Universitat de Girona
Facultat de Medicina

**FINAL DEGREE PROJECT**
Department of Pediatrics

# A COMPARATIVE STUDY OF DUPILUMAB VERSUS OMALIZUMAB IN SEVERE PEDIATRIC ASTHMA

A multicenter, randomized and controlled clinical trial

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# 1. ABSTRACT

**TITLE:** A comparative study of dupilumab versus omalizumab in severe pediatric asthma.

**BACKGROUND:** Asthma is a very common chronic respiratory disease The prevalence is increasing in many countries, especially among children. Majority of children with asthma respond well to standard therapies, however a significant proportion still have severe disease that is resistant to conventional therapies.

Biologic therapies are increasingly being considered in children with severe asthma. Monoclonal antibodies as add-on therapy have been shown to reduce exacerbations and improve symptom control, improving patients' quality of life. Although all biologic therapies have demonstrated significant benefits, each has its own particular characteristics. Selecting the most appropriate therapy for an individual patient is a challenge for specialists, as there are no established algorithms available to assist choice.

**AIM:** To compare the efficacy of different biologic therapies, dupilumab and omalizumab, in children with uncontrolled asthma with a combination of high dose inhaled corticoesteroids (ICS) and long-acting $\beta_2$-adrenergic agonist (LABA). This strategy is expected to reduce the number of emergency department visits and admissions to hospital due to asthma worsening. A reduction in the use of systemic corticosteroids and a better control of the disease are also expected.

**METHODS:** A prospective multicenter clinical trial will be conducted in 388 patients diagnosed with asthma who remain uncontrolled with high dose of ICS combined with LABA. All hospitals in the province of Girona will participate in this study. Hospitals participating will recruit study subjects by consecutive sampling and divide them into two groups, the intervention group and the control group. Intervention: Both groups will be equally informed of all non-pharmacological strategies for asthma management and both will continue with their baseline treatment. The intervention group will receive add-on treatment with dupilumab while the control group will receive omalizumab. Outcomes: Asthma control level, ACT score and total number of exacerbations, emergency department visits, hospital admissions and use of systemic corticosteroids during the intervention time will be evaluated. At the end, a statistical analysis of the data collected will be performed, taking into account all covariates.

**KEY WORDS:** Asthma, severe asthma, stepwise treatment strategy, exacerbation, asthma control test, emergency department visits, admissions to hospital, oral glucocorticoids, monoclonal antibodies, biologic therapies, omalizumab and dupilumab.

## 2. ABBREVIATIONS

ACT: Asthma Control Test.

AE: Asthma Exacerbation.

AH: Admissions to Hospital.

ASM: Airway Smooth Muscle.

BAL: Bronchoalveolar Lavage.

c-ACT: Childhood Asthma Control Test.

CEIm: Comitè d'Ètica d'Investigació amb Medicaments.

ECM: Extracellular Matrix.

ED: Emergency Department.

EMA: European Medicines Agency.

$FE_{NO}$: Fractional Exhaled Nitric Oxide.

$FEV_1$: Forced Expiratory Volume in the first second.

$FEV_1$/FVC: Relation between Forced Expiratory Volume in the first second and Forced Vital Capacity.

FOB: Fiberoptic Bronchoscopy.

FVC: Forced Vital Capacity.

GEMA: Guía Española para el Manejo del Asma.

GRANMO: Sample calculator.

ICS: Inhaled Corticoesteroids.

ICU: Intensive Care Unit.

IgE: Immunoglobulin E.

INF-α: Interferon α.

ISAAC: International Study of Asthma and Allergies in Childhood.

LABA: Long-acting $\beta_2$-adrenergic Agonist.

LAMA: Long-acting Muscle Receptor Antagonists.

LTRA: Leukotriene Receptor Antagonist.

mAb: Monoclonal antibody.

MDI: Metered Dose Inhaler.

OGC: Oral Glucocorticoids.

PICU: Pediatric Intensive Care Unit.

SABA: Short-acting $\beta$-agonist.

$SaO_2$: Oxygen Saturation.

sIgE: Serum specific IgE.

SPT: Skin Prick Test.

TSLP: Thymic Stromal Lymphopoietin.

# 3. INTRODUCTION

Asthma is a heterogeneous disease characterized by chronic inflammatory of the airways involving different cells and inflammatory mediators with bronchial hyperresponsiveness and variable airflow obstruction, fully or partially reversible, either by drug action or spontaneously (1).

## 3.1 PREVALENCE

Asthma is a common chronic disease in childhood and adolescence, with a prevalence that varies between geographical regions and age groups (2). The global prevalence, morbidity and mortality related to childhood asthma among children has increased significantly over the last years (3).

According to the International Study of Asthma and Allergies in Childhood (ISAAC) the prevalence of childhood asthma in Spain is 10%, similar for the European Union (4,5), being more predominant in coastal areas (2).

## 3.2 PHYSIOPATHOLOGY

The pathophysiological features of asthma are chronic inflammation of the entire airway system, associated with hyperreactivity of the epithelium to direct or indirect triggers and consequent bronchoconstriction leading to expiratory airflow limitation and the manifestation of respiratory symptoms. Allergens, viruses or tobacco smoke are known factors that induce chronic airway inflammation (6).

Chronic airway inflammation is the common pathologic feature of all asthma phenotypes and is always present although it does not necessarily correlate with severity and symptoms (1). Both innate and adaptive immune system are involved in the chronic airway inflammation. Chronic airway inflammation subsequently causes airway edema, mucus hypersecretion, mucus plugging and airway remodeling.

The main immune cells involved in the inflammatory response are T helper lymphocyte types 1, 2 and 17, with a predominance of Th2. These cells lead the eosinophilic inflammation producing interleukin that induces B lymphocytes increasing IgE production. The underlying genetic predisposition is also relevant, there are some genes know to be associated with asthma such as ADAM33, PHF11, DPP10, GPRA and SPINK5.

**Th1 response:** The Th1 response is often activated in infections, particularly by viruses, but are also involved in airway inflammation.

**Th2 response:** Airway dendritic cells present inhaled allergens to naive T cells, activating the production of Th2 cells, which release cytokines including IL-4, IL-5, IL-9 and IL-13. IL-4, IL-9 and IL-13 stimulate B cells to liberate IgE. IgE then triggers mast cell degranulation and the secretion of mediators (histamine and leukotrienes) that cause bronchoconstriction.

These pathways are mediated by cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin. IL-25 induces the expression of IL-4, IL-5, IL-9 and IL-13, while IL-33 activates dendritic cells to produce IL-5 and IL-13. IL-5 is important for the maintenance of eosinophils, while IL-9 and IL-13 contribute to the production of mucus.

**Th17 response:** Th17 cells produce both IL-17 and IL-22, which induce asthma airway remodelling. IL-17 promotes neutrophilic airway infiltration and induces the airway epithelial to mesenchymal morphological transition, while IL-22 increases smooth muscle mass. (7)

Other immune cells that participate in this inflammatory response are mast cells, which induce bronchoconstriction and generate proinflammatory factors (8).

We already know there is extensive remodeling of the airways in asthmatic disease. Such remodeling is characterized by thickened abnormal epithelium with mucus gland hypertrophy, subepithelial membrane thickening and fibrosis with altered extracellular matrix (ECM) composition and deposition, angiogenesis, and importantly increased airway smooth muscle (ASM) mass. The increase in the deposition of ECM proteins and associated fibrosis also contributes (9). This airway remodeling is associated to a progressive decrease of lung function (1).

The ASM is a modulator of airways responsiveness. Because of the activity of breathing, the ASM is subject to a constant stress and strain load, which fluctuates. Tidal breathing leads to muscle elongation, which can effectively depress the active force generated. This endogenous bronchodilating response due to periodic stretch from breathing or from involuntary or voluntary deep inspirations prevents airway closure in normal individuals but is ineffective in asthma. Bronchoconstriction compresses the epithelium and results in increased ASM mass and increased contraction, which, in turn, may further increase the degree of constriction. Therefore, there is a positive feedback loop of bronchoconstriction in asthma involving ASM remodeling (10).

Bronchial hyperresponsiveness, a key feature of asthma, causes a narrowing of the respiratory tract in response to stimuli that are innocuous in individuals without asthma. It is linked with airway inflammation and healing and is partially or totally reversible with treatment.

All these pathophysiological factors described above lead to airway narrowing, the origin of most symptoms. This airflow limitation and the symptoms it triggers may resolve spontaneously or in response to medication (reversibility) and even be absent for certain periods of time (1).

## 3.3 RISK FACTORS

In reference to risk factors, there are factors that are related to asthma development and others that can trigger asthma symptoms. Several genetic and epigenetic factors are involved in asthma's pathophysiology in different ways (11). Genes are likely to interact with other genes and environmental factors to define susceptibility to asthma (12).

Sex-related prevalence differences are greatly associated with age. In childhood, asthma is more common in boys, while adult asthma is more common in women. This fact suggests that sex hormones may play a role in the pathogenesis of certain types of asthma.

A lot of environmental factors seem to play a role in asthma development. While some of them may trigger asthma symptoms, other factors, depending on the time of exposure, may be both protective factors for the development of asthma and triggering factors, this is observed with cat or dog exposure (13). Most important factors are:

- **Allergens**: Most school-aged children with asthma are sensitized to at least one indoor allergen. Dust mites are one of the most common allergens involved in the development of asthma, and sensitization has been linked to asthma exacerbation. Other usual allergens are cats, dogs, mold, trees, or pollen. Many allergens are indoor and therefore hard to be avoided.
- **Air pollution**: Air pollution is linked to asthma exacerbations, as well as the development of asthma. Ozone, nitrogen dioxide, sulphury dioxide, carbon monoxide, heavy metals and particulate matter have been implicated as the likely causative agents. Pollution contributes through oxidative damage which stimulates airway remodeling, increased inflammation and boosting of aeroallergen sensibilization (14).
- **Tobacco smoke exposure**: Maternal and paternal smoking during pregnancy and infancy has been shown to increase the risk of wheezing episodes and childhood asthma. In addition to increasing the risk of asthma, tobacco smoke causes worsening asthma symptoms and higher rate of asthma exacerbations. This risk does not appear to be dose dependent (13).
- **Vitamin D deficiency:** The activation of Vitamin D and its receptor has been shown to have immunomodulatory and anti-inflammatory properties.

Vitamin D may also play a role in airway remodeling, through changes on epithelial cells and alveolar macrophages and guide transcription of proinflammatory cytokines. Deficiency of vitamin D is related to poor asthma outcomes including lung function, worse symptomatology, and more frequent exacerbations. Moreover, low maternal levels of vitamin D during pregnancy have been associated with increased incidence of wheezing in children.

- **Gastrointestinal and respiratory microbiome:** Exposure to various environmental microorganisms early in life may contribute to limiting atopic disease. It is suggested that exposure is protective due to immunological changes stimulated by exposure to endotoxins, muramic acid and extracellular polysaccharides. Inhalation is the main mechanism of exposure, but oral exposure can also result in a diverse microbiome, for example children who consume unpasteurized milk are at lower risk of atopic diseases. However, some exposures in early life can cause microbial dysbiosis, which is the case with long-term antibiotic use.
- **Infections**: The theory known as the "Hygiene Hypothesis" proposes that exposure to infections at an early age is related to a lower incidence of asthma and a lower prevalence of allergic disease (15).
- **Stress**: Stress disrupts immune, neuroendocrine, and autonomic function causing changes to normal lung growth and development.

## 3.4 DIAGNOSIS

In order to diagnose asthma in a child, the health care professional needs a combination of a history of symptoms that explain the typical clinical features, such as wheezing, and also a pulmonary function test that demonstrates both expiratory airflow limitation and its reversibility.

### 3.4.1 CLINICAL FEATURES

There are some signs and symptoms known as guide symptoms that help the physician to create a pattern to evaluate the patient. These symptoms are wheezing (most distinctive), dyspnea, coughing and chest tightness.

Often these symptoms vary over time and in intensity, also can be worse at night or in the early morning, and are caused by different triggers (viral infections, allergens, tobacco smoke…). However, none of these symptoms are specific for asthma.

**Anamnesis:** During anamnesis it is very important to ask about onset of symptoms, presence of chronic rhinosinusitis with or without polyps, rhinitis, dermatitis and family history of asthma or atopy. The presence of both personal

and familiar atopy is the strongest risk factor for the subsequent development of asthma (16).

**Physical examination:** Most characteristic is wheezing on auscultation and sometimes nasal obstruction on anterior rhinoscopy and dermatitis or eczema. However, a normal physical examination does not exclude the diagnosis of asthma (16). In children, wheezing is an important sign but difficult to assess in early childhood (17).

### 3.4.2 LUNG FUNCTION TESTS

A patient with suspected asthma usually is not diagnosed until a lung function test demonstrates, objectively, an expiratory airflow limitation.

Assessing the diagnosis of asthma in children younger than 6 years old with lung function tests is very difficult due to the difficulty in performing an adequate technique. However, it has proven feasible with confidence in a large percentage of cooperating preschool children (18).

In children, lung function tests are less useful than in adults because most children with asthma, have values of $FEV_1$ in a normal range. This is because young children have a proportionally longer airway relative to lung volume compared to older children and adults. These tests could help in asthma diagnosis in children but have little power discriminating according to severity (18,19).

The most used lung function tests used in the diagnosis of pediatric asthma are:

#### SPIROMETRY

Spirometry is the gold standard test for asthma. It measures lung volumes and flows generated in a voluntary maximal expiratory manoeuvre and provides information about airflow obstruction. The main parameters to determinate are both forced expiratory volume in the first second ($FEV_1$) and forced vital capacity (FVC), and the ratio $FEV_1$/FVC. $FEV_1$ is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration. FVC is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration (20).

Three respiratory functional patterns are considered: obstructive, restrictive, and mixed. The obstructive pattern is defined by a decrease in $FEV_1$ and $FEV_1$/FVC ratio (< 80-85%) and is the one found in asthmatic patients. A reduced score in $FEV_1$ helps to assess asthma severity and risk of exacerbation. However, since $FEV_1$ can be found to be decreased in many other lung pathologies, the most

important parameter for identifying an obstructive impairment in patients is the $FEV_1$/FVC ratio (18,21).

### BRONCHODILATOR TEST

The bronchodilation test is used to study the reversibility of intrapulmonary airflow obstruction. It requires a basic spirometry test to be performed and repeated some time after the administration of a bronchodilator drug, β-adrenergic agonists are used, especially salbutamol 100 µg four doses separated by 30-second intervals. It is very useful for the diagnosis of asthma and should be used as a routine at the first appointment. However, most children have intermittent or mild asthma so in many cases the test will be negative (18).

Values of reversibility that define a positive bronchodilator test are an increment of $FEV_1$ greater than 12%, or ≥ 9% with respect to the theoretical value and 200mL with respect to basal spirometry. It is quite specific, but not highly sensitive. In children, just with the increment of $FEV_1$ being greater than 12% it's possible to establish asthma diagnosis even if it's below 200mL (21,22).

### PROVOCATION TEST

When in doubt, the exercise provocation test is of special interest as it is a simple, reproducible test with high specificity for the diagnosis of asthma, although with low sensitivity. It is positive if causes a fall in $FEV_1$ > 12%. Other bronchial provocation tests can be performed with methacholine, histamine, adenosine, mannitol, hypertonic saline or hyperventilation, although these are less used in pediatrics (16,22).

## 3.4.3 ALLERGY TESTS

The aim of allergy studies is to determine the existence of sensitization to aeroallergens that influence the development of the allergic asthma phenotype, or that trigger exacerbations. For the diagnosis of allergic asthma, in addition to sensitization to inhaled allergens, it is necessary to verify the clinical relevance of the results obtained.

It is essential to include in the anamnesis the season of the year and the location where asthma symptoms are most prevalent, for example if a patient only reports symptoms in the summer, and the results of allergy tests are positive for tree or grass pollen, the trigger is likely to be grass pollen allergy because the pollination period of trees occurs in early spring. Although it can be difficult at sometimes to associate clinical allergy with exposure to the allergen.

The tests performed are skin prick test (SPT) or serum specific IgE (sIgE), both tests show comparable results in the identification of clinically sensitizations. SPT is the method of choice because of its high sensitivity, low cost and immediate assessment. Testing serum IgE has the advantage that can be performed on patients who are taking antihistamines (23).

### 3.4.4 OTHER TESTS

Other tests can be performed to obtain more information such as fractional concentration of exhaled nitric oxide ($FE_{NO}$) or peak flow variation, but have less weight in diagnosis (16).

## 3.5 EXACERBATIONS

Asthma exacerbation (AE), also termed asthma “attack” or “episode” is a frequent condition in pediatric practice. Exacerbations are characterized by acute or subacute episodes of progressively increasing asthma symptoms (cough, wheeze, or breathlessness) associated with fall in lung function. The most frequently included outcomes of exacerbations are the need for systemic corticosteroids, emergency department (ED) visits, and admissions to hospital (AH).

AE are more prevalent in patients with severe or poorly controlled asthma but can appear in all asthmatic patients. Aggravations are usually due to a combination of different factors such as exposure to environmental triggers or low treatment adherence but sometimes no trigger can be identified. The most frequent contributing factors are viral respiratory infections and exposure to allergens but there are others including outdoors air pollution such as tobacco smoke or seasonal changes (24).

### 3.5.1 DIAGNOSIS

The diagnosis of an AE is mainly based on clinical findings, it is more sensitive than other lung function tests and can be explored faster. Severe attacks can lead to a fatal outcome, so it is important to recognize red flag symptoms for them to receive more intensive care.

Severe AE are events that require urgent action to prevent a serious outcome, such as hospitalization or death. The definition should include at least one of the following:

- Use of systemic corticosteroids or an increase from a stable maintenance dose for at least 3 days. Courses of corticosteroids separated by one week or more should be treated as separate severe exacerbations.

- A hospitalization or ED visit because of asthma requiring systemic corticosteroids.

Moderate AE should include one or more of the following: deterioration in symptoms, deterioration in lung function, and increased use of short-acting β-agonist (SABA) bronchodilator. These symptoms should last for two days or more but not be severe enough to require use of systemic corticosteroid and/or hospitalization or ED visits (25).

### 3.5.2 SEVERITY CLASSIFICATION

The time of evolution of the crisis, pharmacological treatment administered, existence of associated diseases and possible risk factors (previous intubation or ICU admission, hospitalization in the previous year, frequent ED visits in the last year and/or use of oral glucocorticoids (OGC) and excessive use of SABA in the previous weeks) should be considered.

The estimation of severity is based on clinical criteria (respiratory frequency, wheezing and the existence of sternocleidomastoid muscle retractions). Although no well-validated scale is available, Pulmonary Score is simple and can be applied to all age groups. The clinical findings, combined with oxygen saturation ($SaO_2$), provide an assessment of the severity of the episode (26).

*Table 1 Pulmonary Score for clinical assessment of asthma attacks in children*

| Punctuation | Respiratory rate | | Wheezing | Use of sternocleidomastoid |
|---|---|---|---|---|
| | < 6yo | ≥ 6yo | | |
| **0** | < 30 | < 20 | Absent | Absent |
| **1** | 31 – 45 | 21 – 35 | End of exhalation | Slight increase |
| **2** | 46 – 60 | 36 – 50 | Whole exhalation (stethoscope) | Increased |
| **3** | > 60 | > 50 | Inspiration and expiration without stethoscope* | Maximum activity |
| Each item is scored from 0 to 3 (minimum 0, maximum 9). *If there is no wheezing and sternocleidomastoid activity is increased, score the wheezing section with a 3. | | | | |

*Table 2 Global assessment of the severity of asthma exacerbation in children integrating Pulmonary Score and oxygen saturation ($SaO_2$)*

| | Pulmonary score | $SaO_2$ |
|---|---|---|
| **Slight** | 0 – 3 | > 94% |
| **Moderate** | 4 – 6 | 91 – 94% |
| **Severe** | 7 – 9 | < 91% |
| In case of discordance between clinical score and oxygen saturation, the most severe one will be used. | | |

## 3.5.3 MANAGEMENT OF EXACERBATIONS

### MANAGEMENT OF ACUTE ASTHMA AT HOME

Families with children already diagnosed with asthma should have a clear plan for the treatment of exacerbations and the right medication. The appropriate treatment to be administered in such instances is a short-acting β2-agonist (SABA) inhaler, the early administration of SABA and review by parents is more important than the actual dose administered. Child should be re-evaluated 15-20 min after administration and the dose should be repeated if there is persistence of symptoms. If there is an improvement, the child returns to receiving daily regular medication as prescribed but if the symptoms persist after two or three such doses, parents are advised to seek medical assistance.

Controversy continues over whether it is better to use home nebulizers vs metered dose inhaler (MDI) with spacer. Studies have shown equal efficacy between both methods and the superiority of MDI with spacer as it is more economic, easily transportable, and quicker to use.

Most children who require only a few doses of SABA at home do not benefit from oral corticosteroids. However, children who have had major exacerbations in the past or who have been previously in pediatric intensive care unit (PICU) for asthma should take oral prednisolone 1-2 mg/kg in 1 or 2 divided doses for 3 to 5 days (27).

### MANAGEMENT OF SEVERE ACUTE ASTHMA IN THE ED

Management should start with a structured ABCDE approach (airway, breathing, circulation, disability, and exposure) followed by a detailed history and examination if the patient's clinical condition allows it.

SABA, particularly salbutamol, is always the first choice and given preferably using an MDI with spacer, 4–8 puffs are given in over three cycles in 20-min intervals over an hour. Typically, in severe cases with inability to complete short sentences, inspiratory and expiratory wheezing, and $SaO_2$ below 92%, nebulizers are used (27). Although this is changing as MDI and valved holding chamber have been shown to be more effective than nebulizers in reducing hospital admissions, better $SaO_2$, and fewer tachycardia even in severe exacerbations (28).

Children are then reassessed and, if necessary, given an additional course of SABA, but this time with the addition of ipratropium. In certain severe attacks, ipratropium may be administered at first. Systemic glucocorticoids are also the other mainstay of treatment, and are administered as soon as possible, preferably oral prednisone (27).

Intravenous magnesium sulphate can be started as an additional treatment in patients resistant to standard therapy. In smooth muscle, magnesium decreases intracellular calcium causing muscle cell relaxation and bronchodilation. Magnesium also reduces inflammatory mediators. Even though it is generally safe, patients need to be monitored for hypotension (29).

If there is an inadequate response to the treatment provided so far and the child is cyanotic, lethargic, unable to maintain respiratory effort and with altered mental status, he/she should be sent to the PICU (27).

## 3.6 ASTHMA MANAGEMENT AND TREATMENT

The main goals of asthma treatment should focus on achieving good control of symptoms and minimizing future risk. Optimal treatment should provide a good quality of life, where symptoms do not impede patients from exercising, and with no need for reliever medication (30).

### 3.6.1 NON-PHARMACOLOGICAL STRATEGIES

Apart from the pharmacological treatment, it is very important for the patient to follow certain routines to aid in the control of the disease. In general, these recommendations focus on the avoidance of triggers.

#### EDUCATION

Educating patients about asthma management is an essential piece in treatment strategy. Asthma self-management education programs improve lung function and sense of self-control, reduce school absence, number of days with restricted activity, number of ED visits, and number of disrupted nights (31). Patients need to be well informed on how to use inhalers because a large majority of patients make inhalation errors. Suboptimal inhaler technique is associated with increased risk of hospitalization and poor disease control (32).

#### TOBBACO AVOIDANCE

Passive and active smoking increases the risk of asthma-related hospitalization and poor asthma control. It has been shown that since smoke-free law was implemented, visits to ED for asthma have decreased (33).

#### AVOIDANCE OF INDOOR ALLERGENS

It's difficult sometimes to establish measures to avoid those substances because multiple factors are involved, and patient reactions can depend on other multiple factors. Most evidence recommendations are encasing bedding in mite-impermeable covers (34) and cockroach baits placed in the household (35).

### DIETARY-HYGIENICAL RECOMMENDATIONS

Physical activity is known to be an important triggering factor of exercise-induced bronchoconstriction. However, it has been proven that exercise is very safe in children with asthma if there is adequate asthma control. Better fitness can improve asthma symptoms, control, and quality of life, in addition to the known benefits for cardiovascular health.

Following a healthy diet is also relevant, a high refined cereal diet, highly processed foods, red meat, fried foods and low intake of fruits and vegetables has been shown to have a pro-inflammatory effect, which worsens the outcome of asthma. In contrast, the Mediterranean diet, rich in fruits, vegetables, and whole grains, has anti-inflammatory properties. Moreover, obesity is a risk factor for both asthma development and increased asthma morbidity (36). Higher body mass index has been studied to involve worse asthma control and quality of life, independent of age, sex, and asthma severity (37).

## 3.6.2 PHARMACOLOGICAL TREATMENT

Pharmacologic treatment is the mainstay of asthma management, it is vital to follow a consensual plan between patient and physician to establish the main objectives and the best way to achieve them.

In the management of asthma, drugs are expected to act locally in the airway to provide a faster response, a greater amount of drug in the lung cells and fewer or nonexistent systemic effects. Therefore, the preferred way of administration is inhaled therapy, which gives better results than other methods but has some associated disadvantages, such as problems in adopting the correct inhaled technique. Inhalation devices are used incorrectly in many asthmatic children as the technique involves a good coordination. It is important to have a good training in order to ensure that drug intake is accurate (38,39).

## 3.6.3. ASTHMA MEDICATION CATEGORIES

A distinction must be made between preventive or maintenance medication and rescue medication. Maintenance drug therapy is administered daily and there are several options available such as inhaled corticoesteroids (ICS), leukotriene receptor antagonists (LTRA), long-acting $\beta_2$-adrenergic agonists (LABA), long-acting muscle receptor antagonists (LAMA), monoclonal antibodies (mAb) and oral glucocorticoids (OGC). Rescue medicines are used on demand to treat bronchoconstriction rapidly. These include inhaled SABA (of choice), inhaled anticholinergics (ipratropium bromide) and systemic corticosteroids (40).

There are also add-on therapies, proposed for patients with persistent severe asthmatic symptoms and exacerbations, despite treatment with high doses of controller medications (41).

## 3.6.4 MEDICATION OPTIONS

Among all pharmacological alternatives, the most commonly used as maintenance tratment are the following:

### INHALED CORTICOSTEROIDS (ICS)

Low-dose ICS are the treatment of choice for the maintenance therapy of asthma due to their high local anti-inflammatory effect (42). Other characteristics are their high affinity and selectivity for their receptor, their prolonged permanence in the lung and their low oral and systemic biodisponibility. The most used ones are budesonide and fluticasone, although there are several more.

The dose-response curve shows an increasing trend up to medium doses, after which the curve flattens. Increasing doses add little therapeutic effect at the cost of a higher risk of adverse effects. Therefore, from medium to high doses, it is more effective to add a second drug in combination with ICS (40). The most worrying adverse effect is delayed stature, so the minimum effective dose should always be used to prevent it. The use of the inhaled via minimizes its systemic side effects (43).

### LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA)

LTRA drugs have demonstrated their efficacy in mild to moderate asthma due to their anti-inflammatory and bronchodilator properties. The most widely used is montelukast, which blocks the binding of LTE4 (the most common in the airways) to its receptor (40). They can be used in combination with ICS or in monotherapy, although ICS are more effective than LTRA in monotherapy (44). LTRA may produce side effects such as abdominal pain and sleep disturbances (40).

### LONG-ACTING β2-ADRENERGIC AGONISTS (LABA)

The use of LABA associated with ICS is recommended as an alternative treatment for uncontrolled patients receiving medium doses of ICS. LABA should always be associated with an ICS, since their use in monotherapy as preventive medication or as a rescue bronchodilator in children is not indicated. There are different combinations available such as salmeterol/fluticasone propionate or formoterol/budesonide among others. The side effects that may occur are tremor, headache, tachycardia, palpitations, arrhythmias, dizziness, chest pain and in rare cases bronchospasm (45).

### LONG-ACTING MUSCLE RECEPTOR ANTAGONISTS (LAMA)

Tiotropium bromide is the only LAMA authorized for management of patients ≥ 6 years old with severe asthma who have experienced one or more severe asthma exacerbations in the last year despite treatment with a high-dose ICS and a second controller drug (46). Acetylcholine is responsible for stimulating bronchoconstriction. Tiotropium bromide reversibly binds to the M1, M2, and M3 receptors of the airway smooth muscles, and prolongedly blocks the effects of the acetylcholine released by parasympathetic nerve endings. LABA have shown improvement in lung function and reduction in the risk of exacerbations (47). Adverse effects are mild to moderate in intensity and include nasopharyngitis, bronchitis and pharyngitis (46).

### ORAL GLUCOCORTICOIDS (OGC)

Add-on low dose OGC may be considered but may be associated with potential side effects especially in long-term treatments. Prednisolone is the most used steroid for maintenance therapy. Potential adverse effects of OGC are growth retardation, adrenal suppression and alteration of skin and bone metabolism. For this reason, blood pressure, urine, blood sugar, cholesterol, bone mineral density and growth should be regularly monitored (41,48).

### MONOCLONAL ANTIBODIES (mAb)

Biologic therapies are increasingly being considered in patients with severe asthma. They are targeted to treat the underlying inflammation through blockade of different mediators. There are currently four mAb therapies available for children with severe asthma (49). mAb will be explained in detail below.

## 3.6.5 CONTROL-BASED ASTHMA MANAGEMENT

Initial control therapy based on ICS should be initiated as soon as possible after the diagnosis of asthma, as it has been shown to improve the patient's quality of life as well as improve future levels of asthma control.

Both pharmacological and non-pharmacological treatments should be adapted and individualized to each patient on a continuous cycle of evaluation, adjustment, and revision (50).

## 3.6.6 STEPWISE TREATMENT STRATEGY

Considering that the main objective is to achieve control with as few medications as possible, treatment should be adjusted continuously, always considering nonpharmacological measures, therapeutic adherence and risk factors that can be modified. Maintenance treatment will be initiated based on the initial severity

level. Subsequently, severity will be rated according to treatment level needed to maintain symptom control.

GEMA (Guía Española para el Manejo del Asma) updated last 2023 has published a personalized stepwise management protocol, with progressively increasing treatment potency. The following figure summarizes the information on relief and control medication at each level, with preferred options and other available treatments (26).

| Stepwise treatment | Maintenance treatment ≥ 4 years | Maintenance treatment < 4 years |
|---|---|---|
| 1 | Without control medication. | |
| 2 | **Low-dose ICS** or LTRA. | **Low-dose ICS** or LTRA. |
| 3 | **Average-dose ICS** or **low-dose ICS + LABA** or low-dose ICS + LTRA | **Average-dose ICS** or low-dose ICS + LTRA |
| 4 | **Average-dose ICS + LABA** or average-dose ICS + LTRA | **Average-dose ICS + LTRA** |
| 5 | **High-dose ICS + LABA**. If no control, add LTRA or tiotropium. | **High-dose ICS + LTRA**. If no control, consider adding LABA**, macrolides, tiotropium** or OGC. |
| 6 | **High-dose ICS + LABA** + omalizumab* or other biologic therapies or OGC. | |

Consider immunotherapy

RELIEF MEDICATION

*Table 3 Stepwise treatment of asthma in pediatrics according to level of control. Data extracted from GEMA 5.3 guideline.*

ICS: Inhaled corticosteroids; LTRA: Leukotriene receptor antagonists; LABA: Long acting β2-adrenergic agonists; OGC: Oral glucocorticoids. *For ages 6 years or older. **Off-label.

**Step 1:** Children with occasional asthma symptoms, without night-time symptoms and with no risk factors for exacerbation. Only the use of on-demand bronchodilators (SABA) is recommended. If there is any risk factor for exacerbation, step 2 treatment should be initiated, even if asthma symptoms are not frequent. From 12 years of age onwards, the use of formoterol associated with ICS may be considered, same as in adults.

**Step 2**: Children with a need for SABA two or more monthly, without inter-crisis symptoms and with normal lung function. Low doses of ICS are prescribed although montelukast (LTRA) can also be recommended as an alternative.

**Step 3-4**: Children with more than 6-8 asthma episodes in a year, symptoms in inter-crisis intervals, asthma awakenings once a week and/or lung function compromise. Three options are considered: ICS at medium doses, associating a LABA to low doses of ICS (step 3), associating it to medium doses (step 4) and, in children under four years of age, associating montelukast to low doses of ICS.

**Step 5-6**: Children with persistent symptoms, requirement of short cycles of OGC, wheezing with minimal effort and lung function affectation. Treatment should be initiated at step 5 (high-dose ICS/LABA) and, as soon as control is established, step down to the lowest effective dose.

If control is not achieved, add one or more of the following drugs in children under 4 years old: LABA (off-label), tiotropium (off-label), macrolides or even OGC. In those older than 6 years we consider adding tiotropium, mAb or OGC.

## 3.7 SEVERE ASTHMA IN CHILDREN

### 3.7.1 SEVERE ASTHMA: DEFINITION AND EVALUATION

Severe asthma is defined as asthma which requires treatment with high dose ICS plus a second controller (and/or systemic corticosteroid) to prevent it from becoming uncontrolled or remains uncontrolled despite this therapy. Majority of children with asthma respond well to standard therapies, however a significant proportion still have severe disease (51). Almost 5% of asthmatic children are considered to have severe asthma, although some studies estimate its prevalence to be around 8.8% (49).

Children with severe asthma experience frequent AE, loss of lung function, poorer quality of life and high risk of adverse effects from the medication they receive, all of which leads to an increase in the number of unscheduled visits, ED visits, hospitalizations and days of absence from school and work for their caregivers. Moreover, they have an increased risk of future chronic obstructive pulmonary disease (49).

Misdiagnosis of non-asthmatic conditions as uncontrolled asthma has been described in 12-30%. Conditions that may mimic asthma include vocal cord dysfunction, cardiac insufficiency, poor physical fitness, cystic fibrosis or tracheomalacia.

Therefore, the first step is confirming the diagnosis of asthma. To confirm the diagnosis, the first thing to do is a detailed anamnesis, family history and a complete physical examination. The next step is obtaining a spirometry with pre and post bronchodilator responses to evidence reversibility of intrapulmonary airflow obstruction. If there is no evidence of obstruction, then bronchoprovocation testing should be performed. In severe cases we may perform a thoracic X-ray to rule out anatomical abnormalities of the airways, lung parenchyma and heart. Additional testing to exclude other diagnoses should be guided by clinical suspicion or atypical presentation.

After confirming the diagnosis of asthma, it is important to differentiate between severe asthma and difficult-to-treat asthma. Difficult-to-treat asthma is linked to

poor control due to associated comorbidities, poor medication adherence, or psychological or environmental factors. By contrast, treatment-resistant asthma is defined as difficult asthma even though these factors are managed and controlled (51,52).

Control failure is evidenced by:

- c-ACT (Childhood Asthma Control Test) or ACT (Asthma Control Test) score below 20. ACT is used to make a subjective evaluation of the patient's symptom control.
- ≥ 2 Severe AE or having received ≥ 2 cycles of OGC (of ≥ 3 days each each) in the previous year.
- ≥ 1 Admission to hospital for severe AE in the previous year.
- Chronic airflow limitation ($FEV_1$/FVC ratio < 0.7 or $FEV_1$ < 80% of predicted) after use of adequate treatment (if best $FEV_1$ is greater than 80%) (53).

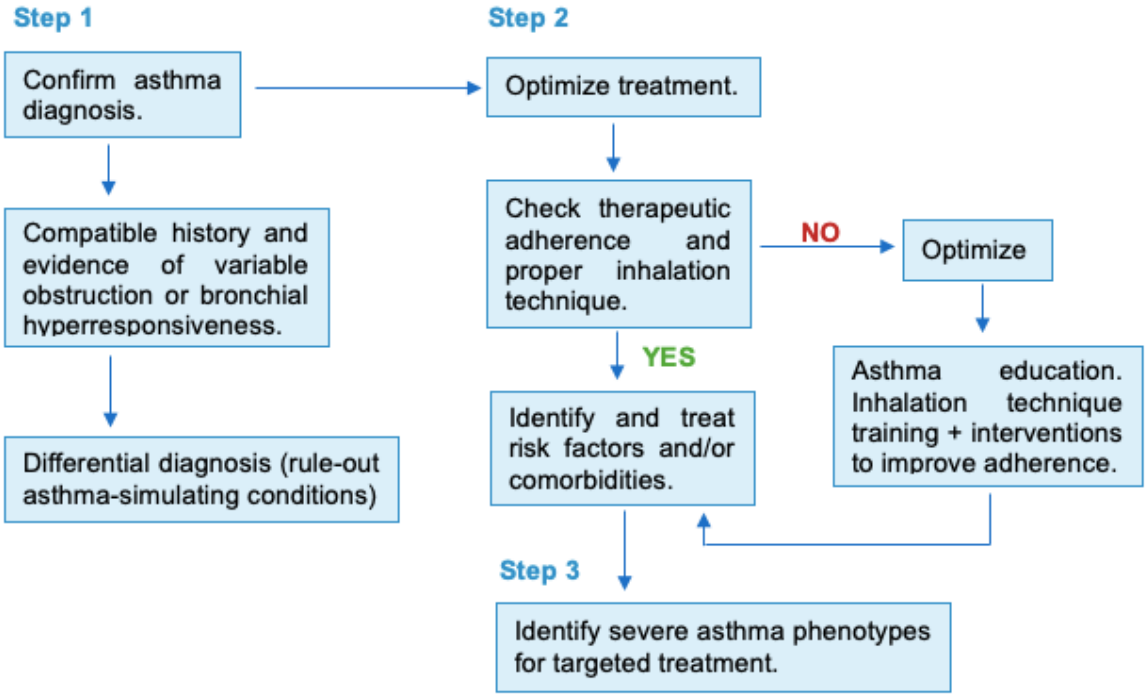



*Figure 1 Stepwise sequential diagnostic decision algorithm in the management of severe uncontrolled asthma. Data extracted from GEMA 5.3 guideline.*

## 3.7.2 PHENOTYPES OF SEVERE ASTHMA

Severe asthma is a heterogeneous syndrome with multiple clinical variants. Over the past years, phenotypes of severe uncontrolled asthma have been studied exhaustively. Phenotype is defined as an observable feature of severe asthma that may be linked to an underlying mechanism called endotype. Establishing phenotype in patients with severe uncontrolled asthma is important as it may lead to differential treatment and prognostic implications (53).

In childhood, asthma has been classified in different phenotypes and endotypes which can be summarized in two main groups according to airway inflammation: type 2 (T2)-high (eosinophilic inflammation) asthma or T2-low (neutrophilic/ paucigranulocitic inflammation) (51).

## T2-HIGH ASTHMA: THE ALLERGIC PHENOTYPE

T2-high asthma is the most common phenotype, 85% of asthmatic children present with it. This phenotype is associated with allergic sensitization and is mediated by T-helper type 2 (Th2) cells.

T2-high asthma is characterized by eosinophilic airway inflammation and activated by innate epithelial cytokines such as iL-25, iL-33 and thymic stromal lymphopoietin (TLSP) secreted by the airway epithelium in response to various stimuli like allergens, smoke, pollutants, or microorganisms.

This pathway leads to the release of iL-4, iL-5, and iL-13 from innate (innate lymphoid cells type 2) and adaptive immunity (CD4 T cells, eosinophils, and basophils). These type 2 cytokines are responsible for eosinophil and mast cells maturation and activity and for IgE synthesis (54).

There are invasive tests such as fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL), endobronchial biopsy and brushing that provide information on airway eosinophilia. Such tests are also able to identify anatomical abnormalities or subacute infections. Although in clinical practice we dispose of less invasive biomarkers that can suggest airway eosinophilia such as $FE_{NO}$, blood eosinophils and total serum IgE. Blood eosinophilia has been shown to be predictive of AE (54,55).

T2 phenotype can be differentiated into allergic or eosinophilic although both tend to overlap. T2 allergic asthma is more common and has an atopic origin. Diagnosis requires the demonstration of sensitization to an allergen and the triggering of symptoms with exposure to such allergen. Eosinophilic T2 asthma is characterized by the presence of eosinophils in bronchial samples and sputum and although its prevalence of atopy is lower, IgE and $FE_{NO}$ may be elevated. (53).

## T2-LOW ASTHMA

T2-low asthma is usually mediated by neutrophilic inflammation or, rarely, by a paucigranulocitic inflammation when both eosinophils and neutrophils coexist. iL-8, iL-22 and IL-17 are the main inflammatory cytokines.

In adults the neutrophilic phenotype is often associated to high levels of iL-17a and severe steroid resistant asthma with less evidence of atopy. In contrast,

neutrophilic airway inflammation in children has been correlated with improved lung function, lower doses of ICS, and better asthma control.

There is an association between neutrophilic inflammation of the respiratory tract and the presence of bacteria in the airways such as *Moraxella catharralis*. This is why macrolides are administered in these patients. However, it is rarely used in children because the neutrophilic phenotype is uncommon (54).

### 3.7.3 MANAGEMENT OF SEVERE ASTHMA

Children with persistent symptoms and frequent AE despite appropriate inhaler technique and good adherence to treatment should be referred to an asthma specialist with expertise in management of severe asthma. A step-up therapy is recommended if the symptoms are confirmed to be due to asthma, inhaler technique and adherence are satisfactory, and modifiable risk factors such as allergen or smoke exposure have been addressed (51). Environmental triggers in the school setting should be taken into account, as children spend great part of their day at school (52).

Psychosocial factors should also be considered, it has been proved that children exposed to severe and chronic stressors are at a higher risk of developing severe disease. Additionally, children with severe persistent asthma have higher rates of anxiety, depression and conduct problems, particularly attentional disorders. Parents of children with severe asthma experience significantly higher rates of depression, anxiety and post-traumatic stress disorder, which can influence their ability to manage their kids' asthma (52).

Children with severe asthma ≥ 4 years of age should be treated with high doses of ICS, combined with LABA and other add-on therapies, in accordance with steps 5-6 of the GEMA guidelines. For children under 4 years of age, the recommended treatment is high-dose ICS combined with LTRA (montelukast). There is no strong evidence for secondary prevention of symptoms or prevention of lung function deterioration however, some studies suggest that early treatment with daily ICS may modify disease severity when initiated in childhood, resulting in less severe AE (48).

Medications that may be added to the treatment include LAMA or OGC. Tiotropium bromide is the only LAMA authorized for management of patients ≥ 6 years old with severe asthma. In selected cases, it can be administered in children younger than 6 years old off label (26). Lowest effective dose should be used in OGC treatment, and dose should be gradually reduced to the minimum effective dose that can maintain adequate asthma control. Long-term use of systemic corticosteroids increases risk of systemic side effects such as growth

retardation, adrenal suppression, and altered skin and bone metabolism. Therefore, children undergoing this treatment should be closely monitored (48).

Biologic therapies are increasingly being considered in patient with severe asthma. Biologic therapies currently in market are targeting T2-high asthma. Omalizumab, a mAb against IgE, was the first biologic developed for the treatment of severe allergic asthma. New biologic agents have recently been approved for use in patients with severe asthma, and these will be described in the following section (51).

There are also demonstrated benefits of allergen-specific immunotherapy in symptom control, medication use, and airway hyperresponsiveness. However, most studies include immunotherapy with a unique allergen, while most children with severe asthma are polysensitized. Moreover, allergen immunotherapy should not be initiated in patients with unstable asthma, a situation that is more common among children with severe asthma. Even so, it should be reconsidered once their asthma is better controlled (48).

To conclude, pediatric severe asthma represents a clinical challenge and requires a multidisciplinary approach. The management requires careful evaluation to confirm the diagnosis, rule out asthma masqueraders, address and treat the comorbid diseases, optimize medication compliance, and address environmental and psychosocial factors that affect asthma control.

## 3.8 BIOLOGIC THERAPIES IN PEDIATRIC ASTHMA

Biologic therapies are increasingly being considered in patients with severe asthma. They are targeted to treat the underlying inflammation through blockade of different mediators (49). There are currently four mAb therapies available for children with severe asthma younger than 18. Not long ago, only omalizumab had approval, originally in the United States since 2003 and subsequently in Europe in 2005. European Medicines Agency (EMA) approved mepolizumab in 2015, dupilumab in 2019 and tezepelumab in 2021-2022 (56).

### 3.8.1 THERAPEUTIC OBJECTIVES

Therapeutic objectives may be inherent to the disease itself or be related to comorbidities that patients can present. The objectives inherent to the disease will be discussed in more detail below.

- **Exacerbations**: Intensity of AE is variable, sometimes presenting severe symptoms that can be life-threatening. Suffering one or more severe AE per year or having a course of systemic corticosteroids to treat exacerbations, poses an independent risk of future exacerbations. So,

reducing exacerbations decreases the risk in each individual (57). All approved mAb have been demonstrated to significantly reduce exacerbations to a greater or lesser extent compared to placebo (58). Considering the potential risk of AE, the optimal goal should be the absence of exacerbations.

- **Symptom control**: All approved mAb have been demonstrated to significantly improve symptom control compared to placebo. Therapeutic objective is to obtain a score equal to or higher than 20 on the c-ACT or ACT. Although an increase of ≥ 3 points in ACT score compared to the initial value should also be assessed as relevant (57).

- **Avoid using OGC**: While OGC are effective for many asthma patients, their significant negative side effects make the benefit/risk ratio unfavourable and should be avoided as much as possible. Undesirable effects occur both when administered daily at fixed doses as well as when administered cyclically in the context of AE. The aim is to avoid the patient taking OGC on a fixed regimen and to avoid cyclic use with the control of AE. Reducing the use of both fixed and cyclic OGC to ≤ 50 % of the previous annual rate should also be contemplated as a partial response (57). Mepolizumab and dupilumab reduce the daily dose of OGC with high certainty of evidence (58).

- **Improve bronchial obstruction**: Although all approved mAb seem to be able to improve $FEV_1$ to a greater or lesser extent, the one which have clearly evidenced this feature is dupilumab. Therapeutic aim is to achieve a $FEV_1$ within the normal range (80%) and avoid its decrease (57).

## 3.8.2 APPROVED MONOCLONAL ANTIBODIES

### ANTI Ig-E THERAPY: OMALIZUMAB

#### Mechanism of action

Omalizumab is an anti-IgE humanized mAb produced using recombinant DNA technology. It is approved for children older than 6 years and focused against the constant region of heavy ε chain of free systemic IgE. Omalizumab-IgE complex prevents fusion of FcεR1 binding on B lymphocytes, monocytes, mast cells and basophils, leading to a decrease in the downstream inflammatory cascade and consequently an attenuated allergic response. It was the first mAb approved to manage severe asthma in children (56).

Omalizumab is administered subcutaneously 75-600 mg every 2-4 weeks depending on body weight and serum total IgE levels before starting treatment. Treatment can be carried out at home (53). Omalizumab treatment has been shown to generate a reduction in free IgE levels, suggesting that therapeutic effect may be due to binding of free IgE to prevent IgE-receptor interaction in immune cells and subsequent initiation of an allergic response (59).

Evidence from studies demonstrates that add-on therapy with omalizumab reduces the rate of AE in children with inadequately controlled moderate-to-severe asthma, resulting in better asthma control. Moreover, omalizumab greatly decreases the fall/spring peaks of exacerbations (60).

Interestingly, in a study of a subset of patients treated with omalizumab, investigators, after isolating peripheral blood mononuclear and dendritic cells and stimulating them ex vivo with rhinovirus, found that decreased expression of high-affinity FcεRI was associated with increased secretion of interferon α (INF-α) from dendritic cells. Thus, increased IFN-α response to viruses could be one of the underlying mechanisms explaining the reduction of virus-induced exacerbations in fall (61).

**Common eligibility criteria**

Children with severe asthma from 6 years of age with sensitization to inhaled allergens and total serum IgE levels between 30-1500 UI/ml and $FEV_1$ below 80%. Usually used for IgE-mediated persistent allergic asthma (53).

**Safety profile**

Current guidelines state that omalizumab is an effective and well-tolerated adjunctive therapy in patients with severe persistent asthma. Prescribing information warns of adverse events such as pyrexia, headache, upper abdominal pain, injection-site reactions (erythema, edema, pain and/or pruritus), anaphylaxis, malignancy, serum sickness-like symptoms, eosinophilic conditions, parasitic (helminth) infection, and low blood thrombocyte count (59). Omalizumab is generally related to an overall frequency of adverse effects similar to placebo. Most common adverse effects are mild to moderate in severity (90%) (62).

Despite the low risk of anaphylaxis or malignancy (0,2%) in pediatric patients treated with omalizumab, the studies conducted to date are of relatively short duration. To adequately assess the risk of malignancy in children, longer-term studies may need to be designed, as drug-induced cancers often occur after prolonged exposure (59).

## ANTI-IL5 THERAPY: MEPOLIZUMAB

### Mechanism of action

IL-5 is a cardinal cytokine which regulates miscellaneous features of respiratory track eosinophilic inflammation, which is commonly related to augmented asthma severity, including the promotion of eosinophil's maturation, activation, and survival. It is well known that eosinophils as well as their mediators have a major role in airway inflammation.

Mepolizumab is a humanized mAb targeting circulating IL-5 and blocking IL-5/IL-5Rα interaction approved as an add-on treatment for severe eosinophilic asthma. (56). It is administered subcutaneously at a dose of 100 mg every 4 weeks from 12 years of age and 40 mg every 4 weeks from 6-11 years of age. Treatment can be carried out at home (53).

Mepolizumab has been demonstrated to reduce AE reducing ED visits and hospitalizations. Mepolizumab additionally increased $FEV_1$ by approximately 0,1L compared to placebo and demonstrated to reduce OGC (63,64).

### Common eligibility criteria

Mepolizumab is approved for children with severe asthma from 6 years of age with baseline blood eosinophils ≥ 500/μL or < 500 with 2 severe AE or 1 AH during last year. Mepolizumab has shown decrease in AE in patients with ≥ 300 eosinophils/μl in blood in the previous year or with ≥ 150/μl at the time of treatment, but with historically elevated values (53).

### Safety profile

Adverse reactions to mepolizumab can range from mild, the most common, to severe. The most common adverse events are headache, injection-site reactions, eczema, and nasal congestion. Rare cases of anaphylaxis have also been described (56).

Anti-IL-5 therapies are not to be used in patients with parasitic infestations, given the fundamental role that this cytokine plays in the immune response against such microorganisms. For this reason, in patients potentially eligible for mepolizumab therapy, investigations must be carried out to exclude a parasitic infestation (65).

## ANTI- IL-4 Rα THERAPY: DUPILUMAB

### Mechanism of action

IL-4 and IL-13 are two correlated triggers of TH2 inflammation. IL-4, and to a lesser degree IL-13, encourage IgE synthesis; while IL-13 has a role primarily in airway hyperreactivity, mucus production, and airway remodeling. Dupilumab is a fully humanized anti-IL-4 receptor α mAb, which selectively binds to IL-4Rα, thus inhibiting both IL-4 and IL-13 signaling (56).

From 12 years of age, an initial dose of 400 mg is administered followed by 200 mg every 2 weeks if severe eosinophilic asthma or T2 or 300 mg if corticodependent or associated atopic dermatitis. It is administered subcutaneously and can be performed at home. In children aged 6 to 11 years, a dose of 100 mg every 2 weeks or 300 mg every 4 weeks is administered in patients weighing less than 30 kg and 200 mg every 2 weeks or 300 mg every 4 weeks in those weighing 30-60 kg and 200 mg every 2 weeks in those weighing more than 60 kg (53).

Dupilumab has been proven to reduce AE, improve lung function in terms of baseline $FEV_1$ (increasing $FEV_1$ by approximately 0,32L) and achieve statistically significant greater asthma control. Several studies have shown that children taking dupilumab have lower exposure to OGC than those on placebo. Moreover, dupilumab quickly and sustainably reduces markers of type 2 inflammation in airways ($FE_{NO}$) and in circulation (serum total IgE) (66,67).

### Common eligibility criteria

Dupilumab is approved in children older than 6 years for severe asthma with T2 markers (eosinophils ≥ 300/μL and/or $FE_{NO}$ ≥ 25 ppb) or need for maintenance OGC (53).

### Safety profile

Current guidelines state that dupilumab is an effective and well-tolerated treatment in children with severe persistent asthma. Dupilumab has a generally acceptable adverse effect profile in pediatric population, with safety outcomes like those in adult and adolescent patients. Most common adverse effects are mild to moderate in severity. Injection-site reactions and viral upper respiratory tract infection are the most common adverse effects. Another less common undesirable effect is eosinophilia, although most episodes of eosinophilia are self-limited laboratory findings without accompanying symptoms (66).

### ANTI-TSLP THERAPY: TEZEPELUMAB

#### Mechanism of action

Tezepelumab is a humanized IgG2λ mAb that inhibits thymic stromal lymphopoietin (TSLP), an airway epithelial cytokine. It has demonstrated extended therapeutic action in patients with severe high and low T2 asthma. TSLP is crucial for TH2 immunity, which is implicated in the pathophysiology of asthma, as it induces the expression of TH2-associated drivers of inflammation, such as IL-4 and IL-5 (56).

A dose of 210 mg is administered subcutaneously every 4 weeks. Home administration is possible (53).

Tezepelumab has shown to reduce AE and bronchial hyperresponsiveness and to improve lung function, resulting in better asthma control (68). While it provides a reduction in the rate of severe AE that is more intense the higher the blood eosinophil count and the higher the baseline $FE_{NO}$ values, is also effective when blood eosinophil count is <150/µl and $FE_{NO}$ < 25ppb. Therefore, it is the only mAb currently showing efficacy in T2-low asthma (53,56).

#### Common eligibility criteria

Tezepelumab is approved as an add-on therapy in patients from 12 years of age with severe asthma with no type 2 biomarkers. Tezepelumab is approved by EMA but no therapeutic positioning report was available in Spain at the time of publication of GEMA 5.3 (53).

#### Safety profile

Regarding the safety profile of tezepelumab, it is a well-tolerated mAb. Most of the adverse effects are mild, the most frequent ones being injection-site reactions, pharyngitis, arthralgia, or back pain. Rare cases of anaphylaxis have been described (56).

## 3.8.3 SELECTING THE MOST APPROPIATE mAb

Selecting the most appropriate biologic therapy for a specific patient is a challenge for the specialist. The European Academy of Allergy and Clinical Immunology has suggested some recommendations and believes that the introduction of mAb should consider three main elements: phenotypic features (AE, deterioration of lung function and comorbidities), biomarkers (eosinophils, $FE_{NO}$ and IgE) and clinical outcomes (AE, lung function, control, comorbidities, quality of life and safety).

In this case, it is important to assess the phenotype and endotype, knowing that most children will have allergic asthma, with sensitization to aeroallergens and high levels of IgE and $FE_{NO}$. Although this approach has some limitations for pediatric patients that require some reflection. The consideration of the eosinophil as the predominant cell comes from the findings obtained both in BAL or sputum samples and in the endobronchial biopsy-derived tissue itself. Their relevance in contributing to the pathogenesis of asthma in children appears to be different from that in adults, therefore features should not be extrapolated directly.

It has been noted that the relation between pulmonary and peripheral eosinophilia is quite complex, since the presence of blood eosinophilia does not always predict a higher airway eosinophilia, although normal serum counts do not always exclude the presence of pulmonary eosinophilia. Also note that the value of $FE_{NO}$ and sputum eosinophil count are not interchangeable. There is no perfect biomarker for T2 asthma, although bronchoscopic evaluation is done exclusively in selected cases since is an invasive test.

To summarize, different mAb with different mechanisms of action are currently available and the choice of personalized treatment should be guided by the patient's phenotype. Furthermore, research is needed into new biomarkers that will allow the best choice of biologic therapy and also to establish the timing and process of treatment discontinuation once asthma control has been achieved (49).

### 3.8.4 PATIENT FOLLOW-UP

Once treatment has been started, an assessment should be made between 4 and 6 months, having previously established, on an individual basis, the criteria for good response and, according to this, different alternatives should be considered (49).

# 4. JUSTIFICATION

Asthma is a very common chronic respiratory disease affecting all age groups. The prevalence of asthma is increasing in many countries, especially among children (69). Majority of children with asthma respond well to standard therapies, however a significant proportion still have severe disease that is resistant to conventional therapies (51). Almost 5% of asthmatic children are considered to have severe asthma, although some studies estimate its prevalence to be around 8,8%.

Children with severe asthma, especially if poorly controlled, suffer frequent severe AE, loss of lung function, poorer quality of life and high risk of adverse effects from the medication they receive, all of which leads to an increase in the number of unscheduled visits, ED visits, AH and missed school and work days for their caregivers, as well as significant costs. Furthermore, they have an increased risk of future chronic obstructive pulmonary disease (49). Children with severe persistent asthma have higher rates of anxiety, depression and conduct problems, specially attentional disorders. Parents of these infants often experience depression, anxiety and post-traumatic stress disorder, which can influence their ability to manage their child's asthma (52).

Biologic therapies are increasingly being considered in children with severe asthma. Biologic therapies currently available target T2-high asthma, typically characterized by eosinophilic inflammation. The most frequent phenotype in childhood is T2-high or allergic asthma with sensitization to aeroallergens. There are currently four mAb available for children with severe uncontrolled asthma. Not long ago, only Omalizumab (anti-IgE) had approval. In the past years, new treatments have emerged such as Dupilumab (anti-IL-4 R$\alpha$) (49).

MAb as add-on therapy has been shown to reduce AE and improve symptom control, improving patients' quality of life and reducing ED visits and AH due to AE. It has also been proven that mAb reduce the use of OGC, especially dupilumab, which is very relevant since they have significant adverse effects. Adverse effects of OGC are growth retardation, adrenal suppression and alteration of skin and bone metabolism. Moreover, dupilumab has also been shown to increase $FEV_1$, resulting in an improvement of bronchial obstruction (57,58).

Although all mAb have demonstrated benefits in children with severe asthma, each has its own particular characteristics. Selecting the most appropriate mAb for an individual patient is a challenge for specialists, as there are no established algorithms or biomarkers available to assist choice. Even though there are various randomized controlled trials in adults comparing the efficacy of different biologic therapies, in children the number of clinical trials remains limited.

# 5. HYPOTHESIS

## 5.1 MAIN HYPOTHESIS

Dupilumab reduces more than omalizumab the incidence of emergency department (ED) visits and admissions to hospital (AH) due to asthma exacerbations (AE) in children with type T2 asthma uncontrolled with standard treatment.

## 5.2 SECONDARY HYPOTHESIS

- Dupilumab may reduce the incidence of AE more than omalizumab.
- Dupilumab can result in a reduction in the daily dose of oral glucocorticoids (OGC) compared to treatment with omalizumab.
- Dupilumab treatment could improve children's asthma control levels compared to omalizumab, with better results in Childhood Asthma Control Test (c-ACT) or Asthma Control Test (ACT).

# 6. OBJECTIVES

## 6.1 MAIN OBJECTIVE

Analyze if the administration of dupilumab reduces the incidence of ED visits and AH because of AE in children aged 6 to 17 years with type T2 asthma uncontrolled with a combination of high dose ICS/LABA compared to omalizumab.

## 6.2 SECONDARY OBJECTIVES

- Study if the administration of dupilumab reduces the incidence of AE compared to omalizumab.
- Determinate if the use of dupilumab reduces the daily dose of OGC compared to omalizumab treatment.
- Analyze if the administration of dupilumab improve subjective asthma control level, experiencing less symptoms and limitations, compared to omalizumab and measured with c-ACT or ACT.

# 7. METHODOLOGY

## 7.1 STUDY DESIGN

This study is designed as a prospective, multicenter, double-blind randomized clinical trial with parallel groups.

Patients diagnosed with asthma that remains uncontrolled with a combination of high dose ICS/LABA will be randomly assigned in a 1:1 ratio to be either in the intervention or in the control group. The intervention group will follow high-dose ICS and LABA therapy together with dupilumab as an add-on treatment. Instead, control group will receive high-dose ICS and LABA therapy together with omalizumab.

The duration of the intervention will be one year. Control appointments will be scheduled at sixth month and at the end of the study.

## 7.2 STUDY SUBJECTS

The target population of this clinical trial is children aged from 6 to 17 years old diagnosed with type T2 asthma uncontrolled with a combination of high dose ICS/LABA.

### 7.2.1 INCLUSION CRITERIA

- Patients aged from 6 years old to 17 years old, diagnosed with asthma defined as a positive history of respiratory symptoms and a variable expiratory airflow limitation confirmed with lung function tests.
- Patients with asthma diagnosis and classified as Step 5 or Step 6 of the stepwise treatment strategy published by GEMA asthma guidelines.
- Patients must be treated with a combination of high dose ICS/LABA and remain uncontrolled.

### 7.2.2 EXCLUSION CRITERIA

- Patients diagnosed with asthma who are sufficiently controlled with monotherapy with ICS or with ICS combined with LABA.
- Patients with concomitant severe morbidity or disease.
- Patients with hypersensitivity to the active pharmaceutical ingredient or to any of its excipients.
- Patient with other pharmacological active treatment.
- Patients without the informed consent sheet signed.

## 7.3 SAMPLING AND SAMPLE SIZE

### 7.3.1 SAMPLING

Our sampling will be a consecutive sampling. All patients will be Girona province residents and the participating hospitals will be the following: Hospital Universitari Doctor Josep Trueta de Girona, Hospital de Figueres, Hospital de Palamós, Hospital d'Olot i Comarcal de la Garrotxa, Hospital Santa Caterina, Hospital de Campdevànol and Hospital Comarcal de Blanes. All asthmatic children not well controlled with high doses of ICS and LABA in the intervention hospitals will be invited to participate in the trial. We will evaluate whether they meet all the inclusion criteria and none of the exclusion criteria.

### 7.3.2 SAMPLE SIZE

To calculate the sample size, we used the GRANMO software. Our main dependent variable will be the presence or not of ED visits or AH due to AE during study time. The group ratio will be 1:1.

Accepting an alpha risk of 0.05 and a power of 0.8 in a two-tailed test 194 subjects are necessary in the first group and 194 in the second to find as statistically significant a proportion difference, expected to be of 15% in group 1 and 6% in group 2. A drop-out rate of 10% has been anticipated.

## 7.4 VARIABLES

### 7.4.1 INDEPENDENT VARIABLE

The intervention of our study will be the administration of dupilumab.

The first group will follow treatment with omalizumab plus standard treatment with high dose ICS/LABA. This group will be identified as the control group.

The second group will follow treatment with dupilumab plus standard treatment with high dose ICS/LABA. This group will be identified as the intervention group.

This is considered a dichotomous qualitative variable.

### 7.4.2 DEPENDENT VARIABLE

The main dependent variable of this study is the presence or not of ED visits or AH due to asthma worsening.

Main dependent variable is a discrete quantitative variable.

### 7.4.3 SECONDARY DEPENDENT VARIABLES

Other secondary variables studied are:

- The number of AE, defined as acute or subacute episodes of progressively increasing asthma symptoms associated with fall in lung function. This is a discrete quantitative variable.
- The daily dose of OGC. This is a continuous quantitative variable.
- Patient's subjective evaluation of symptoms control using a questionnaire called Childhood Asthma Control Test (c-ACT) for children aged 4-11 years. The test consists of 7 questions, 4 for the child and 3 for the parents/caregivers (70,71). In patients 12 years of age and older we use the Asthma Control Test (ACT) (72). The test will be performed at the start of the project to determine the baseline situation of our patients and at follow-up visits during the study. This will be treated as a dichotomous qualitative variable.
    - c-ACT or ACT score below 20: Asthma poorly controlled.
    - c-ACT or ACT score equal or greater than 20: Good asthma control levels.

### 7.4.4 COVARIABLES

As the sample will be randomized, there will be no confusion factors. But as randomization will be done by each hospital, there may be differences between hospitals, so possible residual confounding will be controlled for.

We will collect baseline characteristics of the patients to obtain epidemiological and clinical data at the beginning of the study, such as:

- **Age**: We will assess the patient's age by looking at their date of birth. Age will be measured in years. This is a quantitative discrete variable.
- **Sex**: Male or female. This is a qualitative dichotomus variable.
- **Age of diagnosis***: A diagnosis of asthma requires a compatible clinical findings and a positive bronchodilator test that evidences reversibility of intrapulmonary airflow obstruction. The test is positive if the increase of $FEV_1$ is greater than 12% respect to basal spirometry. This variable will be expressed in years and will be considered quantitatively discrete.
- **Baseline $FEV_1$**: Forced expiratory volume in the first second ($FEV_1$) is the maximum volume of air exhaled in the first second of a forced expiration from a fully inspired position. It is measured through spirometry and is expressed as a percentage (%). This is a quantitative continous variable.

- **Baseline $FEV_1$/FVC ratio**: Forced vital capacity (FVC) is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration. A decrease in $FEV_1$/FVC ratio is a good sign of obstructive impairment. $FEV_1$ and FVC are determined through spirometry and subsequently $FEV_1$/FVC ratio is calculated. This parameter is expressed as a percentage (%) and is considered a quantitative continous variable.
- **ED visits in the last year due to AE*:** ED visits will be measured in number and are considered a discrete quantitative variable.
- **AH in the past year due to AE*:** AH will be measured in number and are considered a discrete quantitative variable.
- **Number of total AE in the past year**: To establish if the patient has suffered acute AE not requiring a visit to the ED or AH, we will ask the parents or tutors. This variable will be measured in number and is treated as discrete quantitative.

*In order to obtain the moment of diagnosis and number of ED visits and AH due to exacerbations in the last year we will access the patient's shared medical history with the parental or tutor's authorization. In case we are unable to have access to the medical history, we will ask to the parents or caregivers of the patient.

## 7.5 STUDY INTERVENTIONS

### 7.5.1 PATIENTS SELECTION AND RANDOMIZATION

Hospitals in the province of Girona participating in the clinical trial will recruit study subjects by consecutive sampling. Patients will be recruited simultaneously in each of the participating centers until the required sample is collected. For this reason, a common computerized registry will be available to be accessed by all participating hospitals in the province. We will evaluate whether they meet all the inclusion criteria and none of the exclusion criteria.

**Group 1:** This group will follow high-dose ICS and LABA therapy together with omalizumab as an add-on treatment. This group will be identified as the control group.

**Group 2:** This group will receive high-dose ICS and LABA therapy together with dupilumab as an add-on treatment. This group will be identified as the intervention group.

### 7.5.2 STUDY INTERVENTIONS

After recruiting patients who meet all the inclusion criteria and none of the exclusion criteria, they will receive one add-on treatment or another, according to

whether they belong to the intervention or control group. A double-blind method will be used.

**Group 1:** This group will receive high-dose ICS and LABA therapy together with omalizumab as an add-on treatment. It is administered subcutaneously and can be performed at home or at the medical center of reference. The administered dose is 75-600 mg every 2-4 weeks depending on body weight and serum total IgE levels before starting treatment. Recommended maximum dose is 600 mg every 2 weeks.

Following tables are used for the determination of omalizumab doses according to weight (kg) and baseline IgE values (UI/ml). Data extracted from "Comité de Medicamentos" of “Asociación Española de Pediatría” (73).

| | **Body weight (kg)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (UI/ml)** | >20-25 | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125 | >125-150 |
| 30-100 | 75 | 75 | 75 | 150 | 150 | 150 | 150 | 150 | 300 | 300 |
| > 100-200 | 150 | 150 | 150 | 300 | 300 | 300 | 300 | 300 | 450 | 600 |
| > 200-300 | 150 | 150 | 225 | 300 | 300 | 450 | 450 | 450 | 600 | |
| > 300-400 | 225 | 225 | 300 | 450 | 450 | 450 | 600 | 600 | | |
| > 400-500 | 225 | 300 | 450 | 450 | 600 | 600 | | | | |
| > 500-600 | 300 | 300 | 450 | 600 | 600 | | | | | |
| > 600-700 | 300 | | 450 | 600 | | | | | | |
| > 700-800 | | | | | | | | | | |
| > 800-900 | | | | | See administration table every 2 weeks. | | | | | |
| > 900-1000 | | | | | | | | | | |
| > 1000-1100 | | | | | | | | | | |

*Table 4 Dose of omalizumab (milligrams per dose) administered by subcutaneous injection every 4 weeks.*

| | **Body weight (kg)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline IgE (UI/ml)** | >20-25 | >25-30 | >30-40 | >40-50 | >50-60 | >60-70 | >70-80 | >80-90 | >90-125 | >125-150 |
| 30-100 | See administration table every 4 weeks. | | | | | | | | | |
| > 100-200 | | | | | | | | | | |
| > 200-300 | | | | | | | | | | 375 |
| > 300-400 | | | | | | | | | 450 | 525 |
| > 400-500 | | | | | | | 375 | 375 | 525 | 600 |
| > 500-600 | | | | | | 375 | 450 | 450 | 600 | |
| > 600-700 | | 225 | | | 375 | 450 | 450 | 525 | | |
| > 700-800 | 225 | 225 | 300 | 375 | 450 | 450 | 525 | 600 | | |
| > 800-900 | 225 | 225 | 300 | 375 | 450 | 525 | 600 | | | |
| > 900-1000 | 225 | 300 | 375 | 450 | 525 | 600 | | | | |
| > 1000-1100 | 225 | 300 | 375 | 450 | 600 | | | | | |
| > 1100-1200 | 300 | 300 | 450 | 525 | 600 | Do not use, insufficient data are available for dose recommendation. | | | | |
| > 1200-1300 | 300 | 375 | 450 | 525 | | | | | | |
| > 1300-1500 | 300 | 375 | 525 | 600 | | | | | | |

*Table 5 Dose of omalizumab (milligrams per dose) administered by subcutaneous injection every 2 weeks.*

**Group 2:** This group will follow high-dose ICS and LABA therapy together with dupilumab as an add-on treatment. It is administered subcutaneously and can be performed at home or at the medical center of reference. In children aged 6 to 11 years, a dose of 100 mg every 2 weeks or 300 mg every 4 weeks is administered in patients weighing less than 30 kg and 200 mg every 2 weeks or 300 mg every 4 weeks in those weighing 30-60 kg and 200 mg every 2 weeks in those weighing more than 60 kg. From 12 years of age, an initial dose of 400 mg is administered followed by 200 mg every 2 weeks.

A follow-up visit will be performed at 6 months after starting treatment and at 12 months, at the end of the study. During these controls a forced spirometry will be performed and ACT or the version for children between 6 and 11 years old (c-ACT) will be applied. An assessment will be made of whether during this time the patient has suffered moderate and/or severe AE and whether these have required ED visits or AH. Furthermore, the need of OGC use will also be evaluated.

The aim of this intervention is to demonstrate that dupilumab is more effective than omalizumab in achieving good levels of asthma control. With that, we want to achieve less number of future AE, especially those requiring AH or ED visits. It is also expected to reduce the consumption of OGC in these children.

It is important to highlight that all participants cannot change their baseline treatment or initiate immunotherapy during the study and that the use of reliever medication is always allowed.

## 7.6 DATA COLLECTION AND STUDY CIRCUIT

For data collection we will work together with the physicians, in charge of children asthma managing, working in Pediatrics Department of each hospital in the Girona province. We will also collaborate with doctors in charge of asthma management in adults who work in Pneumology Departments of the different hospitals, since those patients over 14 years of age will be seen by adult specialists. After a first coordination meeting, before recruitment begins, the main investigators and the collaborators will keep in contact via e-mail or telephone.

All patients previously diagnosed with asthma who attend their follow-up visits will be evaluated to see if they meet all inclusion criteria and none of the exclusion criteria. Patients who meet all eligibility requirements will receive the clinical trial information sheet. Once we ensure that both patient and parents or legal tutors understand the research project and if they agree with our study, they will sign the informed consent document. Participants aged 12 years and older who want to participate in the trial must sign a provided assent document. In this case, their parents must also sign the informed consent sheet.

During first visit we will evaluate the baseline characteristics of the patient described below:

- Age.
- Sex.
- Age of diagnosis.
- Baseline $FEV_1$.
- Baseline $FEV_1$/FVC ratio.
- Number of AE over the last year.
- Number of ED visits due to asthma worsening over the last year.
- Number of AH due to asthma worsening over the last year.
- ACT / c-ACT score.
- Daily dose of OGC.

All participants will receive information on the new complementary treatment that will be administered to them, in additional to the one they are currently receiving. They will also be provided with information on when and how to seek advanced medical care in case of exacerbation or worsening of symptoms.

Follow-up visits will be scheduled at sixth months and at the end of the study. In all visits, the patient will be asked about their asthma status and will answer the ACT or c-ACT, depending on their age. Afterwards, a forced spirometry will be performed. We will also ask if the patient has suffered severe exacerbations and if these have required a visit to the ED or AH. The use of OGC will also be assessed.

# 8. STATISTICAL ANALYSIS

## 8.1 DESCRIPTIVE ANALYSIS

The results will be expressed as percentages for categorical variables (95% confidence interval). For continuous variables, we will use mean and standard deviation (if a normal distribution can be assumed) or median, first and third quartile (if a normal distribution cannot be assumed).

## 8.2 BIVARIATE INTERFERENCE

Categorical variables will be compared with Chi Square test or Fisher exact tests. For continuous variables, a two-sided Student's t-test will be used.

## 8.3 MULTIVARIATE ANALYSIS

A multivariate analysis will be performed adjusting for co-variables to avoid confusion caused by the effect of other variables on the effect of the treatment. In this study a Cox's regression model will be performed to describe the relationship between the analyzed variables because with this model the time to reach the endpoint is considered.

# 9. ETHICAL AND LEGAL CONSIDERATIONS

This clinical trial, motivated by the basic ethical principles of Beauchamp and Childress, will be conduced according with the human rights and ethical principles guaranteed by the World Medical Association Declaration of Helsinki of "*Ethical Principles for Medical Research Involving Human Subjects*", first adopted in 1964 and last revised in 2013 (74).

To preserve the principle of patient autonomy, the signature of the informed consent (*annex 4*) form will be required to participate in our study, as well as free enrollment with the necessary time for the patients to contemplate their participation. The trial information sheet (*annex 3*) for the patient will be included with the informed consent form. In our study, participants are younger than 18 years of age; therefore, informed consent will be signed by their parents or legal caregivers. Participants aged 12 years and older who want to participate in the trial have to sign a provided assent document (*annex 5*). In this case, their parents must also sign the informed consent sheet.

Dupilumab appears to be a mAb that demonstrates more reduction in OGC use and improvement in bronchial obstruction compared to omalizumab, resulting in an improvement of the patients' quality of life, this study will be conducted according to the principle of beneficence.

Studies have demonstrated that dupilumab is effective in children with severe uncontrolled asthma. Therefore, no lower efficacy is expected in the experimental group (dupilumab) of the study compared to the control group (omalizumab), respecting the principle of non-maleficence.

Among all ethical principles respected in this study, the principle of justice will be guaranteed by avoiding any kind of discrimination between those patients who meet the inclusion criteria and do not meet the exclusion criteria, inviting all of them to participate in our study.

The development of this protocol was carried out in accordance with the Spanish legal framework, as it will respect the precepts of "Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos".

Furthermore, respect for Spanish laws on patient confidentiality, such as the "Reglamento (UE) 2016/679 del Parlamento y del Consejo Europeo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos" and the "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y

Garantía de los Derechos Digitales", they will be guaranteed by assigning a numerical code to each patient participating in the study, with the aim of preserving their anonymity.

Once the protocol has been completed, the clinical trial will be submitted for approval to the "Comitè d'Ètica d'Investigació amb Medicaments" (CEIm). All the centers in the province of Girona participating in the study share the same CEIm, so validation by CEIm Girona will be enough for all centers. Each research committee of each collaborating hospital must approve it.The clinical trial will only be carried out in those centers that have approved it, and the signature of all participating investigators from each hospital will be required.

# 10. DRUGS AND SAFETY

Drugs used in this clinical trial are dupilumab and omalizumab, both monoclonal antibodies. Both are administered subcutaneously. Doses depend on the drug, patient age and body weight.

The administered dose of omalizumab is 75-600 mg every 2-4 weeks depending on body weight and serum total IgE levels before starting treatment. Tables 4 and 5 show the doses according to weight (kg) and baseline IgE values (UI/ml). The administered dose of dupilumab varies depending on patient's age and weight. In children aged 6 to 11 years, a dose of 100 mg every 2 weeks or 300 mg every 4 weeks is administered in patients weighing less than 30 kg and 200 mg every 2 weeks or 300 mg every 4 weeks in those weighing 30-60 kg and 200 mg every 2 weeks in those weighing more than 60 kg. From 12 years of age, an initial dose of 400 mg is administered followed by 200 mg every 2 weeks (53).

Most frequent adverse effects of omalizumab are pyrexia, headache, upper abdominal pain and injection site reactions such as swelling, erythema, pain or pruritus. Other rare adverse effects are anaphylaxis, serum sickness-like symptoms, eosinophilic conditions, parasitic (helminth) infection and low blood thrombocyte count. Most reactions are mild to moderate in severity.

Since IgE may be related to the immune response to some helminth infections, omalizumab may indirectly reduce the efficacy of drugs used for the treatment of helminth infections or other parasites (75).

Most frequent adverse effects of dupilumab are injection site reactions and viral upper respiratory tract infections. Other less common adverse effects include conjunctivitis, allergic conjunctivitis and arthralgia. Another undesirable effect is eosinophilia, although most episodes of eosinophilia are self-limited laboratory findings without accompanying symptoms. The most common adverse effects are mild to moderate in severity.

Dupilumab may influence the immune response against helminthic infections by inhibiting IL-4/IL-13 signaling. Before initiating treatment with dupilumab, patients with previous helminthic infections should be treated (76).

Neither dupilumab or omalizumab should be used to treat acute asthma symptoms or acute exacerbations. They should not be used to treat acute bronchospasm or asthmatic crisis.

Finally, it is important to note that there is no pharmacological reason to expect that drugs commonly prescribed in the treatment of asthma will interact with omalizumab or dupilumab.

# 11. STRENGH AND LIMITATIONS

An inherent feature of clinical trials is the lack of reproducibility understood as the possibility of the results to be extrapolated to the general population. Therefore, more studies will have to be done to confirm the results, and thus be able to support our hypothesis.

Asthma is a very common disease in the pediatric population, it is estimated that 10% of children suffer from asthma. According to data from “Institut d'Estadística de Catalunya” in the province of Girona there are about 15.000 asthmatic children. Of all asthmatic children, only between 5 and 8,8% have severe disease. Therefore, in the province of Girona between about 1.100 children have severe disease.

The recruitment of patients to obtain our sample may be a limitation of the project, so it has been decided to carry out a multicenter study involving different hospitals in the province of Girona. This study protocol has estimated a time for patient recruitment of one year. Once we have the sample, the duration of the study will be one year, therefore, the total expected duration of the project is about two years. Another limitation of the project is that since it is carried out in different centers, the equipment used to perform the spirometry tests may vary slightly.

Another limitation of this clinical trial is its elevated cost since both treatments are pricey. A proposal will be made to the laboratory of the product used to subsidize our trial.

Researchers involved in this study have already shown results in several papers and publications about this topic. They have enough experience in this study area to help ensure the viability of the study.

The principal strength of this study is the possibility to facilitate the decision when choosing add-on treatments in children with severe asthma who are not sufficiently controlled. Consequently, this can lead to better control of asthma and greater efficacy of treatment. Poorly controlled asthma can lead to more severe exacerbations, reduced lung function and increased morbidity.

# 12. WORK PLAN AND CHRONOGRAM

For this study we need 388 patients to be recruited from the hospitals of Girona province, so we estimate a recruitment time of a year. The principal investigators will collaborate with pediatricians and pulmonologists from each participating hospital. Nursing staff will also be involved. As the study involves use of medicines, we will count also with a pharmacologist specialized in pediatrics. To ensure that the collected data are well analyzed we will hire a statistical expert.

## 12.1 PROTOCOL DESIGN AND APPROVAL

In this first stage, study protocol will be developed by main investigators and just after send to the CEIm for revision and approval.
Duration: 4 months, from March 2024 to June 2024.

## 12.2 COORDINATION

Once the study protocol is approved, we will start the coordination phase. It's important to first know which hospitals will be participating in our study as intervention hospitals. As soon as hospital selection is done, we will carry on a face-to-face meeting with all pediatricians and nursing staff of each hospital in Girona to coordinate and have a consensus about chronogram, sample selection, and other features.
Duration: 1 month, July 2024.

## 12.3 PATIENTS SELECTION

A consecutive sampling of patients attending follow-up visits at the participating hospital will be performed. All patients must be properly informed about the study and assessed to know if they meet all the inclusion criteria and none of the exclusion criteria. If they agree, parents will have to sign the informed consent and children over 12 years of age must also give their signature on the provided assent document. During same visit, baseline characteristics of the enrolled patients, previously explained, will be checked. All information about treatment administered will be explained to all participants. Nonpharmacological techniques to follow will also be explained.
Duration: One year, from August 2024 to July 2025.

## 12.4 INTERVENTION, FOLLOW-UP VISITS AND DATA COLLECTION

The intervention time will be one year, and follow-up visits will be scheduled for January 2026 and in July 2026, at the end of the study. In these visits, data will

be collected and recorded in the database for each physician participating. During follow-up visits, pediatrician or pulmonologist should assess the status of asthma by evaluating whether there have been severe AE that have required ED visits or AH. OGC use will also be assessed during study time. A forced spirometry will be performed at each visit to control with baseline. All nonpharmacological strategies will also be explained again. Physicians at different centers will record all the information obtained during follow-up in the patients' medical history. Such data will be automatically collected in a common clinical trial database.
Duration: One year, from August 2025 to July 2026.

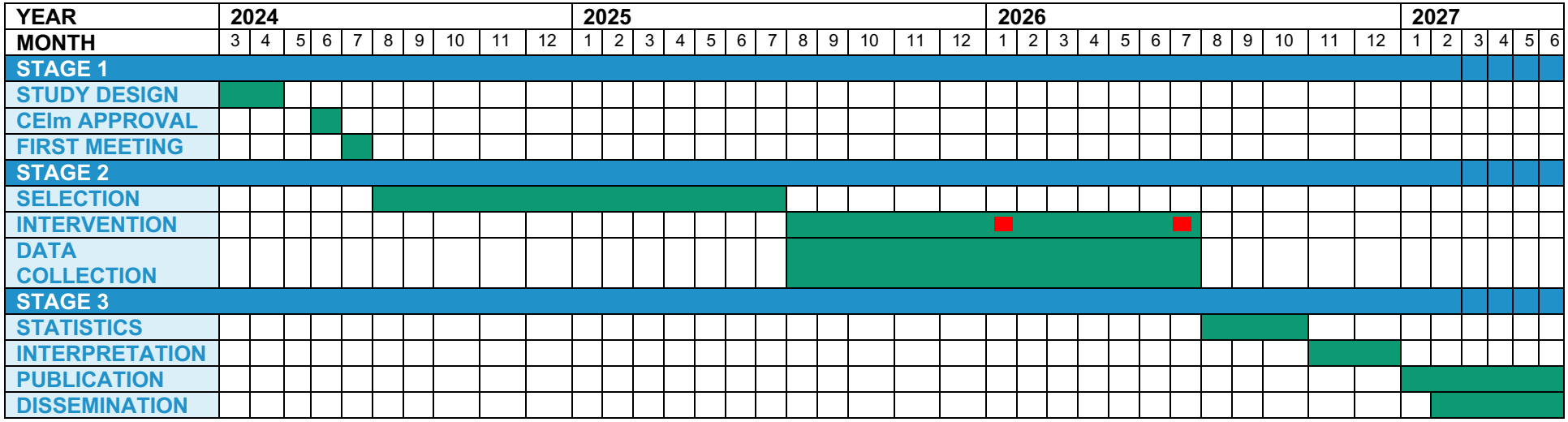
## 12.5 STATISTICAL ANALYSIS

In this stage, the main investigators and the hired statistical expert will perform the analysis of collected data.
Duration: 3 months, from August 2026 to October 2026.

## 12.6 INTERPRETATION, PUBLICATION AND DISSEMINATION

After all the data processing and statistical analysis, results will be interpreted, and conclusions will be extracted. Using all this information, a final report will be drafted including materials and methods, results, discussion, and conclusion. The final project will then be sent to different national and international journals for publication. The results in our study, favorable or not, will be exposed in national and international conferences and congresses to contribute to medicine progress.
Duration: 8 months, from November 2026 to June 2027.

## 12.7 CHRONOGRAM




Follow-up visit

# 13. BUDGET

The main research team members and participants involved in the study are current employees, which means that their activities will be enrolled as part of their normal clinical practice and will not incur additional costs. All pediatricians, pneumologists and nurses from the participating hospitals will assemble in Girona for a coordination meeting before study initiation. A pharmacologist from Josep Trueta hospital in Girona will also attend this first meeting. Travel and dietary expenses will be included in the study budget, estimating around 30€ per participant and an estimated 20 assistants will attend. The final cost will be approximately 600€. Subsequent follow-up meetings will be held via e-mail or telephone.

For this clinical trial, the assistance of a statistical expert will be required. During the statistical analysis, the research team and the statistical expert will work together to summarize the data collected. We expect to need their labor for about 40 hours paid at 30€/hour, resulting in a final cost of approximately 1.200 euros.

The cost of one vial of dupilumab (Dupixent) is about 810 € and its administration is every 2-4 weeks. Therefore, it is estimated that the average cost per patient/year is 13.770 €. In our study, 194 children will be in the intervention group taking dupilumab so the total cost will be 2.671.380 €. The cost of one vial of omalizumab (Xolair) is about 430 € and its administration is every 2-4 weeks depending on the patient, Consequently, the average cost per patient/year is estimated at 7.310€. In our trial, 194 children will be in the control group taking omalizumab so the total cost will be 1.418.140 euros.

To assess lung function, spirometry will be performed at the beginning of the study and subsequently at sixth and twelfth month from the start of the intervention. Asthmatic patients usually visit their physician twice a year to follow up their disease, especially those with severe asthma. Therefore, in our study we will not include spirometry tests in our budget since they are part of the standard control procedures.

We will also need to print some documents, such as the ACT or c-ACT questionnaire, the trial information sheet, the informed consent, and the provided assent document for patients over 12 years of age. In total, there will be necessary 7 pages for each patient, being a total cost of 82€ if we pay 0,03€/page.

Since our study is a low-intervention clinical trial, no insurance payment is required. The costs of publishing the article and attending a national congress with the corresponding expenses (travel and lodging) will also be considered in

the expenses. The publication cost is estimated to be 2.000 €. Attendance at a national congress, together with related expenses, is estimated to cost 600 € for each attendee.

The summary of the estimated costs to perform this clinical trial are listed in the following table.

*Table 6 Budget*

| EXPENSES | AMOUNT | COST | SUBTOTAL |
|---|---|---|---|
| **Personal expenses** | | | |
| Coordination meeting (travel + diet) | 20 participants | 30 € / participant | 600 € |
| Statistical expert | 40h | 30 €/h | 1.200 € |
| **Executive expenses** | | | |
| Dupilumab (Dupixent) | 17 vials per patient/year | 810 €/vial | 2.671.380 € |
| Omalizumab (Xolair) | 17 vials per patient/year | 430 €/vial | 1.418.140 € |
| Spirometry | 1.164 spirometries | 0 € | 0 € |
| Document printing | 7 pages / patient | 0,03 €/page | 82 € |
| Insurance | | 0 € | 0 € |
| **Publication and divulgation expenses** | | | |
| Article publication | 1 publication | 2.000 € | 2.000 € |
| Attendance to a national congress | 1 congress<br>2 attendants | 600 €/congress per attendant | 1.200€ |
| | | **TOTAL** | **4.094.602 €** |

# 14. IMPACT ON HEALTHCARE

This clinical trial paves the way for future studies aimed to improve treatment of severe asthma in the pediatric population. Children with severe asthma, especially if poorly controlled, suffer frequent severe AE, loss of lung function, poorer quality of life, high risk of adverse effects from the medication they receive, loss of school days, increased morbidity, and risk of related diseases. They also have higher rates of anxiety, depression, and behavioral problems.

There are many studies that conclude that biological therapies are effective when used correctly and could help to achieve a good level of asthma control in severe patients. Although, selecting the most appropriate mAb for an individual patient is a challenge for specialists, as there are no established algorithms or biomarkers available to assist choice. More studies in children are needed because data extracted from the adult population cannot always be extrapolated.

Finding solutions to the management of severe asthma and achieving good control of the disease is important. A patient with a well-controlled asthma can perform daily activities with hardly any barrier and can exercise and work normally.

Besides negative consequences on the patient, poor asthma control also indirectly affects the loss of workdays for caregivers and the use of enormous health care resources. These expenses derived from the use of healthcare resources in most cases would have been avoided simply by improving adherence to appropriate treatment.

Investing in the selection of the best treatment for each patient could help to greatly reduce the healthcare costs of emergency and hospital treatment. This means that this money could be used for other necessary purposes.

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# 16. ANNEXES

## Annex 1: ASTHMA CONTROL TEST (ACT)

Nombre del paciente: Fecha: ID# de paciente: Su doctor de cuidado primario:

### Asthma Control Test™–ACT (La prueba de Control del Asma) es:

- Una prueba rápida que produce un resultado numérico para evaluar el control del asma.
- Reconocida por los Institutos Nacionales de la Salud (National Institutes of Health - NIH) en sus directrices sobre el asma de 2007.[1]
- Convalidada clínicamente por espirometría y evaluaciones de especialistas.[2]

**PACIENTES:**

1. Contesten cada pregunta y escriban el número de la respuesta en el cuadro que aparece a la derecha de la pregunta.
2. Sumen sus respuestas y escriban la puntuación total en el cuadro del TOTAL que se muestra abajo.
3. Hablen con su doctor sobre sus resultados.

| | | | | | | | | | PUNTUACIÓN |
|---|---|---|---|---|---|---|---|---|---|
| 1. En las últimas **4 semanas**, ¿cuánto tiempo le ha impedido su **asma** hacer todo lo que quería en el trabajo, en la escuela o en la casa? | Siempre | 1 | La mayoría del tiempo | 2 | Algo del tiempo | 3 | Un poco del tiempo | 4 | Nunca 5 | |
| 2. Durante las últimas **4 semanas**, ¿con qué frecuencia le ha faltado el aire? | Más de una vez al día | 1 | Una vez al día | 2 | De 3 a 6 veces por semana | 3 | Una o dos veces por semana | 4 | Nunca 5 | |
| 3. Durante las últimas **4 semanas**, ¿con qué frecuencia sus síntomas del **asma** (respiración sibilante o un silbido en el pecho, tos, falta de aire, opresión en el pecho o dolor) lo/la despertaron durante la noche o más temprano de lo usual en la mañana? | 4 o más noches por semana | 1 | De 2 a 3 noches por semana | 2 | Una vez por semana | 3 | Una o dos veces | 4 | Nunca 5 | |
| 4. Durante las últimas **4 semanas**, ¿con qué frecuencia ha usado su inhalador de rescate o medicamento en nebulizador (como albuterol)? | 3 o más veces al día | 1 | 1 ó 2 veces al día | 2 | 2 ó 3 veces por semana | 3 | Una vez por semana o menos | 4 | Nunca 5 | |
| 5. ¿Cómo evaluaría el control de su **asma** durante las **últimas 4 semanas**? | No controlada en absoluto | 1 | Mal controlada | 2 | Algo controlada | 3 | Bien controlada | 4 | Completamente controlada 5 | |
| | | | | | | | | | TOTAL | |

**Si obtuvo 19 puntos o menos, es probable que su asma no esté bajo control. Asegúrese de hablar con su doctor sobre sus resultados.**


La Prueba de Control del Asma es para las personas asmáticas de 12 años de edad en adelante.

**Referencias: 1.** Departamento de Salud y Servicios Humanos de EE.UU, Institutos Nacionales de la Salud, Instituto Nacional del Corazón, los Pulmones y la Sangre. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3 2007).* Ítem de NIH No. 08-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Consultado el 10 de septiembre de 2007. **2.** Nathan RA y otros. *J Allergy Clin Immunol.* 2004;113:59-65.

# Annex 2: CHILDHOOD ASTHMA CONTROL TEST

## Childhood Asthma Control Test for children 4 to 11 years old.

## Know the score.

This test will provide a score that may help your doctor determine if your child's asthma treatment plan is working or if it might be time for a change.

### How to take the Childhood Asthma Control Test

Step 1 Let your child respond to **the first four questions (1 to 4)**. If your child needs help reading or understanding the question, you may help, but let your child select the response. Complete the remaining **three questions (5 to 7)** on your own and without letting your child's response influence your answers. There are no right or wrong answers.

Step 2 Write the number of each answer in the score box provided.

Step 3 Add up each score box for the total.

Step 4 Take the test to the doctor to talk about your child's total score.

**19 or less** If your child's score is 19 or less, it may be a sign that your child's asthma is not controlled as well as it could be. No matter what the score, bring this test to your doctor to talk about your child's results.

### Have your child complete these questions.

1. How is your asthma today?

| 0 | 1 | 2 | 3 | SCORE |
|---|---|---|---|---|
| Very bad | Bad | Good | Very good | |

2. How much of a problem is your asthma when you run, exercise or play sports?

| 0 | 1 | 2 | 3 | |
|---|---|---|---|---|
| It's a big problem, I can't do what I want to do. | It's a problem and I don't like it. | It's a little problem but it's okay. | It's not a problem. | |

3. Do you cough because of your asthma?

| 0 | 1 | 2 | 3 | |
|---|---|---|---|---|
| Yes, all of the time. | Yes, most of the time. | Yes, some of the time. | No, none of the time. | |

4. Do you wake up during the night because of your asthma?

| 0 | 1 | 2 | 3 | |
|---|---|---|---|---|
| Yes, all of the time. | Yes, most of the time. | Yes, some of the time. | No, none of the time. | |

### Please complete the following questions on your own.

5. During the last 4 weeks, on average, how many days per month did your child have any daytime asthma symptoms?

| 5 | 4 | 3 | 2 | 1 | 0 | |
|---|---|---|---|---|---|---|
| Not at all | 1-3 days/mo | 4-10 days/mo | 11-18 days/mo | 19-24 days/mo | Everyday | |

6. During the last 4 weeks, on average, how many days per month did your child wheeze during the day because of asthma?

| 5 | 4 | 3 | 2 | 1 | 0 | |
|---|---|---|---|---|---|---|
| Not at all | 1-3 days/mo | 4-10 days/mo | 11-18 days/mo | 19-24 days/mo | Everyday | |

7. During the last 4 weeks, on average, how many days per month did your child wake up during the night because of asthma?

| 5 | 4 | 3 | 2 | 1 | 0 | |
|---|---|---|---|---|---|---|
| Not at all | 1-3 days/mo | 4-10 days/mo | 11-18 days/mo | 19-24 days/mo | Everyday | TOTAL |

# Annex 3: TRIAL INFORMATION SHEET

## FULL D'INFORMACIÓ DE L'ASSAIG CLÍNIC

Títol de l'estudi: A comparative study of dupilumab versus omalizumab in severe pediatric asthma.

Investigadors: _____
Hospital: _____

Apreciat/da:

Ens dirigim a vostè per informar sobre la realització d'un estudi d'investigació en el que es convida al seu fill o a la seva filla a participar. Aquest assaig clínic ha estat aprovat pel "Comitè d'Ètica d'Investigació amb Medicaments" de l'Hospital Universitari Doctor Josep Trueta.

El seu fill o la seva filla pateix d'asma greu i per això se li ha prescrit tractament diari de manteniment amb corticoides inhalats a dosis altes combinats amb un agonista β d'acció perllongada (LABA). És possible però, que l'estratègia de tractament no obtingui els resultats òptims i que el seu fill o la seva filla segueixi patint exacerbacions moderades-greus.

En aquest assaig clínic volem estudiar l'eficàcia de dues teràpies biològiques que poden afegir-se com a tractament complementari. Aquestes teràpies son el dupilumab i l'omalizumab, ambdues han demostrat eficàcia en reduir les exacerbacions i en millorar el control de l'asma però volem investigar quina de les dues funciona millor. Vostè no sabrà quin dels dos fàrmacs rebrà el/la seu/va fill/a.

La nostra intenció en aquest document és que vostè rebi tota la informació necessària de forma correcta i que aquesta sigui suficient per a que vostè pugui decidir si participar o no en aquest estudi. Per això agraïm que llegeixi atentament aquest full d'informació.

Per començar, vostè ha de saber que la participació en aquest estudi és **totalment voluntària**. Si decideix que el seu fill o filla participi en l'estudi ha de saber que podrà abandonar en qualsevol moment sense que això suposi una alteració en la relació amb el seu metge o metgessa habitual ni que es produeixi cap perjudici en el seu tractament.

Si accepta la participació en l'estudi, li garantim la confidencialitat de les seves dades personals ("Reglamento (UE) 2016/679 del Parlamento y del Consejo Europeo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos" y "Ley Orgánica 3/2018 de Protección de Datos Personales y Garantía de los Derechos Digitales") així com dels resultats de l'estudi.

A continuació s'explicarà com es durà a terme l'estudi.

Finalitat: El nostre objectiu és conèixer si el dupilumab com a teràpia complementària resulta en un millor control de la malaltia en comparació a l'omalizumab. Volem estudiar si aplicant aquest fàrmac es poden disminuir les visites a urgències i els ingressos hospitalaris deguts a exacerbacions greus. També volem valorar si permet disminuir l'ús de corticoides sistèmics en comparació a l'omalizumab, ja sigui com a tractament diari o com a tractament de les exacerbacions.

Descripció de l'estudi: Abans de l'inici de l'estudi, informarem dels objectius del protocol i resoldrem tots els dubtes que sorgeixin a les famílies dels nens participants. Tots els nens i nenes amb asma d'entre 6 i 17 anys que prenguin corticoides inhalats a dosis altes combinats amb LABA i que puguin beneficiar-se d'una teràpia biològica se'ls convidarà a participar en aquest estudi.

En aquesta primera visita de control rutinària se li realitzaran un seguit de preguntes per tal d'avaluar si el seu fill o filla és candidat a participar a l'estudi. En cas que sigui un/a candidat/da idoni/a i que vostès com a tutors legals del menor acceptin participar de forma voluntària hauran de firmar el full de consentiment informat. Seguidament es faran més preguntes i proves per avaluar l'estat actual de la malaltia del seu fill o filla. En aquesta visita es realitzarà una espirometria forçada i es passarà el test de control de l'asma (ACT) o la versió per a nens de 6 a 11 anys si s'escau (c-ACT). A més, se li preguntarà pel nombre d'exacerbacions durant l'últim any i si aquestes han necessitat visita a urgències, ingrés hospitalari i/o ús de corticoides sistèmics.

Seguidament, se li donaran un seguit d'instruccions i recomanacions per al maneig de l'asma del seu fill/a. Rebrà informació sobre el tractament biològic, que s'administrarà cada 2-4 setmanes mitjançant injecció subcutània. El tractament pot realitzar-se en l'àmbit sanitari o al domicili. A més, se li explicarà detalladament totes les estratègies no farmacològiques que haurà de seguir per tal que el seu fill/a pugui assolir el millor control de la seva malaltia. També rebrà informació sobre com utilitzar correctament els dispositius d'inhalació.

Controls: Els controls amb el/la seu/va metge/ssa es programaran al 6è mes i al 12è mes, al final de l'estudi. En aquests controls es realitzarà una espirometria forçada i es tornarà a passar el test de control de l'asma (ACT) o la versió per a nens de 6 a 11 anys (c-ACT). Es valorarà si ha patit exacerbacions greus i si aquestes han necessitat atenció a urgències o ingrés hospitalari. A més, es valorarà la necessitat de corticoides sistèmics.

Beneficis i riscos: Si el/la seu/va fill/a participa en l'assaig clínic, és possible que es beneficiï d'un millor control de l'asma amb la conseqüent disminució del risc de futures exacerbacions greus. Tant si pertany a un grup o a l'altre, el/la seu/va fill/a es beneficiarà ja que, ambdós fàrmacs han demostrat ser eficaços. A més, el/la seu/va fill/a no deixarà de rebre el tractament de manteniment que rep actualment. No es preveu en cap cas que el/la seu/va fill/a pateixi cap risc o efecte advers greu si forma part de l'estudi.

Els participants no rebran cap compensació econòmica per participar ja que, això podria suposar un biaix i pèrdua d'evidència científica de l'estudi.

Confidencialitat: La informació obtinguda durant l'estudi serà codificada i arxivada confidencialment d'acord amb el "Reglamento (UE) 2016/679 del Parlamento y del Consejo Europeo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos" i la "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales". L'accés a les dades romandrà restringit al personal de l'estudi i a les autoritats sanitàries corresponents.

Revocació i participació: La participació en aquest estudi és totalment voluntària per tant, vostè pot demanar sortir en qualsevol moment. En aquest cas, totes les dades relacionades amb la seva participació seran eliminades i això no suposarà en cap cas una alteració en la relació amb el/la seu/va metge/ssa habitual.

Més informació: Si en qualsevol moment li sorgeixen nous dubtes o vol més informació, no dubti en posar-se en contacte amb el nostre equip d'investigadors a través del e-mail mireiacrahola@gmail.com o al telèfon +34 605 766 012.

Si té qualsevol dubte o necessita exercir alguns dels seus drets esmentats anteriorment, pot posar-se amb en contacte amb el Delegat de Protecció de Dades de l'Hospital Universitari Josep Trueta mitjançant el correu electrònic protecciodedades@....cat

Moltes gràcies per llegir el full d'informació.

Si accepta participar a l'assaig clínic haurà de signar el consentiment informat que li proporcionarà el/la seu/va metge/ssa. En firmar es compromet a complir amb els procediments de l'estudi que s'han explicat anteriorment en aquest document.

# Annex 4: INFORMED CONSENT

## CONSENTIMENT INFORMAT

Títol de l'estudi: A comparative study of dupilumab versus omalizumab in severe pediatric asthma.

Jo, _____ (nom i cognoms del tutor legal) amb DNI _____ , accepto que el/la meu/va fill/a _____ amb DNI _____ , participi en l'assaig clínic sobre l'ús del dupilumab com a teràpia complementària en asma greu i confirmo que:

- He llegit tota la informació que se m'ha entregat sobre l'estudi.
- He tingut l'oportunitat de preguntar els dubtes sobre l'estudi.
- He rebut respostes satisfactòries a les meves preguntes.
- He rebut suficient informació sobre el projecte.
- He entès els possibles riscs associats a la participació en el projecte.

He parlat amb _____ (nom i cognoms de l'investigador).

Comprenc que la participació és voluntària i puc retirar-me de l'estudi:

- Quan vulgui i sense haver de donar explicacions.
- Sense alteracions en les assistències sanitàries posteriors.

Estic informat/da de:

- L'existència d'un fitxer automatitzat de dades de caràcter personal.
- La informació podrà ser utilitzada únicament per a finalitats científiques respectant la confidencialitat.
- Aquest fitxer estarà en mans de l'investigador principal i com a participant tinc dret a l'accés, rectificació, cancel·lació i oposició.

Accepto lliurement participar en aquest assaig clínic.

Lloc i data: _____, __ de _____ del 20__

Signatura del tutor legal 1 Signatura del tutor legal 2 Signatura de l'investigador

Jo, com a tutor legal confirmo que _____ (nom i cognoms del 2n tutor legal) amb DNI _____ està d'acord en la lliure participació en aquest assaig clínic. ☐

## REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____ (nom i cognoms del tutor legal) amb DNI _____ , revoco el consentiment prèviament signat per la participació en l'assaig clínic.

Lloc i data: _____, __ de _____ del 20__

Signatura del tutor legal

Signatura de l'investigador

# Annex 5: PROVIDED ASSENT DOCUMENT

**DOCUMENT D'ASSENTIMENT DE MENORS**
**(prèviament autoritzats pels seus tutors legals)**

Títol de l'estudi: A comparative study of dupilumab versus omalizumab in severe pediatric asthma.

Finalitat: L'objectiu de l'estudi és comparar dues teràpies biològiques que es donen com a complement del tractament habitual per l'asma. Volem estudiar si aplicant aquests fàrmacs es poden disminuir les visites a urgències i els ingressos hospitalaris deguts a exacerbacions greus. Ambdós medicaments, el dupilumab i l'omalizumab, han demostrat ser eficaços en el tractament de l'asma.

Implicació de la participació en l'estudi: Et demanarem que a més de seguir amb el teu tractament habitual per l'asma, hauràs d'afegir un altre medicament. Aquest s'administrarà en forma d'injecció cada 2-4 setmanes al centre mèdic o a casa. No sabràs quin dels dos tractaments estàs rebent.

Durada de l'estudi: La durada total de l'estudi serà d'un any. Les visites de seguiment amb el/la seu/va pediatre/a es faran al 6è mes i al cap d'un any, al final de l'estudi. A l'inici de l'estudi se't farà una espirometria forçada i hauràs de contestar un test de control de l'asma (ACT). A més, et preguntarem el nombre d'exacerbacions durant l'últim any i si aquestes han necessitat visita a urgències, ingrés hospitalari i/o ús de corticoides sistèmics. A les dues visites de control un cop començat el tractament tornarem a fer una espirometria i hauràs de tornar a contestar les preguntes de l'ACT. També se t'explicarà detalladament les mesures no farmacològiques a seguir per assolir un millor control.

Riscos i beneficis: S'espera que amb el tractament complementari administrat s'aconsegueixin disminuir les exacerbacions greus millorant així el control de la malaltia ja que, ambdós fàrmacs han demostrat ser eficaços. No deixaràs de rebre el tractament de base que prens actualment. No es preveu que en cap cas pateixis efectes adversos greus.

Compensació: No està prevista cap compensació per la participació.

Participació voluntària: La teva participació en aquest estudi és **totalment voluntària**, no passa res si no vols participar-hi.

Dret a retirar-te de l'estudi: Si t'ho repenses pots abandonar l'estudi en qualsevol moment sense conseqüències negatives. Només cal que avisis sense necessitat de cap explicació.

Ús de les dades: Les teves dades només les veuran els investigadors de l'estudi i seran anònimes.

Assentiment

- He entès la informació sobre l'estudi i he tingut l'oportunitat de fer preguntes, les quals m'han respost correctament.
- Estic d'acord a participar-hi de forma voluntària.

Nom i cognoms del/de la menor d'edat participant: _____
DNI del/de la menor d'edat participant: _____

Lloc i data: _____, __ de _____ del 20__

Signatura del/de la menor Signatura de l'investigador

# Annex 6: DATA COLLECTION SHEET

## FULL DE RECOLLIDA DE DADES

Títol de l'estudi: A comparative study of dupilumab versus omalizumab in severe pediatric asthma.

Hospital: _____
Pacient (codi): _____

Instruccions:

- S'han de contestar tots els apartats.
- Si no es coneix la resposta a la pregunta marqui NS (No Sap).
- Si el pacient no ha respòs a la pregunta marqui NC (No Contestada).
- Marqui les caselles de resposta amb una X.

| | Sí | No |
|---|---|---|
| El pacient ha llegit el full d'informació | ☐ | ☐ |

**Informació del participant**

Edat (anys):
Sexe M ☐ F ☐
Edat en el moment del diagnòstic (anys):

Nombre total d'exacerbacions durant l'any anterior:
Nombre de visites a urgències per asma durant l'any anterior:
Nombre d'ingressos hospitalaris per asma durant l'any anterior:

Nombre total d'exacerbacions durant l'estudi:
Nombre de visites a urgències per asma durant l'estudi:
Nombre d'ingressos hospitalaris per asma durant l'estudi:

| | Inici de l'estudi | Visita 6 mesos | Visita 12 mesos |
|---|---|---|---|
| $FEV_1$ | | | |
| $FEV_1$/FVC | | | |
| ACT / c-ACT | | | |
| Dosi diària OGC | | | |