Project funded by the European Commission
within the 7th Framework programme

PR3 – Publishable summary

ASTRO-LAB			
Assessment of the safety of LABAs in asthma in routine care by combining health-care databases and direct patient follow-up			
GA nr:	282593	Call reference:	FP7-HEALTH-2011-single-stage
Start date:	01/12/2011	Duration:	54 months

WP n°	1
Lead beneficiary:	UCBL
Nature:	Report/Other
Dissemination level:	PU*

Contributors:	
Beneficiary name	Contributor(s)'name(s)
UCBL	S. Herbage ; E. Van Ganse
LIP	C. Strano

*PU=Public, PP= Restricted to programme participants, RE= Restricted to a group specified by the consortium, CO=Confidential

Table of contents

1. Publishable summary

1.1. Project context and the main objectives

Asthma is a common disease in European countries: for example, the prevalence in France in the early 2000s was estimated at 6.7%. Long-acting beta2-agonists (LABAs) are now one of the main treatment options in asthma care, combined with ICs or not. However, more information is needed on their benefits and on their risks in special populations (such as young people) and in different treatment combinations (such as LABAs taken with Inhaled Corticosteroids in separate or single inhalers). Moreover, it is known that patients' actual use of LABAs and ICs inhalers may be different from the prescribed use. The actual patterns of drug use may be determined by various beliefs and attitudes about asthma and its treatment, and may lead to unpredicted drug utilisation and thus modify the benefits and the risks of LABA. It is also acknowledged that prescription patterns and asthma self-management support activities may vary in different primary care settings depending on the organization of asthma care, and on clinician training, clinical experience, and personal views.
These various approaches to asthma care may have an impact on patient behaviours and health outcomes.

The ASTRO-LAB project (Assessment of the safety of LABAs in asthma in routine care by combining healthcare databases and direct patient follow-up) aimed to provide new information about the benefits and the risks of long-acting bronchodilators (LABAs, also known as long-acting relievers). ASTRO-LAB investigated the extent to which the use of LABAs in routine care is associated to an increased likelihood of asthma exacerbations, i.e. asthma-related use of oral corticosteroids, hospital contact, unscheduled visits to primary or secondary care, or death. As a central research question targeting the role of patient behaviours in treatment safety, the project also examined how people with asthma use LABAs and ICs inhalers and manage their condition in the long term, what influences the way in which they manage asthma, the care they receive from their health care professionals (HCPs), and what explains HCPs' asthma management.

The ASTRO-LAB consortium undertook systematic investigations of the scientific literature in this area, and conducted a prospective observational cohort study to follow up people with asthma (half under 18 years old) in France and in the UK during a 2-year period.
Data were collected from medical records, insurance claims records, and from patients themselves and their clinicians (via telephone interviews, text

Dissemination level	PU

messages/emails and online surveys). One of the main assets of the ASTRO-LAB study design was to combine 3 levels of data: prescribing data, dispensing data and treatment consumption reported by patients.

The project was funded by the European Commission (EC) through the Seventh Framework Program (FP7) under Grant Agreement n° 282593 and ran for 4,5 years (December 2011-May 2016). It was coordinated by the Université Claude Bernard Lyon 1 (UCBL) and the Consortium included 6 partners: the University of Nottingham (UoN), Kappa Santé SAS (KS), IMS Health (IMS), Consorcio Mar Parc de Salut de Barcelona (PSMAR), Universiteit van Amsterdam (UvA) and Lyon Ingénierie Projets (LIP).

1.2. Work performed since the beginning of the project and the main results achieved so far

The achievements between December 2011 and May 2016 can be summarized as follows:

■ *Literature review*
Synthesis on current knowledge on asthma adherence and on asthma treatments risk/benefit ratio was performed. Conclusions of these reviews resulted in recommendations for the design of the ASTRO-LAB cohort study.

■ *Conception and regulatory approvals*
Protocol, CRF and consent forms have been reviewed and validated by the Ethics and the Advisory Boards in Sep2012. Initial regulatory approvals have been granted in Jan 2013 in the UK by the Research Ethics Committee and in May 2013 in France by the CCTIRS and CNIL. In parallel, the consortium developed the study website.

■ *Prospective Cohort Management*
In total, 1162 patients were included in the study (946 in France and 216 in UK). Among them, 532 (45.8%) were children or teenagers (6-17 years). Patients have been followed with computer-assisted telephone interviews, monthly text messages and online questionnaires. In addition, both UK and French investigators were invited to complete online questionnaires about their medical practice.

■ *Drug exposure validation and adherence*
In France, the prescribing database has been linked (probabilistic method) with claims Data, with a 82.2% success rate. Methodology for the measurement of adherence used direct patient follow-up, prescribing and

Dissemination level	PU

dispensing data. Adherence scales and comprehensive function list for calculating Continuous Medication Availability have been developed.

■ *Ethics reports*

Two interim reports have been delivered. The final Ethics report includes all regulatory and ethic notifications, changes in study protocol and implemented actions that impacted patients (amended documentation, process for consents...). It has been approved in July 2016 by the independent Ethic Board Ethics Report 2.

■ *Safety and Impact analysis*

Data analysis focused on the primary research question regarding LABA safety, as well as questions regarding asthma management by patients and caregivers, the routine asthma care delivered by HCPs, and patients' health-related quality of life (HRQL). No significant increase in patient-reported asthma exacerbations have been observed when patients were daily exposed to LABA during the week preceding the assessments, either in fixed dose combination or in single canister; these results need to be considered with caution due to the limited statistical power. Adherence to controller inhalers was shown to be suboptimal. This contributed to inappropriate disease control, and was influenced by modifiable patient-related characteristics such as treatment beliefs and self-efficacy. Routine asthma care was more comprehensive in the UK than in France, particularly when delivered by nurses or by HCPs with training in asthma and communication. ASTRO-LAB asthma patients reported lower HRQL than the overall population. Final reports on the global cohort and the children cohort have been approved by the Advisory Board in July 2016.

■ *Dissemination*

Results have been disseminated in 6 publications in peer-reviewed scientific journals so far, and more that 50 communications (oral presentations or posters) at international conferences and other scientific events. The final symposium took place in Lyon, in April 2016. Dissemination is still ongoing with 7 articles in advanced stages of preparation.

1.3. Description of the expected final results and their potential impacts and use

Results have been disseminated in 6 publications in peer-reviewed scientific journals so far, and more that 50 communications (oral presentations or posters) at international conferences and other scientific events. The final symposium took place in Lyon, in April 2016. Dissemination is still ongoing with 7 articles in advanced stages of preparation.

Dissemination level	PU

Contributions to scientific evidence:
- Systematic literature reviews of observational and experimental evidence on LABA safety in adults and children, and literature reviews on several topics related to the process of asthma care have been published.
- Regarding LABA safety, results were not significant when comparing the risk of asthma exacerbations between patients daily exposed in the past week to LABA either in fixed dose combination or in single canister. Nonetheless, a signal appeared for LABA used in single canister (the risk of exacerbations increased with 23%) with indication that the risk was further increased in children population.
- The Asthma Care Model (ACMv1), developed following literature reviews and expert consultation during the preparation of the cohort study, represents a first proposal for an integrative model of asthma management that takes into account the impact of patient and health care provider behaviors on health outcomes. The ACMv1 was published as part of a special issue on adherence in a clinical journal for practitioners and is likely to impact both research and practice in the respiratory field by stimulating debate on key elements of the asthma care process, setting a research agenda, and offering practical recommendations for clinicians.
- The findings regarding adherence are in line with prior research on adherence determinants and outcomes, contributing to this field of research by offering a longitudinal perspective on medication use, which is particularly important given the variability in symptoms that characterize asthma. We have shown that there is substantial intra-individual variation in adherence to controller medication, that adherence impacts asthma outcomes, that adherence is influenced by patient-related factors such as treatment beliefs, perceived self-efficacy, and goal-setting, that parent-related factors are important for adherence in children with asthma, and that trigger management plays a role in asthma-related outcomes, especially concerning exacerbations.

Methodological contributions:

- The ASTRO-LAB consortium performed a successful linkage between prescribing data and French claims data (82.2% success rate).
- The consortium developed longitudinal asthma management patient profiles by integrating data on prescription and dispensation events, and patient-reported medication exposure and occurrence of asthma exacerbations (AEx). Longitudinal plots for individual patients allowed

Dissemination level	PU

identification of the regularity and concordance in prescription and dispensation events, and possible relations with patient-reported drug exposure and AEx occurrence.

- Linkage between patient-reported data and claims data allowed investigating how dispensations of oral corticosteroids (OCs) reflect patient courses for asthma exacerbation.
- A new method for assessing adherence via computer-assisted telephone interviews was developed to counter limitations of existing measures and acquire information on medication use over specific time intervals in long-term follow-up.
- New algorithms of adherence based on prescribing and dispensing data have also been developed using R, an open-source environment increasingly used in statistical analysis in academic and business settings. The algorithms will be made freely-available in the R repository in the next months.
- A new R-based algorithm for assessing psychometric properties of item sets in multi-measure survey studies was also developed for ASTRO-LAB analyses, has been already presented in several workshops, and it will be communicated within a dedicated methodological symposium at the EHPS 2016 conference in August 2016.

Project coordinator: Doctor Eric van Ganse (UCBL)
Project website: http://www.astrolab-project.eu

Dissemination level	PU