) and gender.
- Weight (kg), height (cm), BMI (kg/m^2) = weight in kg/ (height in m) ², quantitative and by class (< 18, [18 – 25], > 25 kg/m^2). Calculated BMI will be provided. BMI value entered will be used only when the BMI cannot be calculated.
- Social status:
    - Level of education: cannot read and write / primary / secondary school / university degree / higher education.
    - Professional situation: active / non-active; if non-active: unemployed / retired / sick leave
    - Medical insurance coverage: yes / no
- Associated comorbidities: allergic rhinitis / gastroesophageal reflux / related chronic disease / other, specify. The number of patients and associated percentages suffering from each disease will be presented by decreasing order; combination of diseases will be described if relevant
- Smoking status: non-smoker / former smoker / current smoker
- Regular physical exercise: yes / no

10.2 DISEASE CHARACTERISTICS

- History of disease diagnosis (in years): quantitative and by class (less than 2 years, 2-5 years and more than 5 years)
- History of disease <u>in the last six months</u>
    - Frequency of symptoms: less than once a week / more than once a week and less than once a day / on a daily basis
    - Exacerbation: mild / likely to affect activities and sleep / frequent. The number of patients and associated percentages for each possible answer will be presented; combinations of answers will be described if relevant. Each unticked response will be considered as absence of state.
    - Night-time symptoms: no more than twice per month / more than twice per month / more than once per week / frequent / short acting B2 agonist used daily / physical activity limited. The number of patients and associated percentages for each possible answer will be presented; combinations of answers will be described if relevant. Each unticked response will be considered as absence of state. “No symptom” in the eCRF will be considered as “no more than twice per month” for analysis.
    - Spirometry: PEF <60 / 60-80 / >80% of predicted value; PEF variability <20% / 20-30% / > 30%

11. EVALUATION OF PRIMARY AND SECONDARY OBJECTIVES

11.1 PRIMARY OBJECTIVE: LEVEL OF ASTHMA CURRENT CLINICAL CONTROL

Primary objective is assessment of current clinical asthma control level in patients treated in public or private consultations

Table 1: The GINA 2012 classification (questions 34 to 38 in the CRF)
A. Assessment of current clinical control (preferably over 4 weeks)

	Controlled	**Partly controlled**	**Uncontrolled**
	All items are validated	**One item at least present any week**	**≥ 3 items of partly control Present any week**
Daytime symptoms	None (≤ 2/ week)	> 2 / week	
Limitation of activities	None	Any	
Nocturnal symptoms / awakening	None	Any	
Need for reliever /rescue treatment	None (≤ 2/ week)	> 2 / week	
Lung function (PEF or FEV)	Normal	< 80% (predicted or better)	
B. Assessment of future risk (risk of exacerbations, instability, rapid decline in lung function, side-effects)			
Features that are associated with increased risk of adverse events in the future include: Poor clinical control, frequent exacerbations in past year, ever admission to critical care for asthma, low FEV, exposure to cigarette smoke, high dose medications.			

Controlled asthma: an asthma with none diurnal/ nocturnal symptoms, no activity limitation and no exacerbation, with a need of β_2 rescue less than 2 times a week, and a normal FEV/PEF.
Partly controlled asthma : one of the following items at least present any week: an asthma with diurnal symptoms higher than 2 times a week, any activity limitation and nocturnal symptoms, with a need of β_2 rescue more than 2 times a week, and a FEV/PEF < 80%.
Uncontrolled asthma: an asthma with 3 items of partly controlled asthma present any week
By definition, an exacerbation attack in any week makes that an uncontrolled asthma week.

Number of patients with current clinical controlled asthma, partly controlled asthma and uncontrolled asthma will be presented overall and according to country. Associated percentages will be calculated with their two sided 95% Confidence Interval calculated with the Wilson method.

In cases of missing data of at least one of the 5 variables, then following rules were validated during the Data Review Meeting on April 27th 2016:

- In cases of missing data on 3, 4 or 5 variables then asthma control will be considered as not assessable
- In cases of missing data on 2 variables:
    - If the 3 non-missing variables are uncontrolled asthma items (asthma with diurnal symptoms higher than 2 times a week OR any activity limitation OR nocturnal symptoms OR with a need of β2 rescue more than 2 times a week OR a FEV/PEF < 80%) then asthma control will be considered as uncontrolled

- In other cases, asthma control will be considered as not assessable

- In cases of missing data of one variable:
  - If the 3 or 4 non-missing variables are uncontrolled asthma items (asthma with diurnal symptoms higher than 2 times a week OR any activity limitation OR nocturnal symptoms OR with a need of β2 rescue more than 2 times a week OR a FEV/PEF < 80%) then asthma control will be considered as uncontrolled
  - If two of the non-missing variables are uncontrolled asthma items (asthma with diurnal symptoms higher than 2 times a week OR any activity limitation OR nocturnal symptoms OR with a need of β2 rescue more than 2 times a week OR a FEV/PEF < 80%) and two of the non-missing variables are not uncontrolled asthma items, then asthma control will be considered as not assessable
  - If one of the non-missing variables is uncontrolled asthma item (asthma with diurnal symptoms higher than 2 times a week OR any activity limitation OR nocturnal symptoms OR with a need of β2 rescue more than 2 times a week OR a FEV/PEF < 80%) and 3 of the non-missing variables are not uncontrolled asthma items then asthma control will be considered as partly controlled

Assessment of future risk will be described by the number and proportion of patients presenting each of the following parameters: poor clinical control, frequent exacerbations in the past year, admission to critical care for asthma, low FEV, exposure to cigarette smoke, high-dose medications.
Combination of parameters will be described if relevant. Each unticked response will be considered as absence of state.

11.2 SECONDARY OBJECTIVES

11.2.1 Level of asthma control according to ACT questionnaire

Asthma control test (ACT) aims to assess patient's asthma control. It is based on a simple questionnaire of 5 questions which reflect the impact of the disease on the patient's daily life.
The overall score is the sum of scores for answers to questions 1-4, the overall score may vary depending on the patient from 4 to 20. The higher the score, the better the control.

The score for question 5 is a subjective assessment of the patient for the control of the disease: not controlled at all, very little controlled, little controlled, well controlled or totally controlled.

ACT scores will be automatically calculated by specific software Qualimetric Health Outcome Scoring Software version 4.5.
Handling of missing data will be automatically performed by the software before calculating scores following questionnaire scoring procedures.

Scores for each question will be described (qualitative) as well as overall score (quantitative).
Overall score will be described:

- according to patient's assessment in question 5
- according to investigator assessment of current clinical asthma control using GINA 2012 (not controlled, partly controlled, controlled)

If appropriate, ACT scores will be compared between current clinical asthma control levels using an ANOVA test.

11.2.2 Quality of life assessment according to SF-8 questionnaire

The assessment of quality of life is done using the SF-8 questionnaire.
The SF-8 consists of eight questions concerning the past four weeks before the interrogation divided into eight items: physical activity, life and relationships with others, physical pain, perceived health, vitality, limitations due to mental status, and limitations due to physical and mental health. Results are expressed as scores which range from 0 to 100 (100 indicates the highest level of health). These eight dimensions which allow to calculate two quality of life summarized scores: physical composite score (PCS) and mental composite score (MCS).

SF-8 scores (8 items + 2 main composite scores) will be automatically calculated by specific software Qualimetric Health Outcome Scoring Software version 4.5.
Handling of missing data will be automatically performed by the software before calculating scores following questionnaire scoring procedures.

Scores for each question will be described (qualitative) as well as overall score (quantitative).
Overall score will be described according to investigator assessment of current clinical asthma control using GINA 2012 (not controlled, partly controlled, controlled).
If appropriate, quality of life scores will be compared between current clinical asthma control levels using an ANOVA test.

11.2.3 Asthma treatment compliance assessment according to Morisky questionnaire

Morisky adherence questionnaire, simple, fast and directly applicable in consultation has four questions, of which the marking-scheme is 0 for "Yes" and 1 for "No". The points for each question are summed to obtain a score between 0 and 4. Patients with a score of 4 will be considered as having good compliance.

Morisky questionnaire scores will be described as qualitative parameters. The proportion of good compliance will be described overall and according to investigator assessment of current clinical asthma control using GINA 2012.
Compliance will be compared according to asthma control levels.
Because compliance score assessed by the doctor is not recorded in the CRF, correlation between the compliance score assessed by the patient and the doctor's opinion on this compliance will not be analysed as planned in the protocol.

11.2.4 Therapeutics used in basic asthma treatment in the past 6 months

Therapeutics used in basic asthma treatment during the six months prior to inclusion will be described overall and by country:

- Number and % of patients having received inhaled corticosteroids
- Number and % of patients having received long acting bronchodilator
- Number and % of patients having received oral corticosteroids
- Number and % of patients having received fixed combination (ICS+LAB2)
- Number and % of patients having received antileukotrienes
- Number and % of patients having received theophylline
- Number and % of patients having received anticholinergic bronchodilator
- Number and % of patients having received other medications

This analysis will be repeated to describe treatments ongoing at the time of study inclusion (ongoing ticked in the CRF).

11.2.5 Predictive factors of asthma control

The relationship between asthma control and explanatory variables will be analysed by logistic regression.
The following explanatory variables will be tested using univariate logistic regressions:

- Age in class
- Gender
- Country
- BMI in class
- Level of education
- Professional situation

- Medical insurance coverage
- Comorbidities among allergic rhinitis (yes /no), gastroesophageal reflux (yes/no), related chronic disease (yes/no)
- Smoking status (current smoker / former smoker / non smoker)
- Regular physical exercise
- Time to asthma diagnosis in class
- History of the disease in the last six months (symptoms, exacerbations, night-time symptoms, spirometry)
- Good compliance to asthma treatment according to Morisky questionnaire (i.e. score =4) (yes /no)
- Asthma treatment in the past 6 months (yes/no for each): inhaled corticosteroids, long acting bronchodilator, oral corticosteroids, fixed combination (ICS+LAB2), antileukotrienes, theophylline, anticholinergic bronchodilator, other medications
- Any other appropriate parameter

Univariate logistic regressions will be performed to explain asthma controlled (optimal and acceptable levels, i.e. current clinical controlled or partly controlled) versus uncontrolled (non acceptable level).
The proportion of patients with an acceptable level of asthma control will be calculated in each modality of each explanatory variable and odds ratio will be calculated with their 95% confidence interval.
Significant variables after univariate regressions ($p<0.10$) will be then entered in a backward multivariate model using a 0.10 significant level to stay in the model.

Ordinal logistic regression model will then be constructed to explain current clinical asthma control with three terms. These analyses as the dichotomous logistic regression will be performed.

Following SAS model will be used:

```
ods graphics on;
proc logistic data=ESMAA plots(only)=oddsratio(range=clip);
   class XXX (param=ref ref='XXX');
   model control=XXX / covb;
   oddsratio XXX;
   effectplot / individual polybar;
   title Effect of XXX on Asthma control';
run;
ods graphics off;
```

11.2.6 Exploratory analyses

Exploratory analyses of clinical interest will be performed.

12. CHANGES FROM PROTOCOL

Because compliance score assessed by the doctor is not recorded in the CRF, correlation between the compliance score assessed by the patient and the doctor’s opinion on this compliance will not be analysed as planned in the protocol.

13. INDIVIDUAL LISTINGS

All relevant CRF data will be provided using individual data listings.

All listings will include centre number, patient number and country.

14. APPENDIX

Templates of the planned tables for the Study Report are provided below.

Changes to the data presented or format may be made during the programing on the basis of the output results in agreement with the Sponsor Representative and the Statistician.

Table XX : Demographics – analyzed population

		Algeria (N=xx)	**Egypt (N=xx)**	**Iran (N=xx)**	**Iraq (N=xx)**	**Jordan (N=xx)**	**Kuweit (N=xx)**	**Lebanon (N=xx)**	**Qatar (N=xx)**	**Saudi Arabia (N=xx)**	**Tunisia (N=xx)**	**UAE (N=xx)**	**Total (N=xx)**
Gender	n	x	x	x	x	x	x	x	x	x	x	x	x
	Male	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Female	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Age	n	x	x	x	x	x	x	x	x	x	x	x	x
	Mean ± Std	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx	xx ± xx
	Median	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
	Q1-Q3	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx	xx – xx
	Min-Max	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx	xx - xx

Table XX : Predictive factors of controlled asthma – univariate logistic regrassion – analyzed population

		Controlled asthma (N=xx)	**Uncontrolled asthma (N=xx)**	**Odds ratio [95%CI]**	**Pvalue**
Gender	n	xx	xx		
	Male (ref)	xx (xx%)*	xx (xx%)	1	xxxx
	Female	xx (xx%)**	xx (xx%)	xx [xx – xx]	
Age	n	xx	xx		
	Class1 (ref)	xx (xx%)	xx (xx%)	1	xxxx
	Class2	xx (xx%)	xx (xx%)	xx [xx – xx]	
	Class3	xx (xx%)	xx (xx%)	xx [xx – xx]	

* n and corresponding rate of patient with controlled asthma among male
** n and corresponding rate of patient with controlled asthma among female