AstraZeneca

Non-Interventional Study (NIS) Protocol Amendment

Amendment Number	KSA country specific 1.0
NIS Name/Code	ESMAA/NIS-RME-XXX-2014/1
Date	10 August 2015
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ESMAA

Evaluation of Asthma Management in Middle EAst North Africa Adult population

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

Sponsor: AstraZeneca, Dubai Health Care City, Ibn Sina Bldg 27, D-Block, 2nd Floor, Oud Metha, PO Box 505070.Dubai

AstraZeneca

Signature of investigator

ESMAA

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this revised study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

Centre No.: .....

Signature:

_____ _____

<<Name, title, address and telephone number>> Date

NON-INTERVENTIONAL STUDY 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/or 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 40-50 patients meeting the eligibility criteria.

- Countries planned :

Algeria, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon,Qatar, Saudi Arabia, Tunisia, United Arab Emirates.

Total planned Study period	
Estimated date of first subject in	Q2 2014
Estimated date of last subject in	Q2 2015
Estimated date of last subject last visit	Q2 2015
Estimated date of data base lock	Q4 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 four previous weeks.

- Identify predictive factors of asthma control, such as age, sex, BMI, smoking status, adherence to treatment, asthma history, 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 according to GINA 2012 classification

Exclusion 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 cor pulmonale
    - Rhinitis
    - Sarcoidosis
    - Sleep apnea syndrome

For ESMAA study, rhinitis is not considered, and patient with rhinitis are not excluded.

- 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 4)

- The score of treatment compliance with the Morisky survey (cf. Table 5).

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 assesment

- 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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this NIS Protocol.

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

Abbreviation or special term	Explanation
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
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

1. INTRODUCTION

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 all industrialized countries, the asthma prevalence has increased in recent decades while the asthma mortality has been declining since 2000, particularly among older children and young adults under 45 [3].

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 [4]. In France, this rate is estimated at 6.7% of the general population. [5]

1.1 Background

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.

Asthma is an inflammatory disease of the airways characterized by bronchial mucous hyper responsiveness, whose etiology is still poorly known [8]. It is characterized by recurrent episodes of whistles, chest tightness, breathing difficulty and cough particularly at night [5].

Pulmonary function tests (reversible airway obstruction or bronchial hyper responsiveness) are essential for the diagnosis and following of asthma [5].

Outside the attacks, the management is based on the concept of asthma control (clinical condition during the consultation) and on the disease severity (intensity of background therapy, particularly the inhaled corticosteroids dose needed to obtain and maintain; in a sustainable manner; an acceptable control) [5].

1.2 Rationale for conducting this NIS

In November 2006, were published the revised recommendations of "GINA" (Global Initiative for Asthma) for asthma [9].

The GINA 2004 recommendations were used as reference, the changes have focused on the stages of asthma and treatment steps.

In the recommendations of 2004, the management of asthma was based on severity of asthma (intensity of diurnal and nocturnal symptoms, PEF or FEV value, and PEF variability), making a distinction between four stages [10].

- Intermittent Asthma

- Mild persistent asthma

- Moderate persistent asthma

- Severe persistent asthma

The maintenance treatment was done according to the disease stage.

In the recommendations of 2006, the asthma management is based on the level of asthma control (based on the frequency of diurnal symptoms, activity limitation, the frequency of nocturnal symptoms, the need for bronchodilators, lung function: PEF or FEV, exacerbations) [9]

We distinguish three levels of control:

- Controlled Asthma

- Partially controlled Asthma

- Uncontrolled Asthma

AIR MAG study conducted in the three Maghreb countries (Algeria, Tunisia and Morocco) on an asthmatic patients sample also allowed to assess the level of asthma control according to the GINA classification [11], but the limited number of patients does not allow to draw conclusions about the factors determining the asthma control, hence the importance of this study which will be an overview of the asthma management and frequency control.

In the GINA 2012 recommendations, the asthma management is laid out in five interrelated components of therapy:

-Develop patient/doctor partnership

-Identify and reduce exposure to risk factors

-Assess, treat, and monitor asthma

-Manage asthma exacerbations

-Special considerations (required in managing asthma in relation to pregnancy; obesity; surgery; rhinitis, sinusitis and nasal polyps; occupational asthma; respiratory infections; gastroesophageal reflux; aspirin-induced asthma; and anaphylaxis).

According to the GINA 2012, each patient should be assessed to establish his or her :

- Current treatment regimen

- Adherence to the current regimen, and

- Level of asthma control.

The simplified table below used for recognition of an controlled, partly controlled and uncontrolled asthma in a given week over 4 weeks.

Table 1 : The GINA 2012 Classification

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 controlled asthma** **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.			

Other simple tools of asthma control assessment exist, such as :

- The control questionnaire ACT: based on the number of attacks , the impact on daily life, the need of medical emergencies and patient self-assessment [10].

Despite effective treatments, and the multiplication of international recommendations, the asthma control remains unsatisfactory [13].

Several explanations are possible, explanations confirmed by surveys on nationally representative samples of asthmatic population in seven European countries [13].

- Undervaluation of symptoms by patients

- Insufficient evaluation of patients by physicians

- Non-optimal adherence

- Diagnosis, follow-up and / or treatment tools underused

- No consideration of aggravating factors.

The treatment compliance in asthma is , as for most chronic diseases, a key parameter in the asthma management .[14]

Several questionnaires exist to measure treatment compliance, so, the nature of the interview and the type of person making it will influence the result.

Despite their simplicity and low cost , these approaches have the disadvantage of always overestimate compliance.

Only Morisky questionnaire; that evaluates compliance of taking or not taking medication prior to the questionnaire filling; is used in France in clinical studies [13]. This questionnaire is also used in almost international studies.

The compliance determinants are patient related factors , physician related factors (even worse than the doctor does not respect the recommendations or consensus , also depends on the quality and regularity of consultations) , treatment related factors (β2 agonists CA better taken as inhaled corticosteroids) [13].

The impact on the quality of life is most commonly measured using the SF-36 (Short Form 36), including 36 items divided into 8 dimensions (physical functioning, limitations due to physical condition, bodily pain, life and relationships with others, mental health, role limitations due to emotional condition, vitality, general health perception) [14], this tool is widely validated internationally.

It was decided, in accordance with the Scientific Committee of the study, that the questionnaire to be used for evaluating the quality of life of patients will be the SF-8 [15], given its relevance and ease of use in ESMAA study.

2. NIS OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objectives

Main secondary objectives are:

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

- Describe the characteristics of the disease at enrollment.

- Assess the asthma control level with the ACT questionnaire (Appendix 1).

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

- The average frequency of reliever use in previous four weeks.

- Identify predictive factors of asthma control, such as sex, age, BMI, educational level, occupation, comorbidities, smoking status, social security coverage.

- Evaluate the patients quality of life (Appendix 2)

- Assess patients compliance to treatment (Appendix 3).

3. STUDY PLAN AND PROCEDURES

This Non-Interventional Study Protocol has been subject to an internal review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

Descriptive, epidemiological, multicentric cross-sectional study, conducted among a random sample of general practitioners and specialists (pulmonologists and/or allerguologists) from the public and the private sector.

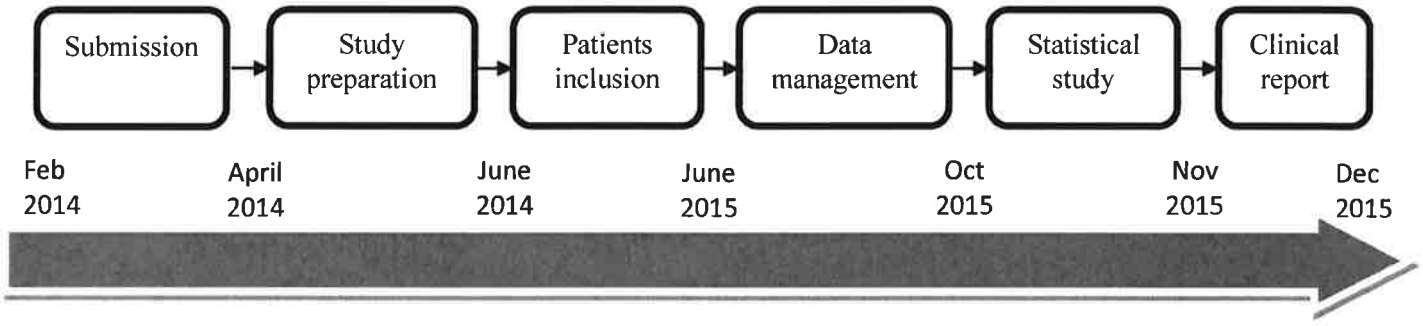
The main variable of ESMAA study is to assess the level of asthma control according to ACT questionnaire and the GINA 2012 classification: controlled, partly controlled, uncontrolled.

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 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 successively recruited from April 2014. Each physician targets to recuit an average of 40-50 patients during this period. Should the investigator feel the possibility of enrolling more than one patient per consultation, then he will be able to do so provided the patients are consecutive patients fulfilling the inclusion criteria.

The study will be conducted in several MENA countries, such as United Arab Emirates, Kuwait, Qatar, Saudi Arabia, Egypt, Tunisia, Iraq, Lebanon, Jordan, Iran, and Algeria.

Figure 1: Study Flow Chart



Study Plan

In ESMAA study, only one patient visit is planned. Informed consent and all following study procedures (ACT, clinical assessment) aligned with physician's clinical practice will be done and completed at this visit.

4. SELECTION OF SUBJECT POPULATION

4.1 Investigators

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

Having no published data on the distribution of asthmatic patients between general practitioners and specialists, 50% of investigators will be general practitioners , and 50% specialists (could be adapted to each country cf. Appendix 5) .

Each investigator involved in the study will enrol an average of 40-50 asthmatic patients meeting the eligibility criteria. The time needed to fill in patient questionnaires is long, that is why only the first patient of each physician consultation will be successively recruited from Q2 2014.

4.2 Inclusion criteria

The patients population that will be included in ESMAA study, should fulfil all of the following criteria:

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

Asthmatic diagnosed patient for at least 12 months according to GINA 2012 classification.

4.3 Exclusion criteria

- If participating in any interventional clinical trial,
- Patients with any other chronic respiratory diseases; which are a group of chronic diseases affecting the airways and the other structures of the lungs*.

***For ESMAA study, rhinitis is not considered, and patient with rhinitis are not excluded.**

- Patients consulting for asthma attack (defined as asthma symptom deterioration resulting in oral/rectal/parenteral GCS medication or emergency room treatment or hospitalisation) within 4 weeks before enrolled
- Patients with any psychotic disorders
- Pregnancy
- Patients who have not signed the consent form.

5. DISCONTINUATION OF SUBJECTS

5.1 Criteria for Discontinuation

Subjects may be discontinued from ESMAA study at any time. Specific reasons for discontinuing a subject from this NIS are:

1. Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the NIS, without prejudice to further treatment

2. Discontinuation decision from the investigator.

5.2 Procedures for discontinuation

Only one patient visit is planned, no specific procedure for discontinuation, data of patients whom inform consent withdraw will not be analysed.

6. STUDY CONDUCT

6.1 Restrictions during the study

No specific restriction for this observational, epidemiological study

7. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

- Target variables / analysis methods planned

✓ Primary variable: Level of asthma control:

The level of asthma control is defined by several classifications; classifications used in this study to assess the primary objective is GINA 2012:

The following information will be collected in CRF (Appendix 1) from medical record of study visit for judging asthma control status:

- Times of daytime symptoms due to asthma (wheezing, breathlessness, chest tightness or coughing) during last four weeks
- Limitation of activities during last four weeks: exist, not exist

- Nocturnal symptoms/awakening during last four weeks: exist, not exist
- Times of reliever use during last four weeks
- FEV1% predicted normal during last four weeks.

Table 2: The GINA 2012 classification

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 controlled asthma** **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 at 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 or more of partly controlled asthma present any week

By definition, an exacerbation attack in any week makes that an uncontrolled asthma week.

✓ Secondary variables

- Asthma control test : ACT

This test aims to assess patient's asthma control. It is based on a simple questionnaire of 5 questions, that reflect the impact of the disease on the patient's daily life. Simply calculate the total score, to whether the patient's asthma is controlled.

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. **During the last 4 weeks, how much of the time has your asthma kept you from getting as much done at work, school or home?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

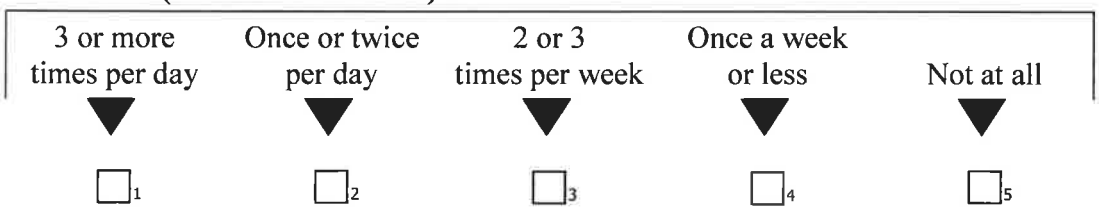
2. **During the last 4 weeks, how often have you had shortness of breath?**

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

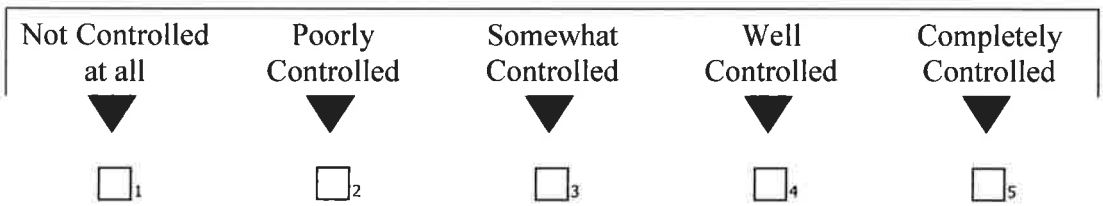
3. **During the last 4 weeks, how often have your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) woken you up at night or earlier than usual in the morning?**

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all

4. **During the last 4 weeks, how often have you used your rescue inhaler or nebuliser medication (such as Salbutamol)?**



5. **How would you rate your <u>asthma</u> control during the <u>last 4 weeks</u>?**



Asthma Control Test™ copyright, QualityMetric Incorporated 2002, 2004. All Rights Reserved.
Asthma Control Test™ is a trademark of QualityMetric Incorporated.
United Kingdom (English) version

Step 2: Add up your points to get your total score.

The overall score is the sum of scores for answers questions 1-4, the overall score may vary depending on the patient from 4 to 20, even higher than the patient is well controlled.

The score for question 5 is a subjective assessment of the patient for the control of the disease.

Level of control during the last four weeks prior to inclusion in the ACT questionnaire (first 4 questions), and consistent with the patient's assessment (fifth question) : not controlled at all, very little controlled, little controlled, well controlled or totally controlled).

Level of asthma control according to ACT questionnaire and the GINA 2012 classification: controlled, partly controlled, uncontrolled.

- General and demographic baseline patient characteristics : gender, age, BMI, educational level, occupation, associated comorbidity, smoking status, social security.

- Disease characteristics (comorbidity, and cocommittant medication, alike: DMARDs, history of asthma during the last six months, emergency treatment, and inhalation devices used and spirometry during the last six months).

Statistical related risk to each factor studied in a non-optimal asthma control, measured by the odds ratio OR (age, sex, BMI, smoking status, adherence to treatment, .smoking status, comorbidity).

✓ **Quality of life assessment**

The assessment of quality of life is done using the SF-8 questionnaire on the quality of life.

Quality of life questionnaire SF-8

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. **Overall, how would you rate your health during the past 4 weeks? [Mark an ☒ in the one box that best describes your answer.]**

Excellent	Very good	Good	Fair	Poor	Very poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

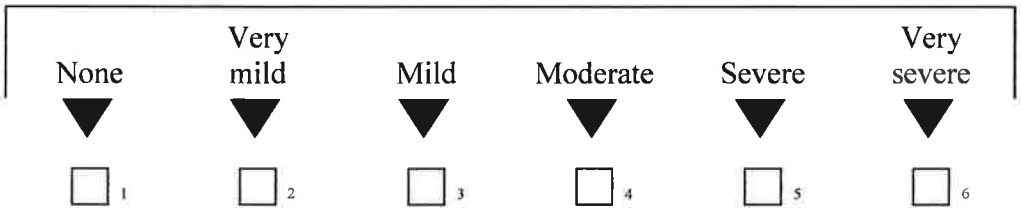
2. **During the past 4 weeks, how much did physical health problems limit your usual physical activities (walking, climbing stairs)?**

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

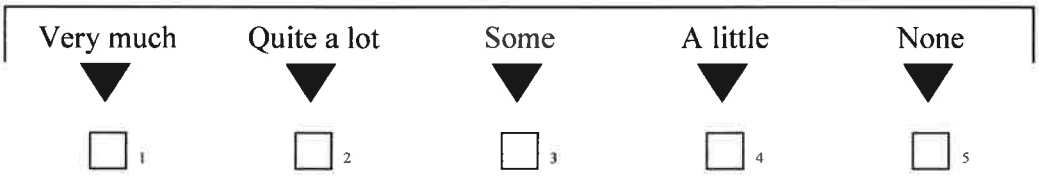
3. **During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?**

None at all	A little bit	Some	Quite a lot	Could not do daily work
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

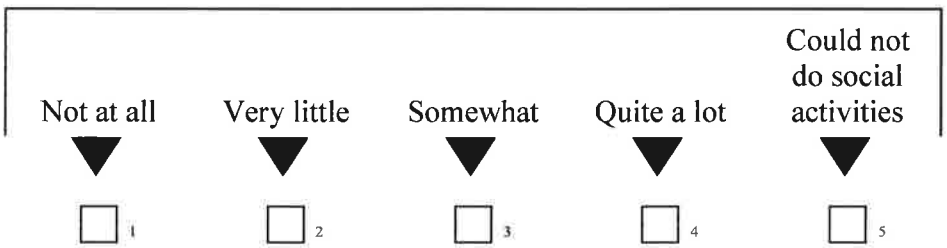
4. How much bodily pain have you had during the past 4 weeks?



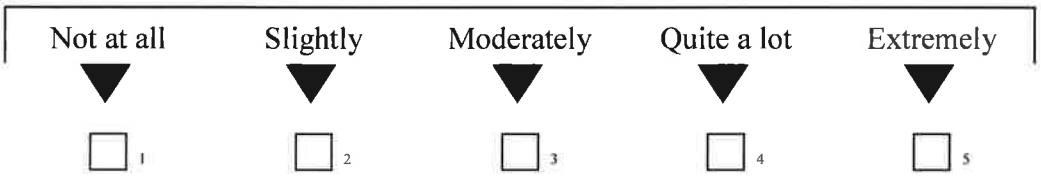
5. During the past 4 weeks, how much energy did you have?



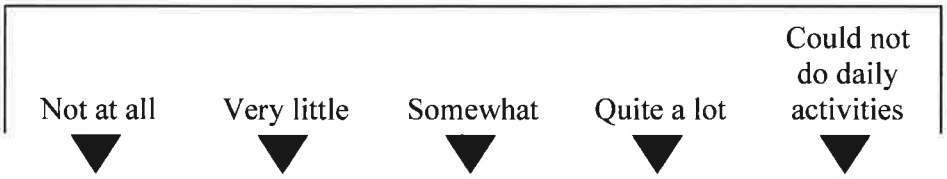
6. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?



7. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?



8. During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?



☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

SF-8™ Health Survey

SF-8™ Health Survey Standard – United States (English Version 1.0)

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, 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).

✓ **Treatment compliance assesment:**

Compliance to treatment is assessed using the Morisky questionnaire

Morisky Medication Adherence Scale (4-item) ©MMAS-4

You indicated that you are taking medication for your asthma. Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experiences with your asthma medication.

(Please check one box on each line)

	Yes	No
1. Do you ever forget to take your asthma medicine?	☐	☐
2*. Do you ever have problems remembering to take your asthma medication?	☐	☐
3. When you feel better, do you sometimes stop taking your asthma medicine?	☐	☐
4. Sometimes if you feel worse when you take your asthma medicine, do you stop taking it?	☐	☐

*modified item from original scale appearing in Medical Care 1986

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 good-observant. The score is proportional to the compliance level.

7.1 Patient Reported Outcomes (PRO)

The patient will respond to three questionnaires independently, without mentionning his name on any of them, with the help of his physician:autoquestionaire or heteroquestionaire. The investigator should review the questionnaires to avoid any uncompleted responses.

- Asthma control assessment according to ACT (Appendix 2).
- Questionnaire on quality of life SF-8 (Appendix 3).
- Questionnaire on treatment compliance Morisky (Appendix 4).

Administration of PRO questionnaires

Patients meeting the eligibility criteria will be invited to participate to the study. Patients consenting to participate will be included in the study. Data referring to each patient will be collected during the single consultation in medical record and CRF which is completed by the investigator.

The patient should complete three questionnaires independantly with the investigator help if needed, one for the asthma control evaluation according to ACT questionnaire; the two others are related to the quality of life and treatment compliance (To be adapted according to local specifications cf.Appendix 5)

8. SAFETY REPORTING

8.1 Definitions

8.1.1 Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product,

whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered

8.1.2 Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase and fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

8.1.3 Definition of Adverse Drug Reactions (ADR)

An ADR is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

8.2 NIS without a specific safety objective

Due to the non-interventional character of this study, no pro-active safety data collection should take place. Only spontaneously mentioned safety events should be reported as required by the post-marketing pharmacovigilance regulations. The method for reporting spontaneously mentioned safety events are described below. It is of the outmost importance that all staff involved in the study is familiar with the content of this section. The investigator is responsible for ensuring this.

8.3 Reporting

8.3.1 Reporting of adverse events

AstraZeneca does not supply any product to be studied in this study. All adverse events related to treatment will be indicated using the procedures established by the manufacturers of the prescribed treatment, and according to the regulations.

8.3.2 Reporting of serious adverse events

Reporting of SAE will be done in accordance with the local regulation requirements of each country.

8.3.3 Reporting of spontaneously mentioned adverse drug reactions

With regards to the reporting of ADRs observed in subjects participating in this study, the following guideline applies: ADRs should be reported to Health Authorities as stated in local regulations and/or, if the investigator considers it appropriate, to AZ (in case of an ADRs of an AZ-product) or the corresponding marketing authorization holder of the drug.

9. ETHICAL CONDUCT OF THE NON-INTERVENTIONAL STUDY

ESMAA is a Non-Interventional Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs and the applicable legislation on Non-Interventional Studies.

The Investigator will perform this NIS in accordance with the regulations and guidelines governing medical practice and ethics in the country of the ESMAA conduction, and in accordance with currently acceptable techniques and know-how.

9.1 Ethics review

The final protocol of the Non-Interventional Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must also review and/or approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

9.2 Subject Informed consent

The Investigator at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the NIS. Subjects must also be notified that they are free to discontinue from the NIS at any time. The subjects should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated subject informed consent must be obtained before any specific procedure for the NIS is performed, including:

- Interview with the investigator

- Fulfil the questionnaires
- CRFs completion.

The Investigator must store the original, signed Subject Informed Consent Form. A copy of the signed Subject Informed Consent Form must be given to the patient.

9.3 Subject data protection

The Subject Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorise the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of Esmaa study.

The Subject Informed Consent Form will explain that NIS data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The Subject Informed Consent Form will also explain that for quality check purposes, a monitor of AZ or a monitor of company representing AZ, will require direct access to the signed subject informed consent forms. In case source data verification will be planned as quality check, the Subject Informed Consent Form will explain that for data verification purposes, monitor of AZ or a monitor of company representing AZ may require direct access to source documents that are part of the hospital or practice records relevant to the Non-Interventional Study.

10. STUDY MANAGEMENT BY ASTRAZENECA

10.1 Monitoring, Quality Control and Archiving

Before the first subject is recruited into the study, the local MC representative or delegate will:

- Establish the adequacy of the facilities and the investigator's capability to appropriately select the sample
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca or its representatives. This will be documented in a NIS Agreement between AstraZeneca/delegate and the investigator.

During the study the local MC representative or delegate can implement different activities to assure compliance with AZ standards of quality. These activities could include but are not limited to:

Contacts with the sites to:

- Provide information and support to the investigator(s)

- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the case report forms (CRFs)
- Ensure that the subject informed consent forms are signed and stored at the investigator's site
- Ensure that the CRFs are completed properly and with adequate quality.

Monitoring activities for:

- Checking a sample of ICFs
- Checking that subjects exist in medical records (a sample)

The extent and nature of monitoring will be decided during the study planning by each country, based on design, complexity, number of subjects, number of sites, etc. Medical Evidence Centre (multi country) /Marketing Company (MC) will give some recommendations that could be locally adapted.

Different signals (eg, low recruitment rate) should be used as potential identification of low protocol compliance by investigators.

If these, or any other signal occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

10.2 Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the NIS is given to investigational staff, and that any new information relevant to the performance of this NIS is forwarded to the staff involved.

10.3 NIS timetable and end of study

Before the first subject is enrolled in the NIS and any NIS related procedures are undertaken the following should be fulfilled

- Written approval of the NIS by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or Regulatory Authorities, according to local regulations
- Proper agreements between AstraZeneca or representative and the Investigator/Institution is signed

The planned timetable for the NIS is estimated to be as follows:

- Estimated first subject in: Q2 2014
- Estimated last subject in: Q2 2015
- Estimated last subject last visit: Q2 2015
- Estimated date of database lock: Q4 2015

Should AstraZeneca decide to discontinue the study prior to what was established in this protocol, the investigator, and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date.

11. DATA MANAGEMENT

11.1 Collection, monitoring, processing of data and archiving

All study evaluation parameters are part of the routine practice surveillance in the population studied and will be collected, when available in the subject source document.

There is only one phase of data collection for this study, 100% of the sample physicians drawn will be monitored: 40% by sites visit monitoring and 60% by remote monitoring (phoning). Site visits will be done by the monitor responsible of the study, and he will ensure the proper conduct of the study and adherence to protocol. during the same visit, the monitor will retrieve documents from the site.

During the remote monitoring, the monitor will update the site status in term of inclusion, ask about the ICF signing by the patients, and motivate the investigator to complete properly the CRF, and request for sending them by courier.

Paper-CRF will be recovred locally in each country by AZ or local CRO and sent to Clinica Group CRO for central datamanagement of the study. Each batch of CRF should be sent by secure courrier (DHL, TNT, UPS, ..etc) accompagned by a transmittal sheet.

A database will be created for each country, and the data will be managed separately, the approval process of the database will be done by an independent data manager.

The data entry guideline should be prepared by the Project Data Manager and should be available to all data processing staff.

Simple data entry of the CRF is required for ESMAA, with a double data entry for 10% of the CRF for each country. The 10% double entry data will be used for quality assurance assessment, no more than 5% of disperancies are allowed.

Data management plan will be established by Clinica Group and approved by the regional AZ team for all the countries. Data Clarification Forms (DCF) will be edited regarding the approved datamanagement plan of each missing/uncorrect data.

Quality control of the edited DCF will be assured vs. CRF before transmission to each country team, who will manage DCF resolution with investigators.

Statistical analysis of ESMAA study will be done for each country and for the global study population . Clinica Group is responsible for countries / global statistical analysis.

11.2 Reporting and publication of data

AstraZeneca will prepare a Non-Interventional Study Report within 12 months after completion of the last subject.

The medical director for each country will be appointed to sign ESMAA report for his country with MEA Medical Director, the national Coordinator and the study statistican.

The global report will be signed by the MEA medical director and the study statistican.

The study results will be presented to the investigators before publication or public communication on a scientific meeting (congress, workshops, ...etc).

AstraZeneca is obliged to analyse and report all Esmaa data as described in the protocol.

In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of the NIS, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. AstraZeneca endeavours to publish the results of NIS and is committed to ensure that the data are reported in a responsible and coherent manner.

AstraZeneca seeks to ensure that publications in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals.

AstraZeneca is committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "*Each author should have participated sufficiently in the work to take public responsibility for the content.*"

AstraZeneca believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to AstraZeneca employees.

Other members of the group should be listed in the acknowledgments as appropriate.

Publication of data subsets from individual institutions participating in multicentre studies should not precede the primary manuscript, and when developed should always reference the primary publication of the entire study.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The complete details of statistical analysis and methods, including conventions relative to data will be pooled in a statistical analysis plan which will be finalized before the database closing.

Considerations for the minimal sample size :

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, 21% of patients have an optimal control of their asthma [5].

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. (Cf.Appendix 5).

The sample size calculating will be done using the application :

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

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 patients' 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,
- Saudi 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.

12.1 Statistical evaluation – general aspects

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

A comprehensive Statistical Analysis Plan will be prepared before database lock.

The statistical analysis approach in this project is descriptive. Continuous data are described by the mean, standard deviation, median, minimum, maximum and quartiles. All abstracts will be presented from all available data. Categorical data are described in terms of the number and percentage of patients in each category.

Missing observations are presented in tables as a separate category. Calculating proportions will not include the missing category.

12.2 Description of outcome variables in relation to objectives and hypotheses

Primary variable:

• GINA 2012 classification assesment: controlled, partly controlled, uncontrolled patients.

Secondary variables:

• General and demographic baseline patient characteristics : gender, age, BMI, educational level, occupation, associated comorbidity, smoking status, social security;

• Characteristics of the disease at baseline;

• Level of control during the last four weeks prior to inclusion in the ACT questionnaire (first 4 questions), and consistent with the patient's assessment (fifth question);

• Risk related to each factor studied in a non-optimal asthma control, measured by the odds ratio (OR);

• Score of the quality of life using the SF-8 questionnaire ;

• Score of treatment compliance with the Morisky questionnaire .

12.3 Method of statistical analysis

- Descriptive analysis of the sample:

Description of the patients' general and sociodemographic characteristics at enrollment , and disease characteristics at enrollment :

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

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

- Predictive factors identification for asthma control :

- Univariate analysis

Link between each studied factor and asthma control using the $\chi 2$ test and the estimation of the OR with confidence interval of 95%.

- Multivariate analysis

  - Dichotomous logistic regression model : built according to a walkthrough at 5 %. The level of asthma control is combined in two modalities : controlled (optimal and acceptable level) , uncontrolled (non- acceptable level) , the 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 it's three terms), the explanatory variables are the factors found significant or borderline significance ($p < 0.10$) in the univariate analysis

- Quality of life :

- Descriptive analysis of different items involved in assessing the quality of life

- Link between quality of life and asthma control using the $\chi 2$ test

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

- Treatment compliance :

- Descriptive analysis of different items involved in the treatment compliance (Morisky questionaire)

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

Appendix 1: Case Report Form (CRF)

SECTION 1: PRE-INCLUSION SELECTION CRITERIA VERIFICATION		
All shaded boxes must be ticked for a patient to be included in the study		
Inclusion criteria:		
▪ Patient aged 18 years and over	Yes	☐ No
▪ Patient asthmatic since 12 months before inclusion	Yes	☐ No
▪ Informed consent form signed	Yes	☐ No

All shaded boxes must be ticked for a patient to be included in the study

Exclusion criteria:

- Patient participating in any interventional clinical trial ☐ Yes
- Patient with any other chronic respiratory diseases except rhinitis ☐ Yes
- Patient with any psychotic disorders ☐ Yes
- Pregnancy ☐ Yes
- Patients consulting for asthma attack within 4 weeks before enrolled ☐ Yes

SECTION 2: GENERAL INFORMATION

Date of birth: |__|__| / |__|__| / |__|__|__|__| (Day / Month / Year) or Age (in years): |__|__|__|

Sex: ☐ M ☐ F

Weight (in kg): |__|__|__|, |__|__| Height (in cm): |__|__|__| BMI (in kg/m^2): |__|__|, |__|

Social status:

- Level of education:
  - ☐ Cannot read and write
  - ☐ Primary
  - ☐ Secondary school
  - ☐ University degree
  - ☐ Higher education
- Professional situation: ☐ Active ☐ Non-active
  - ➢ If non-active (specify position): .....

☐ Unemployed ☐ Retired ☐ Sick leave

- Medical insurance coverage (health insurance): ☐ Yes ☐ No

- **Does the patient suffer from:**

☐ Allergic rhinitis ☐ Gastroesophageal reflux

☐ Related chronic disease ☐ Other, please specify:
.....

- **Smoking status:**

Current Smoker: ☐ Yes ☐ No
(Current or smoked during the 6 last months)

Former smoker *(stopped since more 6 months):* ☐ Yes ☐ No

Non-smoker: ☐ Yes

- **Regular physical exercise:** ☐ Yes ☐ No
(see definition below)

Regular physical exercise: For adults age 18 to 64 years, physical exercise includes hobbies, getting around (i.e. walking or cycling), work activities, housework, fun activities, sports or scheduled exercise, in the daily, family or community context – World Health Organisation - http://www.who.int/fr/-

SECTION 3: CHARACTERISTICS OF ASTHMA ON INCLUSION

1. Years with Asthma disease:

History of disease diagnosis (in years): |__|__|

2. History of the disease in the last six months:

- **Symptoms** (breathlessness, wheezing, chest tightness, cough)

☐ Symptoms less than once per week

☐ Symptoms more than once per week and less than once per day

☐ Symptoms on a daily basis

- **Exacerbation**

☐ Mild exacerbation

☐ Exacerbation likely to affect activities and sleep

☐ Frequent exacerbation

- **Night-time symptoms**

☐ Night-time symptoms no more than twice per month

☐ Night-time symptoms more than twice per month

☐ Night-time symptoms more than once per week

☐ Frequent night-time symptoms

☐ Short-acting β2 agonist used daily

☐ Physical activity limited

- **Spirometry**

☐ PEF ≤ 60% of predicted value

☐ PEF 60-80% of predicted value

☐ PEF ≥80% of predicted value

☐ PEF variability < 20%

☐ PEF variability 20-30%

☐ PEF variability > 30%

SECTION 4: ASTHMA CONTROL

1. **Asthma control assessed by the patient:**

   - **According to Asthma Control Test (ACT) questionnaire:**

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. **During the last 4 weeks, how much of the time has your asthma kept you from getting as much done at work, school or home?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. **During the last 4 weeks, how often have you had shortness f breath?**

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. **During the last 4 weeks, how often have your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) woken you up at night or earlier than usual in the morning?**

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. **During the last 4 weeks, how often have you used your rescue inhaler or nebuliser medication (such as Salbutamol)?**

3 or more times per day	Once or twice per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. **How would you rate your asthma control during the last 4 weeks?**

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

United Kingdom (English) version

2. Asthma control assessed by the doctor:

- **According to GINA 2012 classification**

➢ Daytime symptoms:	☐ None (≤2/wk)	☐ > 2/wk
➢ Limitation of activities:	☐ None	☐ Yes
➢ Nocturnal symptoms/awakening:	☐ None	☐ Yes
➢ Need for reliever/rescue treatment:	☐ None (≤2/wk)	☐ > 2/wk
➢ Lung function FEV/PEF:	☐ Normal	☐ <80% (predicted or better)

➢ Assessment of future risk (risk of exacerbation, instability, rapid decline in lung function, side effects)

Predictive characteristics of an increased risk of adverse events:

☐ Poor clinical control

☐ Frequent exacerbations in past year

☐ Number of admission to critical care for asthma

☐ Low FEV

☐ Exposure to cigarette smoke

☐ High dose medications

SECTION 5: ASTHMA TREATMENT (During the past 6 months)

	International Nonproprietary Name (INN)	Dose/day	Unit	Administration method	Start date	End date (if discontinued)	Reason for discontinuation	Ongoing (If yes, please tick)
Inhaled corticosteroids		☐☐☐·☐		Inhaled	/ /	/ /		☐
Long-acting bronchodilator		☐☐☐·☐			/ /	/ /		☐
Oral corticosteroids		☐☐☐·☐		Oral	/ /	/ /		☐
Fixed combination (ICS+ LA β2)		☐☐☐·☐		Inhaled	/ /	/ /		☐
Antileukotrienes		☐☐☐·☐		Oral	/ /	/ /		☐
Theophylline		☐☐☐·☐			/ /	/ /		☐
Anticholinergic bronchodilator		☐☐☐·☐			/ /	/ /		☐
Other		☐☐☐·☐			/ /	/ /		☐

SECTION 6: PATIENT QUALITY OF LIFE (SF-8 QUESTIONNAIRE)

1. **Overall, how would you rate your health during the past 4 weeks? [Mark an ☒ in the one box that best describes your answer.]**

Excellent	Very good	Good	Fair	Poor	Very poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

2. **During the past 4 weeks, how much did physical health problems limit your usual physical activities (walking, climbing stairs)?**

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?**

None at all	A little bit	Some	Quite a lot	Could not do daily work
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

5. During the past 4 weeks, how much energy did you have?

Very much	Quite a lot	Some	A little	None
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all	Very little	Somewhat	Quite a lot	Could not do social activities
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

Not at all	Slightly	Moderately	Quite a lot	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

8. During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-8™ Health Survey

SF-8™ Health Survey Standard – United States (English Version 1.0)

SECTION 7 : TREATMENT COMPLIANCE (MORISKY)

You indicated that you are taking medication for your asthma. Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experiences with your asthma medication.You indicated that you are taking medication for your asthma. Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experiences with your asthma medication.

(Please check one box on each line)

	Yes	No
1. Do you ever forget to take your asthma medicine?	☐	☐
2*. Do you ever have problems remembering to take your asthma medication?	☐	☐
3. When you feel better, do you sometimes stop taking your asthma medicine?	☐	☐
4. Sometimes if you feel worse when you take your asthma medicine, do you stop taking it?	☐	☐

*modified item from original scale appearing in Medical Care 1986

Appendix 2: ACT questionnaire

Evaluate the score for each question and write the number in the box on the right.

Asthma Control Test™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. **During the last 4 weeks, how much of the time has your asthma kept you from getting as much done at work, school or home?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. **During the last 4 weeks, how often have you had shortness of breath?**

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. **During the last 4 weeks, how often have your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) woken you up at night or earlier than usual in the morning?**

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. **During the last 4 weeks, how often have you used your rescue inhaler or nebuliser medication (such as Salbutamol)?**

3 or more times per day	Once or twice per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. How would you rate your asthma control during the last 4 weeks?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Asthma Control Test™ copyright, QualityMetric Incorporated 2002, 2004. All Rights Reserved.
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United Kingdom (English) version

Appendix 3: Quality of life questionnaire SF-8

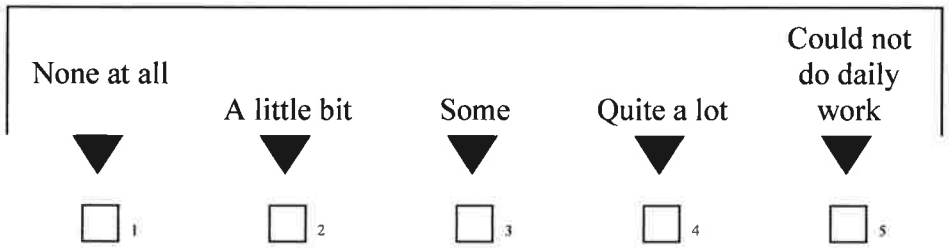
1. Overall, how would you rate your health during the past 4 weeks? [Mark an ☒ in the one box that best describes your answer.]

Excellent	Very good	Good	Fair	Poor	Very poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

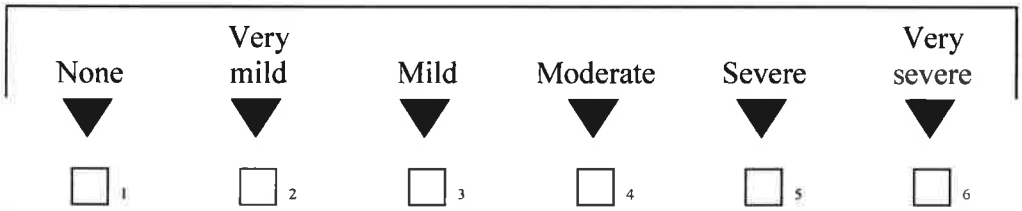
2. During the past 4 weeks, how much did physical health problems limit your usual physical activities (walking, climbing stairs)?

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

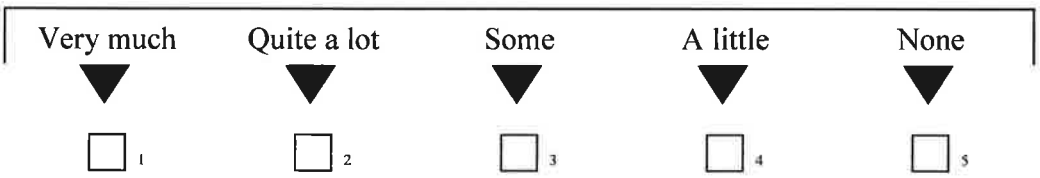
3. **During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?**



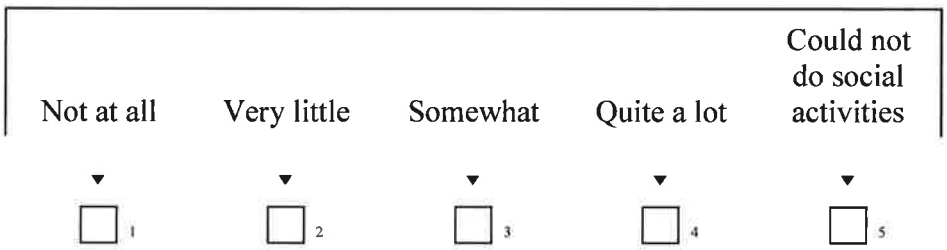
4. **How much bodily pain have you had during the past 4 weeks?**



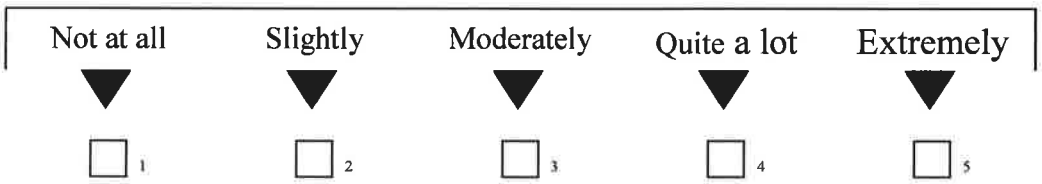
5. **During the past 4 weeks, how much energy did you have?**



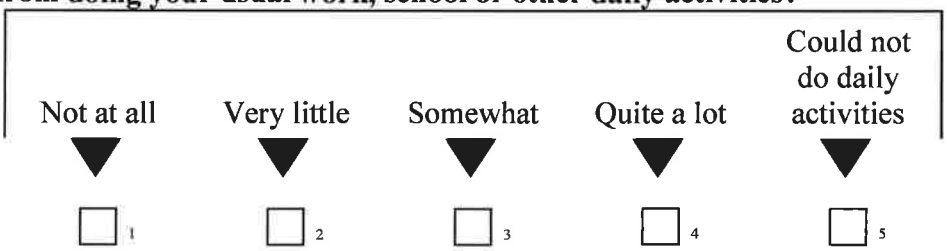
6. **During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?**



7. **During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?**



8. **During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?**



SF-8™ Health Survey

SF-8™ Health Survey Standard – United States (English Version 1.0)

Appendix 4: Treatment compliance Questionnaire Morisky

You indicated that you are taking medication for your asthma. Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experiences with your asthma medication.

(Please check one box on each line)

	Yes	No
1. Do you ever forget to take your asthma medicine?	☐	☐
2*. Do you ever have problems remembering to take your asthma medication?	☐	☐
3. When you feel better, do you sometimes stop taking your asthma medicine?	☐	☐
4. Sometimes if you feel worse when you take your asthma medicine, do you stop taking it?	☐	☐

*modified item from original scale appearing in Medical Care 1986

Appendix 5 : Country specifications

Country: .....

- **Local regulations' requirements :**
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- **Sample size calculation :**
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  .....

- **Physicians number :**
  .....
  .....
  .....

- **Other :**
  .....
  .....
  .....

13. LIST OF REFERENCES

1- Asthme : chiffres clés et prévalence (sources : IRDES 2006)

2- Asthme : Organisation Mondiale de la Santé (OMS) ; Aide-mémoire n° 307 – mai 2008

3- http://www.astrazeneca.fr/sante/asthme/asthme_epidemiologie.asp - consulté le 24-05-2012.

4- New European Asthma figures released in Global Report European Federation of allergy and airways Diseases Patients Associations-EFA – Février 2004

5- Asthme de l'adulte Item 226 ; Collège des enseignants en Pneumologie (CEP) – Référentiel pour la préparation de l'ECN, Mise à jour Décembre 2010

6- Prevalence of Asthma in North Africa: the Asthma Insights and Reality in the Maghreb (AIRMAG) study; S. Nafti and al; Respiratory Medicine 103, S2-2009.

7- http://www.who.int/gard/publications/chronic_respiratory_diseases.pdf-consulté le 02.01.2014

8- Journée mondiale de l'asthme : Dr Philippe Auriol ; France-4 mai 2009

9- Révision des recommandations « GINA » sur l'asthme et « GOLD » sur la BPCO. Folia Pharmacotherapeutica 34, janvier 2007

10- Comment évaluer le contrôle de l'asthme en pratique quotidienne ; A. deschildre – Pneumologie pédiatrique – CHRU de Lille ; Toulouse – Octobre 2008

11- Control of Asthma in the Maghreb : Results of the AIR MAG Study ; Respiratory Medicine 2009 ; 103.

12- Recommandations pour le suivi médical des patients asthmatiques adultes et adolescents; Argumentaire – ANAES- Septembre 2004.

13- Observance thérapeutique chez l'enfant asthmatique; Recommandations pour la pratique clinique; GRAPP Revue maladies respiratoires Vol 24, N° 4 - pp. 419-425- Avril 2007.

14- Le questionnaire généraliste SF-36

15- Cross-Validation of Item Selection and Scoring for the SF-8 Health Survey in Nine Countries: Results from the IQOLA Project- Barbara Gandek et al.-Journal of Clinical Epidemiology Vol. 51,

16- Morisky DE, Green LW, Levine DM. Concurrent and Predictive Validity of a Self-Reported Measure of Medication Adherence and Long-Term Predictive Validity of Blood Pressure Control. Medical Care 1986.

17- Morisky DE, Malotte CK, Choi P, et al. A Patient Education Program to Improve Rate with Antituberculosis Drug Regimens. Health Education Quarterly 1990; 17:253-268

18- Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemio 2011; 64:258-263. PMID:21144706.

Non-Interventional Study (NIS) Protocol Amendment No KSA Country Specific 1.0 Appendix A	
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NIS Primary Protocol Dated	20 August 2014 (version 4)

NIS Primary Protocol Amendment Appendix A Signatures

ASTRAZENECA SIGNATURE(S)

ESMAA

Evaluation of Asthma Management in Middle East North Africa Adult population

Descriptive study on the management of asthma in sthmatic Middle East North Africa Adult population

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This NIS Protocol Amendment has been subjected to an internal AstraZeneca review

I agree to the terms of this amendment KSA country specific 1.0, dated 10 August 2015

AstraZeneca representative

23/8/2015

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