The prolongation of the EPAAC™ trial (Early Prevention of Asthma in Atopic Children), a multi-country, double-blind, placebo controlled, follow-up trial with 3 parallel groups (LCTZ-LCTZ, LCTZ-PLC and PLC-PLC) : Evaluating the long term efficacy and safety of levocetirizine (5 mg/mL oral drops - 0.125 mg/kg b.w. b.i.d.) administered for an additional 18-month period in preventing the onset of asthma in children coming from the EPAAC™ trial (A00309)

Sponsor : UCB S.A. – Pharma Sector
Chemins du Foriest
B-1420 Braine-l’Alleud
Belgium

UCB EMERGENCY CONTACTS (for Serious Adverse Events)
Clinical Research Physician Name : Fabienne Staelens
During working hours Tel nr : +32.2.386 24 43
Outside working hours (UCB Answering machine) Tel nr : +32.2.386 24 68
Fax nr : +32.2.386 24 21

Drug Name: Levocetirizine dihydrochloride

The confidential information in this document is provided to you as an Investigator, a potential Investigator or consultant, for review by you, your staff and applicable review committee(s). It is understood that the information will not be disclosed to any third party without written authorization from the Sponsor, except to the extent necessary to obtain informed consent from those persons to whom the investigational product may be administered, or their legally acceptable representative(s)
2. SIGNATURE PAGE

For UCB:

Clinical Research Physician:       Clinical Trial Manager:
Date: ___________________________   Date: ___________________________
Name:  F. STAELENS                Name:  E. FAYOUX

Signature:                         Signature:

For the trial center:

By my signature below, I hereby attest that I have read, discussed and understood the background information concerning the investigational product. I have read and discussed this Protocol RPCE04B0203 and agree to carry out the trial as set out therein. I agree that the trial shall be conducted in compliance with ICH Good Clinical Practice (GCP) and all applicable regulatory requirements. I accept my obligations relating to the principles that have their origin in the Declaration of Helsinki and specifically to Independent Ethics Committee (IEC), Informed Consent, and also my obligations to the Sponsor, or contracted representatives, as far as safety reporting, providing data, allowing monitoring, auditing, inspection by domestic and foreign Regulatory Authorities and quality control visits are concerned.

Obligations of confidentiality are accepted by both parties.

Investigator:

Date: ___________________________
Name: __________________________
Site number: _____________________
Signature:
### 3. TABLE OF CONTENTS

1. **TITLE PAGE** .................................................................................................................. 1

2. **SIGNATURE PAGE** ....................................................................................................... 2

3. **TABLE OF CONTENTS** ................................................................................................... 3

4. **GENERAL INFORMATION** .......................................................................................... 8

   4.1 Investigator .................................................................................................................... 8

   4.1.1 Signatory Coordinating Investigator: .......................................................................... 8

   4.2 Sponsor ............................................................................................................................ 8

   4.2.1 Clinical Research Physician ....................................................................................... 8

   4.2.2 Clinical Trial Manager ............................................................................................... 8

4.3 Contract Research Organization (including Central Laboratory) ......................................... 9

4.4 List of Abbreviations ........................................................................................................ 9

4.5 Definitions specific for this protocol ................................................................................ 11

   4.5.1 Atopic Child: ............................................................................................................... 11

   4.5.2 Study Disease: ............................................................................................................. 11

   4.5.3 Status of Sensitization to Allergens (normal/elevated): .............................................. 11

   4.5.4 Asthma is defined as either: ........................................................................................ 11

      4.5.4.1 Definition of wheezing episode: ........................................................................... 11

      4.5.4.2 Definition of nocturnal cough episode: .............................................................. 12

      4.5.4.3 Determination of date of onset of asthma: ......................................................... 12

      4.5.4.4 Recording of Wheezing or Nocturnal cough: .................................................... 12

      4.5.4.5 Time to onset of asthma: .................................................................................... 13

   4.5.5 AD definition: .............................................................................................................. 13

   4.5.6 Urticaria: ..................................................................................................................... 13

   4.5.7 Asthmatic status of the mother at baseline: .............................................................. 13

   4.5.8 Parents / legally acceptable representative(s): ......................................................... 13

   4.5.9 Caring person: ............................................................................................................ 13

   4.5.10 Local emollient for AD treatment: ........................................................................ 13

5. **PROTOCOL SUMMARY** ............................................................................................... 14

   5.1 Flow Chart .................................................................................................................... 19

   5.2 Schematic Diagram ....................................................................................................... 20

6. **BACKGROUND INFORMATION** ............................................................................... 21

   6.1 Rationale for the present trial ........................................................................................ 21

   6.2 Cetirizine ....................................................................................................................... 21

   6.3 Levocetirizine ................................................................................................................ 22

      6.3.1 Summary of findings from non-clinical studies .................................................... 22

      6.3.2 Summary of findings from clinical trials ............................................................... 23

         6.3.2.1 Human pharmacokinetics ............................................................................... 23

         6.3.2.2 Human pharmacodynamics ........................................................................... 23
### 6.3.2.3 Clinical studies ................................................................. 24
### 6.4 Summary of the known and potential risks and benefits, if any, to human subjects ................................................................. 24
### 6.5 Description of and justification for route of administration, dosage, dosage regimen, design and treatment duration ................................................. 25
### 6.6 Description of the population to be studied ........................................ 28

### 7. TRIAL OBJECTIVES AND PURPOSE .................................................. 29
#### 7.1 Primary Objective ................................................................. 29
#### 7.2 Secondary Objectives ............................................................ 29
#### 7.3 Exploratory Objectives ........................................................... 29

### 8. TRIAL DESIGN ............................................................................... 31
#### 8.1 Type/Design ........................................................................... 31
#### 8.2 Subjects/Centers Numbers ........................................................ 31
#### 8.3 Measures to Minimize/Avoid Bias .............................................. 31
##### 8.3.1 Randomization ................................................................. 31
##### 8.3.2 Blinding ............................................................................ 31
#### 8.4 Trial Duration ........................................................................... 32

### 9. SELECTION AND WITHDRAWAL OF SUBJECTS .......................... 33
#### 9.1 Subject Inclusion Criteria ........................................................ 33
##### 9.1.1 Inclusion criterion for the site .............................................. 33
##### 9.1.2 Inclusion criteria for the patient ........................................... 33
#### 9.2 Subject Exclusion Criteria ........................................................ 33
#### 9.3 Subject Withdrawal Criteria ....................................................... 33
##### 9.3.1 Withdrawal criteria ............................................................ 33
##### 9.3.2 Follow-up of Withdrawn Subjects ........................................ 34

### 10. TREATMENT OF SUBJECT (INVESTIGATIONAL PRODUCTS AND CONCOMITANT MEDICATIONS) ............................................... 35
#### 10.1 Trial Investigational Products ..................................................... 35
##### 10.1.1 Description of all Investigational Products ................................ 35
##### 10.1.2 Packaging ......................................................................... 36
##### 10.1.3 Labeling ............................................................................ 36
##### 10.1.4 Storage requirements ......................................................... 37
##### 10.1.5 Monitoring of Subject Compliance ........................................ 37
##### 10.1.6 Investigational Products Accountability .................................. 37
##### 10.1.7 Maintenance of Trial Treatment Randomization Codes and Procedures for Blind Breaking .......................................................... 37
#### 10.2 Concomitant Treatments and Rescue Medications .......................... 38
##### 10.2.1 Rescue Medication ............................................................. 38
##### 10.2.1.1 Atopic dermatitis .............................................................. 39
##### 10.2.1.2 Asthma .......................................................................... 41
10.2.2 Not Permitted Concomitant Treatments (Medications and Therapies) ..........................................................42

11. TRIAL PROCEDURES .................................................................................................................................43
11.1 Subject Identifier ...........................................................................................................................................43
11.2 Description of Procedures .........................................................................................................................43
   11.2.1 Urticaria ....................................................................................................................................................43
   11.2.2 Atopic Dermatitis ................................................................................................................................43
   11.2.3 Nocturnal cough episodes and wheezing episodes .............................................................................44
   11.2.4 Direct medical cost parameters ...........................................................................................................44
   11.2.5 Psychomotor assessment .......................................................................................................................44
      11.2.5.1 Global psychomotor development questionnaire ..................................................................44
      11.2.5.2 Behavioral assessment ...............................................................................................................45
11.3 Description Visit by Visit ............................................................................................................................45
   11.3.1 Visit 9 B ................................................................................................................................................45
   11.3.2 Visit 10 B (V10 B) and Visit 11 (V11) ..............................................................................................46
   11.3.3 Visit 12 (V12) End of trial Visit or early discontinuation visit .........................................................46
11.4 Handling of Biological Samples ..................................................................................................................47

12. ASSESSMENT OF EFFICACY .......................................................................................................................49
12.1 Specifications of Efficacy Variables ...........................................................................................................49
12.2 Methods and Timing for Assessing, Recording, and Analyzing the Efficacy Variables ............................49

13. ASSESSMENT OF SAFETY ..........................................................................................................................50
13.1 Specifications of Safety Variables .............................................................................................................50
13.2 Methods and Timing for Assessing, Recording, and Analyzing the Safety Variables ...............................50
13.3 Adverse Events ............................................................................................................................................50
   13.3.1 Definition of Adverse Event (AE) .......................................................................................................50
   13.3.2 Procedures for Reporting and Recording Adverse Events ...............................................................51
      13.3.2.1 Recording/Collection of AEs ..................................................................................................51
      13.3.2.2 Description of AEs ....................................................................................................................51
   13.3.3 Follow-up of Adverse Events .............................................................................................................54
   13.3.4 Rule for Repetition of an AE .............................................................................................................55
   13.3.5 Overdose of Investigational Product: ..............................................................................................55
13.4 Serious Adverse Events ...............................................................................................................................55
   13.4.1 Definition of Serious Adverse Event (SAE) ........................................................................................55
   13.4.2 Procedures for Reporting Serious Adverse Events (SAE) ..............................................................56

14. STATISTICS ....................................................................................................................................................58
14.1 Statistical and Analytical Plans ...................................................................................................................58
   14.1.1 Trial Population(s) .............................................................................................................................58
   14.1.2 Efficacy and Safety Variables .............................................................................................................58
      14.1.2.1 Efficacy Variables .......................................................................................................................58
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.10</td>
<td>Investigator Site File</td>
<td>73</td>
</tr>
<tr>
<td>16.11</td>
<td>Data Handling and Record Keeping</td>
<td>73</td>
</tr>
<tr>
<td>16.12</td>
<td>Clinical Trial Report</td>
<td>74</td>
</tr>
<tr>
<td>16.13</td>
<td>Subject Insurance</td>
<td>74</td>
</tr>
<tr>
<td>16.14</td>
<td>Publication and Presentation Policy</td>
<td>74</td>
</tr>
<tr>
<td>16.15</td>
<td>Archiving and Data Retention</td>
<td>75</td>
</tr>
<tr>
<td>16.16</td>
<td>Allocation of Responsibilities</td>
<td>75</td>
</tr>
<tr>
<td>16.17</td>
<td>Curriculum Vitae (CV)</td>
<td>75</td>
</tr>
<tr>
<td>16.18</td>
<td>Financial Disclosure</td>
<td>76</td>
</tr>
<tr>
<td>17.</td>
<td>REFERENCES</td>
<td>77</td>
</tr>
</tbody>
</table>
4. GENERAL INFORMATION

4.1 Investigator
The complete and updated list of Investigators is maintained in the Trial Master File (TMF) at UCB.

4.1.1 Signatory Coordinating Investigator:

The Chairman of the Scientific Advisory Board will sign the CSR on behalf of the EPAAC Scientific Advisory Board.

4.2 Sponsor

UCB S.A. Pharma Sector
Chemin du Foriest
B- 1420 Braine-l’Alleud
BELGIUM

4.2.1 Clinical Research Physician

F. STAELENS, MD.
UCB S.A. Pharma Sector
Chemin du Foriest
B- 1420 Braine-l’Alleud
BELGIUM
Tel: 32.2.386.24.43
Fax: 32.2.386.24.01

4.2.2 Clinical Trial Manager

E. FAYOUX
UCB S.A. Pharma Sector
Rue de Neuilly, 21
F- 92003 Nanterre
FRANCE
Tel: 33.1.47.29.79.03
Fax: 33.1.47.29.45.44
4.3 **Contract Research Organization (including Central Laboratory)**

Clinical Monitoring\(^{(a)}\)
Central Laboratory\(^{(a)}\)
Central randomization\(^{(a)}\)
e-CRF\(^{(a)}\)

\(^{(a)}\) Details to be found in TMF

4.4 **List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Atopic Dermatitis</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutical Chemical (Classification)</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve extrapolated at infinite time</td>
</tr>
<tr>
<td>b.i.d</td>
<td>Twice a day</td>
</tr>
<tr>
<td>b.w.</td>
<td>Body Weight</td>
</tr>
<tr>
<td>BCL</td>
<td>Behaviour Checklist</td>
</tr>
<tr>
<td>CDMS</td>
<td>Clinical Data Management System</td>
</tr>
<tr>
<td>C(_{\text{max}})</td>
<td>Maximum observed plasma concentration</td>
</tr>
<tr>
<td>CIU</td>
<td>Chronic Idiopathic Urticaria</td>
</tr>
<tr>
<td>cP450</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>CPMP</td>
<td>Committee for Proprietary Medicinal Products</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CRP</td>
<td>Clinical Research Physician</td>
</tr>
<tr>
<td>C-RP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CSU</td>
<td>Clinical Supply Unit</td>
</tr>
<tr>
<td>CTM</td>
<td>Clinical Trial Manager</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
<tr>
<td>DRC</td>
<td>Data Review Committee</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>e-CRF</td>
<td>electronic Case Report Form</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear, Nose and Throat</td>
</tr>
<tr>
<td>EPAAC</td>
<td>Early Prevention of Asthma in Atopic Children, trial A00309</td>
</tr>
<tr>
<td>ETACT(\text{TM})</td>
<td>Early Treatment of the Atopic Child for trial 9322/9913</td>
</tr>
<tr>
<td>FPV</td>
<td>First Patient First Visit</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-intestinal</td>
</tr>
<tr>
<td>GP</td>
<td>Grass Pollen</td>
</tr>
<tr>
<td>HDM</td>
<td>House Dust Mite</td>
</tr>
<tr>
<td>ICAM</td>
<td>Intercellular Adhesion Molecule</td>
</tr>
</tbody>
</table>
ICH  International Conference on Harmonisation
IEC  Independent Ethics Committee
IgE E  Immunoglobulin E
IL  Interleukin
ITT  Intention-To-Treat
kU/L  kilo Units per liter
kUA/L  kilo units per liter for allergen-specific antibodies used in specific IgE determination
LCTZ  Levocetirizine
LPLV  Last Patient Last Visit
MD  Medical Doctor
MED  Medications
MedDRA  Medical Dictionary for Regulatory Activities
mg  milligram(s)
mL  milliliter(s)
o.d.  Once a day
PAR  Perennial Allergic Rhinitis
PDF  Portable Document Format (Adobe Acrobat)
PK/PD  Pharmacokinetic/Pharmacodynamic
PLC  Placebo
PP  Per-Protocol
Q1  First quarter of the year
QT  QT-interval on the ECG
QTc  QT-interval on the ECG corrected for the heart rate (Bazett's formula)
RAST  Radio-Allergo Sorbent Test
SAB  Scientific Advisory Board
SAE  Serious Adverse Event
SAP  Statistical Analysis Plan
SAR  Seasonal Allergic Rhinitis
SD  Source Document
SGOT  Serum glutamic oxalacetic transaminase (same as AST or ASAT)
SGPT  Serum glutamic pyruvic transaminase (same as ALT or ALAT)
SOP  Standard Operating Procedure
TMF  Trial Master File
V  Visit
VAS  Visual Analog Scale
VCAM  Vascular Cell Adhesion Molecule
vs  Versus
Vₜ/F  Apparent Distribution Volume

Note:
In this protocol, unless explicitly specified otherwise, the term "Case Report Form" and its abbreviation "CRF", refer to both the electronic and the paper version.
4.5 Definitions specific for this protocol

4.5.1 Atopic Child:

• A child suffering from AD, with atopy in the family (biological mother or father, or one sibling suffering or having suffered from AD, allergic rhinitis or asthma).

4.5.2 Study Disease:

• For the purpose of this trial, the study disease is defined as either Atopic Dermatitis or Asthma or Allergy.

4.5.3 Status of Sensitization to Allergens (normal/elevated):

• Total IgE, IgE specific to grass pollen, house dust mite, egg, cat, peanuts, cow’s milk, alternaria and one center specific aeroallergen

<table>
<thead>
<tr>
<th></th>
<th>Normal (= not sensitized)</th>
<th>Elevated (= sensitized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IgE:</td>
<td>&lt; 30 kU/L</td>
<td>≥30 kU/L</td>
</tr>
<tr>
<td>Specific IgE:</td>
<td>&lt; 0.35 kUA/L</td>
<td>≥ 0.35 kUA/L</td>
</tr>
</tbody>
</table>

Values under the detection limit will be considered as corresponding to normal values.

4.5.4 Asthma is defined as either:

a) 3 separate episodes of wheezing in a clinical setting where asthma is likely and other conditions have been excluded,
b) 3 separate episodes of nocturnal cough with sleep disturbances lasting each for at least 3 consecutive nights,
c) A combination of 3 episodes of (a) and (b).

Two episodes of a or b being separated by at least 7 days without symptoms of wheezing or nocturnal cough.

4.5.4.1 Definition of wheezing episode:

• Any high pitch sound coming from the chest during expiration.
• Duration and numbering
  • The day of onset of this episode is defined as the first day of symptoms for this single episode.
The duration of a single episode is defined as the number of days with the symptom, occurring once or more during that day.

- Each time a wheezing free interval lasts more than 7 days, the occurrence of a new wheezing is considered as a new episode.
- In case of continuous symptoms for more than 7 days, the number of episodes will be calculated as follows:
  Number of wheezing episodes = 
  \((\text{total number of symptomatic days}/7) + 1\) (rounded to lower value)
- When the interval between symptomatic days is less than 7 days, the number of episodes will be calculated using the same rule.
- When wheezing and nocturnal cough take place in the same entity (separated by less than 7 days) the rules for wheezing supersedes the rules for nocturnal cough (nocturnal cough is disregarded).

4.5.4.2 Definition of nocturnal cough episode:

- One single episode of nocturnal cough is defined as at least 3 consecutive nights with nocturnal cough inducing sleep disturbances during each night. Nocturnal cough is defined as coughing between 19:00 and 7:00.

- Duration and numbering:
  - Two episodes should be separated by a minimum of 7 days without any nocturnal cough inducing sleep disturbances.
  - A period of continuous nocturnal cough (>3 nights) or several periods separated by less than 7 days will be considered as one episode, whatever the duration.

4.5.4.3 Determination of date of onset of asthma:

- The date of onset of asthma will be based on the dates of the third episode of either wheezing or nocturnal cough:
  - if the third episode is an episode of wheezing only, date of onset will be the first day of this third episode
  - if the third episode is an episode of nocturnal cough only, date of onset will be the third day of this third episode
  - if wheezing and nocturnal cough occurred together in the third episode, date of onset will be the first day of this third episode

4.5.4.4 Recording of Wheezing or Nocturnal cough:

- Any episode occurring during the night from day X to day X+1 will be ascribed to day X+1
4.5.4.5  *Time to onset of asthma:*

- Period between the randomization visit (V2), from the A00309 trial, and the date of onset of asthma.

4.5.5  *AD definition:*

- Atopic Dermatitis (Atopic Eczema or prurigo Besnier or neurodermitis constitutionalis) is defined as an erythematous-papulo-vesicular chronic skin disease with pronounced itching, typical localisations (cheeks, extensor surface of limbs) and dry skin \(^{(8,9)}\).

4.5.6  *Urticaria:*

- Typical hives or areas of skin swelling, redness and itching distinctly different from the child’s usual inflamed skin lesions of atopic dermatitis; associated with an infection or food allergen ingestion/contact or other trigger.

4.5.7  *Asthmatic status of the mother at baseline:*

- The mother has suffered from asthma after the age of 3 years.

4.5.8  *Parents / legally acceptable representative(s):*

- Refers to the person(s) legally responsible of the child and who give(s) his/her/their written consent for the inclusion of the child in this trial.

4.5.9  *Caring person:*

- Refers to the person who takes care of the child, adheres to the protocol and collects the data on the diary cards.

4.5.10  *Local emollient for AD treatment:*

- Refers to any substance used to hydrate the skin which is available without medical prescription.
### 5. PROTOCOL SUMMARY

<table>
<thead>
<tr>
<th>Trial number :</th>
<th>A00384</th>
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**Title of the trial:**
The prolongation of the EPAAC™ trial (Early Prevention of Asthma in Atopic Children), a multi-country, double-blind, follow-up trial with 3 parallel groups (LCTZ-LCTZ, LCTZ-PLC and PLC-PLC):
Evaluating the long term efficacy and safety of levocetirizine (5 mg/mL oral drops - 0.125 mg/kg b.w. b.i.d.) administered for an additional 18-month period in preventing the onset of asthma in children coming from the EPAAC™ trial (A00309)

<table>
<thead>
<tr>
<th>Trial primary objectives :</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary objective</strong></td>
</tr>
<tr>
<td>To assess the effect on the time to onset of asthma of a 36-month treatment with LCTZ (LCTZ-LCTZ), as compared to PLC (PLC-PLC) in asthma free young atopic children sensitized to GP and/or HDM.</td>
</tr>
</tbody>
</table>

**Secondary objectives**
- To investigate the clinical benefit on the time to onset of asthma after 36 months of treatment in the LCTZ-LCTZ group as compared to the LCTZ-PLC group.
- To investigate whether the benefit on the time to onset of asthma after 18 months of treatment with LCTZ can be maintained over an additional 18 month period, once active treatment is stopped (LCTZ-PLC versus PLC-PLC, after 36 months).
- To investigate the clinical benefit, on the time to onset of asthma, of an additional 18-month treatment period in the subset of subjects still asthma-free after the first 18-month treatment period (LCTZ-LCTZ versus LCTZ-PLC).
- To assess the safety of the long-term use of LCTZ in a large population of children aged between 30 and 60 months.

**Exploratory objectives**
- To describe the symptoms and the medications used for asthma during the additional 18-month treatment period.
- To describe the difference of symptoms and medications used for asthma between the first 18-month treatment period and the additional 18-month treatment period.
- To describe the use of topical corticosteroids, topical tacrolimus and pimecrolimus, oral antihistamines and local antibiotics or antiseptics for atopic dermatitis (AD) during the additional 18-month treatment period, overall and according to the severity of AD at baseline.
- To describe the incidence of urticaria and the number of episodes of urticaria per subject during the additional 18-month treatment period, overall and in the following subgroups: subjects who had never shown symptoms of urticaria prior to inclusion in
the trial and subjects who suffered at least one episode of urticaria prior to inclusion in the trial.

- To describe the time to onset of asthma considering an alternative definition of asthma based on wheezing only and/or a new definition (should the latter be adopted by the scientific community during the course of the trial), in each of the 3 treatment groups.
- To describe the symptoms of atopic dermatitis as assessed by the caring person.
- To describe the status of sensitization to allergens at the end of the additional 18-month treatment period.
- To compare, between groups, direct medical cost parameters related to asthma during the 36-month treatment period.
- To describe the psychomotor development of the children during the additional 18-month treatment period

**Methodology:**
Double-blind, randomized, placebo controlled trial with 3 parallel groups (LCTZ-LCTZ, LCTZ-PLC and PLC-PLC) for an additional 18-month treatment period.

The LCTZ-LCTZ treatment group consists of the subjects allocated to LCTZ in the A00309 trial and allocated to LCTZ for the additional 18-month treatment period (A00384 trial).

The LCTZ-PLC treatment group consists of the subjects allocated to LCTZ in the A00309 trial and allocated to PLC for the additional 18-month treatment period (A00384 trial).

The PLC-PLC treatment group consists of the subjects who were allocated to PLC in the A00309 trial and allocated to PLC for the additional 18-month treatment period (A00384 trial).

**Trial Type/Phase:** Therapeutic confirmatory / phase III

**Diagnosis and main criteria for inclusion:**

1) **Inclusion criteria which must be verified at visit 9 to allow subjects entering the new protocol with the additional 18-month treatment period:**

   **Inclusion criterion for the site:**
   - Site having randomized at least 2 subjects from the previous trial (A00309)

   **Inclusion criteria for the patient:**
   - Having completed the previous 18-month treatment period of the EPAAC trial
   - Written informed consent signed for the additional 18-month treatment period and dated by parent(s)/legally acceptable representative(s) according to local regulations.

2) **Withdrawal criterion after treatment allocation for the additional 18-month treatment period (V9 B):**

   Safety laboratory results are not within the normal range of the central laboratory and are considered as clinically significant by the Investigator unless trial disease related or part of usual and benign pathology for this age group.
**Trial period (years):**
FPFV: Q1 2004  
LPLV: Q1 2007 (end of additional 18-month treatment period)

**Number of subjects (planned):**
The number of subjects who will be involved in the additional 18-month treatment period is estimated around 300 (75 in the LCTZ-LCTZ group, 75 in the LCTZ-PLC group, 150 in the PLC-PLC group).

**Number of centers (planned):** around 60 to 70 centers

**Countries (planned):**
Australia, Austria, Belgium, Czech Republic, France, Germany, Italy, The Netherlands, Poland, Spain, United Kingdom and Republic of South Africa.

**Investigational product:** Levocetirizine 5 mg/mL – oral drops – 20 mL bottles.  
**Reference product:** placebo – oral drops – 20 mL bottles

**Trial duration per subject:** an additional 18-month treatment period

**Criteria for evaluation:**

**Efficacy variables:**
The primary efficacy variable is the time to onset of asthma evaluated during the 36-month treatment period. The time to onset of asthma is defined as the period elapsed between the randomization visit (V2 of trial A00309) and the date of onset of asthma.

The secondary efficacy variable is the time to onset of asthma during the additional 18 month treatment period, defined as the period elapsed between the end of the first 18 month treatment period (V9) and the date of onset of asthma. The diagnosis of asthma will be determined using the episodes of wheezing and nocturnal cough, including those recorded during the A00309 trial. This variable is defined only for the subjects entering the A00384 trial still asthma-free after the first 18 months of treatment with LCTZ.

**Exploratory efficacy variables:**
- Symptoms and use of medications for asthma (described according to the definition mentioned in section 4.5.4) during the additional 18-month treatment period, as measured by:
  - Percentage of days with symptoms of either wheezing or nocturnal cough,  
  - Percentage of days with symptoms of wheezing,  
  - Percentage of days with symptoms of nocturnal cough,  
  - Use and percentage of days of use of asthma medication.
- Use and percentage of days of use of the following medications for Atopic Dermatitis during the additional 18-month treatment period: topical corticosteroids; topical tacrolimus and pimecrolimus, oral H₁-antihistamines; local antibiotics or antiseptics.
- Incidence of subjects with urticaria and the number of episodes of urticaria per subject during the additional 18-month treatment period,
• The time to onset of asthma based on an alternative definition of asthma based on wheezing only and/or a new definition (should the latter be adopted by the scientific community during the course of the trial).
• The severity of atopic dermatitis and pruritus scores, as assessed by the caring person each week during the additional 18-month treatment period
• The status of sensitization to allergens at the end of the additional 18-month treatment period
• The direct medical cost parameters related to asthma during the 36-month treatment period.
• The risk factors for early sensitization (IgE), atopic dermatitis severity, history of urticaria.

Safety variables:
Safety assessments will be made during the additional 18-month treatment period using physical examinations, adverse events, body mass parameters, laboratory test results and the psychomotor evaluation.
The Global Psychomotor Development questionnaire will be applied to all children in all countries at each visit.
The behavioral development of the child will be evaluated by the caring person at each scheduled visit, using the following questionnaire: Behaviour Checklist (BCL). This evaluation will be restricted to the United Kingdom and Australia.

Statistical methods:
Summary statistics will consist of frequency tables for binary or categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum and maximum) will be tabulated.

Two populations are defined for this trial:
• The A00309 ITT population is the ITT population as defined in trial A00309,
• The A00384 ITT population will consist of the subjects of the A00309 ITT population enrolled in trial A00384 and who took at least one dose of medication during trial A00384.

Efficacy
Primary efficacy analysis:
The primary efficacy variable will be analyzed descriptively on the A00309 ITT population. This analysis will consist of the number and percentage of subjects with asthma during the 36 month treatment period and the cumulative incidence curves of asthma, estimated using the Kaplan-Meier approach. If applicable, the median time to onset of asthma will be estimated with its 95% confidence interval.
The examination of the results of primary efficacy analysis for the treatment groups LCTZ-LCTZ and PLC-PLC will allow to evaluate the primary objective of the trial.

The primary efficacy analysis will also allow to evaluate the first two secondary objectives of the trial.

Secondary efficacy analysis:
The analysis of the secondary efficacy variable will be performed on a subset of the A00384 ITT population, consisting of those subjects still asthma-free after the first 18 month of treatment with LCTZ. This analysis will be performed similarly to the primary efficacy variable, considering only the treatment groups LCTZ-LCTZ and LCTZ-PLC.

Exploratory analysis of the time to onset of asthma based on an alternative definition of asthma will be performed similarly to the primary and secondary efficacy variables. Other exploratory variables will be analyzed descriptively on the A00384 ITT population using summary statistics by treatment group.

Safety.
Safety variables will be listed individually for detailed clinical review, when needed. Laboratory values, body mass parameters, and changes from baseline in laboratory values and body mass parameters will be presented descriptively by treatment group. Ninety-five % confidence intervals will be calculated on the median of the difference between the on-treatment values and the baseline values. Adverse events will be summarized descriptively by treatment group, body system, and preferred term. Additional tables will summarize adverse events by severity and relationship to trial drug as well as separate tables for adverse events leading to withdrawal from the trial and SAEs. The psychomotor assessments will be analyzed descriptively by treatment group. These safety analyses will be performed on the A00384 ITT population.
5.1 Flow Chart

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Visit</th>
<th>V9 B</th>
<th>V10 B</th>
<th>V11</th>
<th>V12&lt;sup&gt;(c)&lt;/sup&gt;</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.2.2</td>
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<tr>
<td>Demographic data&lt;sup&gt;(a)&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>11.3.1</td>
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<tr>
<td>Verification of inclusion / exclusion criteria</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Withdrawal criteria</td>
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<td>9.2</td>
</tr>
<tr>
<td>Medical / Surgical history&lt;sup&gt;(a)&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>11.3.1</td>
</tr>
<tr>
<td>Physical examination / Body Mass</td>
<td>(X)&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>11.3.1</td>
</tr>
<tr>
<td>Nocturnal cough episodes</td>
<td>(X)&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>11.2.3</td>
</tr>
<tr>
<td>Wheezing episodes</td>
<td>(X)&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>11.2.3</td>
</tr>
<tr>
<td>Urticaria episodes</td>
<td>(X)&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>11.2.1</td>
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<tr>
<td>Blood sampling</td>
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</tr>
<tr>
<td>Population PK</td>
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<td></td>
<td></td>
<td>11.4</td>
</tr>
<tr>
<td>Recording medications + procedures</td>
<td>(X)&lt;sup&gt;(b)&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Recording of Adverse Events</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Direct medical cost parameters</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>11.2.4</td>
</tr>
<tr>
<td>Psychomotor assessment&lt;sup&gt;(d)&lt;/sup&gt;</td>
<td>(X)&lt;sup&gt;(b)&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
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<td>11.3.3</td>
</tr>
</tbody>
</table>

<sup>(a)</sup> Those data are the same as for the A00309 trial and do not need to be recorded again.
<sup>(b)</sup> Those data are already recorded at Visit 9 (V9) of the A00309 trial.
<sup>(c)</sup> Or early discontinuation visit, as noted in section 11.3.3.
<sup>(d)</sup> BCL questionnaires will be restricted to the United Kingdom and Australia.
Global Psychomotor Development questionnaire will be applied to all children.
5.2 Schematic Diagram

![Schematic Diagram](image-url)

- **Placebo**
- **Levocetirizine**

<table>
<thead>
<tr>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Levocetirizine</td>
<td>Levocetirizine</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

- **n = 500**
6. BACKGROUND INFORMATION

6.1 Rationale for the present trial

The purpose of this protocol is to assess whether the continuation of active treatment would maintain the benefit observed on prevention of asthma at the end of the first 18-month treatment period of the previous trial A00309.

This protocol comes up in line with the advancement of the scientific knowledge in the allergy field gained recently in the prevention of allergic disease and asthma, and from the analysis of last data generated during the follow-up period of the previous ETAC™ (Early Treatment of the Atopic Child) trial.

Indeed, in the ETAC™ trial, where the children were treated during 18 months with cetirizine, the data observed after a 5-year follow-up period, showed that following study drug interruption, trial benefit began to evolve, with 2 different patterns. For the grass pollen sensitized subgroup, there was a maintained lower cumulative prevalence of asthma, while for the house dust mite sensitized subgroup loss of efficacy was observed, as at the end of the 5 years, there was no difference between the cetirizine and placebo groups (1).

In addition, recent scientific studies in the allergy field point out that some interventions in very early childhood can bring about an effect in the development of allergic disease in the first years of life, however sustainability of effect in later childhood (1) is not always observed (e.g. allergen avoidance (2), breast feeding (3), hypoallergenic milk (4), …).

On the other hand, other studies showed that long-term treatments might prevent the onset of new allergies and the development of asthma:

- Long term treatment over 3 years with immunotherapy may prevent further sensitizations in young symptomatic allergic children monosensitized to HDM (5), and reduce the development of asthma in children with seasonal rhinoconjunctivitis (6).
- Likewise, long term treatment with ketotifen showed also after a 3-year treatment study, efficacy in preventing the onset of asthma (7).

In conclusion, the rationale of adding an 18-month treatment follow-up period is that a 3-year course of treatment in young children at risk may achieve a long-lasting efficacy in preventing the onset of the asthma.

6.2 Cetirizine

Cetirizine is a well-known and potent H1-antihistamine, registered and marketed virtually worldwide for administration to adults and children over 12 years of age at a daily dose of 10 mg for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.
In children above 6 years or above 30 kg, the dose of cetirizine is 10 mg/day in one or two intakes. Cetirizine is registered for administration to children from 2 to 6 years in the majority of the countries at a dose of 5 mg/day in two intakes. Cetirizine is also registered, in some countries, for administration to infants younger than 2 years, at the recommended dose of 2.5 mg b.i.d. (11).

In addition to its H₁-antihistamine effect, cetirizine was shown to display anti-allergic activities: at a dose of 10 mg once or twice daily, it inhibits the late phase recruitment of inflammatory cells, notably eosinophils, in the skin (12) and conjunctiva (13) of atopic subjects submitted to antigen challenge, and the dose of 30 mg/day inhibits the influx of eosinophils in the bronchoalveolar lavage fluid during a late-phase bronchial constriction induced by allergen inhalation in asthmatic subjects (14). Moreover, cetirizine inhibits the late-phase inflammatory reaction induced in chronic urticaria patients by intradermal administration of kallikrein (15).

It also downregulates the expression of adhesion molecules, such as ICAM-1 (16) and VCAM-1 (17), which are markers of allergic inflammation.

Cetirizine is a racemate of two enantiomers, ucb 28556 (levocetirizine dihydrochloride) the R-enantiomer and ucb 28557, the S-enantiomer.

6.3 Levocetirizine

ucb 28556 (levocetirizine dihydrochloride) is the R-enantiomer of cetirizine dihydrochloride (Zyrtec®). The ratio of levocetirizine/racemate cetirizine content is 1 / 2 (i.e.5 mg levocetirizine = 10 mg cetirizine).

Levocetirizine dihydrochloride will be called levocetirizine in this protocol. Levocetirizine is registered in 25 countries under the name of Xyzal® (Xuzal® in Germany) in adults and children above the age of 6 years at the dose of 5 mg once a day for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.

6.3.1 Summary of findings from non-clinical studies

Pre-clinical studies have shown that:

- Levocetirizine has 2-fold higher affinity for human H₁-receptors than cetirizine and it dissociates much lower from H₁-receptors than ucb 28557; its selectivity is similar to that reported for the racemic compound cetirizine;
- Levocetirizine has superior activity over ucb 28557 in specific animal models, where histamine is used to induce wheal and flare cutaneous reaction (18, 19, 20)
- There is no interconversion of the enantiomers in vivo.
- Like the racemic compound cetirizine, levocetirizine demonstrated a low toxicity after oral administration in rat and dog.

Therefore, it was considered justified to develop levocetirizine as an improvement on cetirizine.
The development of a single enantiomer from an approved racemate can utilize such data on the corresponding racemate as is applicable to the enantiomer. Suitable “bridging” studies have been carried out to link the complete racemate data to the incomplete data on the selected enantiomer\(^{(21)}\). Therefore, cetirizine was used as comparator in several bridging studies. These bridging studies proved that levocetirizine is the eutomer (i.e. the active enantiomer of the racemate cetirizine, as the S-enantiomer does not contribute to the antihistamine effects). This means that the disposition of levocetirizine is comparable when given alone or as the racemate and no chiral inversion occurred. The data obtained with cetirizine can thus be used to describe the effects of levocetirizine\(^{(22)}\).

### 6.3.2 Summary of findings from clinical trials

#### 6.3.2.1 Human pharmacokinetics

In adult humans, levocetirizine is rapidly and extensively absorbed after oral intake. The pharmacokinetic profile is the same when given as such (levocetirizine) or when given as the racemate (cetirizine). No chiral inversion occurs during the process of absorption or elimination. The pharmacokinetics of levocetirizine are dose- and time-independent. The apparent body clearance is 0.63 mL/min/kg and the elimination \(t_\frac{1}{2}\) is approximately 8 hours. Levocetirizine binds extensively to plasma proteins (95%) and the distribution is restrictive \((V_z/F = 0.4 \text{ L/kg})\). Steady state is achieved after two days of administration. Food delays the rate but not the extent of its absorption. Levocetirizine is excreted predominantly unchanged in the urine by glomerular filtration and active tubular secretion. Less than 14% of the dose is metabolized and the metabolism does not exhibit genetic polymorphism. Due to the low extent of metabolism and to the absence of any inhibitory effects on human liver cP450 enzymes, levocetirizine is unlikely to produce or to be subject to metabolic interactions. Total and renal clearances are reduced in subjects with renal impairment. Daily dose adjustments and/or longer dosing intervals should be recommended for patients with moderate or severe renal impairment\(^{(23,24)}\).

#### 6.3.2.2 Human pharmacodynamics

Bridging pharmacodynamic studies established the comparable antihistaminic activity of levocetirizine at half the dosage of cetirizine both in the skin and in the nose in adults\(^{(25,26)}\).

The safety of levocetirizine was excellent. The only adverse events reported in these studies were a headache of mild severity and a severe bronchitis, with no causal relationship with the investigational product.
6.3.2.3 Clinical studies

Two studies in Seasonal Allergic Rhinitis (SAR) have clearly demonstrated the therapeutic efficacy of 5 mg levocetirizine in terms of relief of the total mean score of the four symptoms of allergic rhinitis (sneezing, rhinorrhea, nasal pruritus and ocular pruritus): the dose-ranging study \(^{(54)}\) confirmed that 5 mg once daily has the best benefit/risk ratio, and the formal bridging study \(^{(27)}\) showed that the doses of 5 mg levocetirizine and 10 mg cetirizine are clinically equivalent in this major indication for antihistamines.

Two studies in Perennial Allergic Rhinitis (PAR) \(^{(28,29)}\) including subjects aged over 12 years have confirmed the efficacy and tolerability of levocetirizine.

The adverse events profile of 5 mg levocetirizine is comparable in nature and incidence to that of 10 mg cetirizine.

In the clinical development program for rhinitis and chronic urticaria, no child under the age of 12 years was exposed to levocetirizine alone. This is explained by the similarity of levocetirizine to the active component of the racemate cetirizine, the lack of activity as well as lack of interaction of the other isomer, the similarity of PK/PD behavior, and the possible extrapolation of efficacy-safety conclusions made from adults to children in this disease area. Thus, the use of levocetirizine in patients aged 6 to 12 years and suffering from SAR, PAR or CIU is justified from a scientific and ethical point of view.

The same conclusion is applicable to the children under the age of 6 years, provided that an adequate pharmaceutical form is available. Therefore an oral drops formulation has been developed.

6.4 Summary of the known and potential risks and benefits, if any, to human subjects.

As levocetirizine is the active isomer of cetirizine, its efficacy/safety ratio can be extrapolated from that of cetirizine. In addition, its pharmacokinetic behavior appears similar to cetirizine.

The safety of levocetirizine has been validated in a database of 1136 patients exposed to the compound (as of June 2001).

The post marketing surveillance experience of levocetirizine is limited, as it has only been marketed since February 2001.

In therapeutic studies with levocetirizine, the most common adverse events (occurring in more than 1% of subjects) and considered related to the study drug were somnolence, dry mouth, headache, fatigue and asthenia. Of these, only somnolence (including also drowsiness and sleepiness) appeared to occur more frequently in levocetirizine-treated subjects compared with those taking placebo.

It is doubtful that this increased rate of somnolence is of concern in the population which is going to be studied in the EPAAC™ trial; indeed somnolence was not observed in ETACT™ trial (as described in the next paragraph). In addition, it is known that the incidence of
somnolence/sedation following antihistamine treatment is different in children as compared with adults (as recently confirmed in a study carried out in school-age children, where incidence of somnolence or decreased alertness, following intake of loratadine or the 1st generation antihistamine diphenhydramine, was not different from placebo (30)). The safety of levocetirizine in the 1-2 years age range can be inferred from the safety profile displayed by cetirizine in the ETACTM trial: drop-outs and serious adverse events, including hospitalizations, occurred infrequently and were less common in the children receiving cetirizine than in those children receiving placebo, although the differences were not statistically significant. Most reported symptoms and events were mild and were attributed to intercurrent respiratory or gastrointestinal infections, exacerbation of allergic disorders, or age-related concerns rather than to medication-related adverse effects. There were no clinically relevant differences between the groups for neurologic or cardiovascular symptoms or events, growth, behavioral or developmental assessments, laboratory test results, or electrocardiograms, and no children receiving cetirizine had prolongation of the QTc interval (10).

More detailed information about levocetirizine can be found in the Investigators’ Brochure (31).

6.5 Description of and justification for route of administration, dosage, dosage regimen, design and treatment duration.

The dose of levocetirizine for this trial was selected in order to provide this infant/young children population:

- With a dose of levocetirizine similar to that given in the ETACTM trial.
- This dose had been determined, for ETACTM, taking into account the specificity of pharmacokinetic behavior of cetirizine in the young population, and with the aim of maintaining an activity over 24 hours, whilst not exceeding the Cmax values seen in the adult population.

Dose selection of cetirizine in pediatric population (ETACTM)

The PK parameters of cetirizine in infants, children and adults are summarized in the following table:
Table 6:1  
Cetirizine pharmacokinetic parameters observed in children and in adults

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean [range]</th>
<th>Dose (mg [mg/kg])</th>
<th>AUC (µg/L/h)</th>
<th>T1/2 (hours)</th>
<th>Cmax (ng/mL)</th>
<th>Clearance (mL/min/kg)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
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<tr>
<td>1.3 [0.6-2]</td>
<td>2 to 3 [0.25]</td>
<td>2704 ± 1829</td>
<td>3.1±1.8</td>
<td>390±135</td>
<td>2.13±1015</td>
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<td>(34)</td>
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<tr>
<td>2.7 [2-4]</td>
<td>5 (≈ 0.34)</td>
<td>4009 ± 867</td>
<td>4.9±0.6</td>
<td>660±191</td>
<td>1.48±0.41</td>
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<td>(35)</td>
</tr>
<tr>
<td>3.8 [2-6]</td>
<td>5 (≈0.32)</td>
<td>4772 ± 1318</td>
<td>5.6±1.0</td>
<td>607±231</td>
<td>1.27±0.80</td>
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<tr>
<td>10 [6-12]</td>
<td>5 (≈0.14)</td>
<td>2201</td>
<td>6.2±1.6</td>
<td>275±58</td>
<td>0.93±0.16</td>
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<tr>
<td>8 [6-12]</td>
<td>5 (≈0.16)</td>
<td>2872</td>
<td>7.1±1.6</td>
<td>427.6 ± 144</td>
<td>1.04±0.20</td>
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<td>8 [6-12]</td>
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<td>25 [21-35]</td>
<td>20 (≈0.31)</td>
<td>7206 ± 2020</td>
<td>9.4±2.4</td>
<td>775 ± 176</td>
<td>0.74±0.19</td>
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<td>(32)</td>
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<tr>
<td>24 [-]</td>
<td>10 (≈0.15)</td>
<td>3721 ± 325</td>
<td>10.6±1.5</td>
<td>337±34</td>
<td>0.64±0.14</td>
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<td>(33)</td>
</tr>
</tbody>
</table>

**Differences in clearance between adult and pediatric population**

The pharmacokinetic and efficacy/safety of cetirizine have been assessed in a pediatric population aged 2 to 12 years and in infants. The apparent total body clearance of cetirizine is increased in the pediatric population. In 11-month old infants, the apparent total body clearance is 2.2 mL/min/kg, as compared with 0.6-0.7 mL/min/kg in adults.

**Adjustment of the total daily dose**

Therefore the body weight daily doses (mg/kg) have to be adjusted, based on these differences in clearance. The recommended daily dose of cetirizine in ETACTM (infants aged 12 months and more) was thus adjusted to 0.5 mg/kg compared to approximately 0.15 mg/kg in adults. This adjustment also took into account the fact that pilot studies in atopic dermatitis, the primary disease in the ETACTM trial, indicated that doses of cetirizine higher than that registered were more effective.

**Adjustment in dose frequency**

In infants, a shorter half-life is observed for cetirizine (approximately 3 hours compared with 9 hours in adults). This questions the possibility of maintaining pharmacodynamic activity over 24 hours, with an o.d. administration schedule. Indeed, in children aged 6 to 12 years, maintenance of inhibition of wheal was less effective after an o.d. than a b.i.d. dose schedule (increased wheal area 38.55 mm² vs 6.85 mm²). At 12 hours, in the age range of 1 to 2 years, the inhibition following a b.i.d. administration was at a level of 90% for wheal and 87% for flare. Thus, a b.i.d. administration schedule was selected in order to maintain the pharmacodynamic activity.
Safety aspects
The unit dose was selected in order to have a $C_{\text{max}}$ in infants/young children of the same level of magnitude as those observed in the adult population.

These daily dose adjustments and b.i.d. administration provide:
- A $C_{\text{max}}$ concentration close to those in adults following a standard 10 mg oral dose ($\approx 390$ vs $337$ ng/mL),
- A pharmacodynamic activity maintained over 24 hours,
- A daily AUC value ($\approx 5400 \mu g/L/h$ [2 times $\approx 2704 \mu g/L/h$].) which is around 145% of that observed in adults ($\approx 3300 \mu g/L/h$).

Dose selection of levocetirizine in pediatric population (EPAAC™)

Selection of the 5mg levocetirizine dose in adults
In histamine induced wheal and flare reactions, the pharmacodynamic effect of levocetirizine (2.5 mg) was equivalent to that of cetirizine (5 mg) in a trial performed in 18 healthy volunteers. The S-enantiomer, ucb 28557 (2.5 mg) did not show any relevant effect. In a nasal provocation test performed in 24 healthy volunteers, the median histamine-induced nasal reaction threshold was increased from 8 mg/mL to 32 mg/mL by levocetirizine (5 mg) and cetirizine (10 mg) respectively. The S-enantiomer, ucb 2857, was inactive and equivalent to the placebo (42, 43).

In a bridging equivalence trial conducted in 696 adult patients with seasonal allergic rhinitis, it has been shown that levocetirizine (5 mg) is clinically equivalent to cetirizine (10 mg) (27).

Similarity of behavior of levocetirizine as a single enantiomer or within racemate mixture
In a trial specifically designed to compare the absorption and disposition of levocetirizine when given as a single enantiomer (10 mg) or as the racemate, cetirizine (20 mg), it was demonstrated that the pharmacokinetic parameters of levocetirizine were similar when levocetirizine was given as the single enantiomer or as the racemate. In addition, the trial demonstrated that levocetirizine did not undergo in vivo chiral inversion (44).

Selection of the levocetirizine dose for the EPAAC™ trial
The disposition of levocetirizine is not influenced by the S-enantiomer and the pharmacodynamic and therapeutic activities of cetirizine are supported by the R-enantiomer, levocetirizine. The ratio of levocetirizine/racemate cetirizine content is 1 / 2. Thus, in order to provide the same infant/young children population with the same level of exposure to levocetirizine as in the ETACTM trial, the total daily dose of levocetirizine will be 0.25 mg/kg/d (half the 0.50 mg/kg/d ETACTM cetirizine dose) with a maximum dose of 2.75 mg b.i.d.
6.6 Description of the population to be studied

The trial population is defined as children aged between 30 and 42 months who have completed the previous 18-month treatment period of the EPAAC trial.

Statement
The present trial will be conducted in accordance with:

• This protocol
• International Conference on Harmonization: ICH E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
• The principles that have their origin in the Declaration of Helsinki
• Local laws and regulations
7. TRIAL OBJECTIVES AND PURPOSE

The LCTZ-LCTZ treatment group consists of the subjects allocated to LCTZ in the A00309 trial and allocated to LCTZ for the additional 18-month treatment period (A00384 trial). The LCTZ-PLC treatment group consists of the subjects allocated to LCTZ in the A00309 trial and allocated to PLC for the additional 18-month treatment period (A00384 trial). The PLC-PLC treatment group consists of the subjects allocated to PLC in the A00309 trial and allocated to PLC for the additional 18-month treatment period (A00384 trial).

7.1 Primary Objective

To assess the effect on the time to onset of asthma of a 36-month treatment with LCTZ (LCTZ-LCTZ), as compared to PLC (PLC-PLC) in asthma free young atopic children sensitized to GP and/or HDM.

7.2 Secondary Objectives

- To investigate the clinical benefit on the time to onset of asthma after 36 months of treatment in the LCTZ-LCTZ group as compared to the LCTZ-PLC group.
- To investigate whether the benefit on the time to onset of asthma after 18 months of treatment with LCTZ can be maintained over an additional 18 month period, once active treatment is stopped (LCTZ-PLC versus PLC-PLC, after 36 months)
- To investigate the clinical benefit, on the time to onset of asthma, of an additional 18-month treatment period in the subset of subjects still asthma-free after the first 18-month treatment period (LCTZ-LCTZ versus LCTZ-PLC)
- To assess the safety of the long-term use of LCTZ in a large population of children aged between 30 and 60 months

7.3 Exploratory Objectives

- To describe the symptoms and the medications used for asthma during the additional 18-month treatment period.
- To describe the difference of symptoms and medications used for asthma between the first 18-month treatment period and the additional 18-month treatment period.
- To describe the use of topical corticosteroids, topical tacrolimus and pimecrolimus, oral antihistamines and local antibiotics or antiseptics for atopic dermatitis (AD) during the additional 18-month treatment period, overall and according to the severity of AD at baseline.
- To describe the incidence of urticaria and the number of episodes of urticaria per subject during the additional 18-month treatment period, overall and in the following subgroups: subjects who had never shown symptoms of urticaria prior to inclusion in
the trial and subjects who suffered at least one episode of urticaria prior to inclusion in the trial.

- To describe the time to onset of asthma considering an alternative definition of asthma based on wheezing only and/or a new definition (should the latter be adopted by the scientific community during the course of the trial), in each of the 3 treatment groups.
- To describe the symptoms of atopic dermatitis as assessed by the caring person.
- To describe the status of sensitization to allergens at the end of the additional 18-month treatment period.
- To compare, between groups, direct medical cost parameters related to asthma during the 36-month treatment period.
- To describe the psychomotor development of the children during the additional 18-month treatment period
8. **TRIAL DESIGN**

8.1 **Type/Design**

This is a multi-country, double blind, placebo-controlled, randomized phase III trial with 3 parallel groups (LCTZ-LCTZ, LCTZ-PLC and PLC-PLC) for an additional 18-month treatment period.

8.2 **Subjects/Centers Numbers**

- The number of subjects who will be involved in the additional 18-month treatment period is estimated to around 300.
- It is estimated that around 60 to 70 centers will be involved in Europe, Australia and Republic of South Africa.

8.3 **Measures to Minimize/Avoid Bias**

8.3.1 **Randomization**

All randomized subjects in trial A00309, including withdrawals or subjects not entering trial A00384, will be retrospectively re-allocated to either LCTZ or PLC for this additional 18-month treatment period. This will allow to include all subjects in the statistical analysis of the time to onset of asthma during the 36-month treatment period (survival analysis).

This re-allocation for the additional 18-month treatment period will proceed as follows:
- all subjects that were randomized to the PLC group in trial A00309 will be re-allocated into PLC,
- all subjects that were randomized to the LCTZ group in trial A00309 will be re-allocated into either LCTZ or PLC. This re-allocation will be performed using a one to one randomization, by blocks and the subjects will be re-allocated using the same order they were randomized for the randomization of trial A00309.

8.3.2 **Blinding**

The 2 solutions will be identical in aspect to allow the double-blind design.

The allocation of the treatment for the additional 18-month treatment period (trial A00384) will be performed by an external party (Clinphone) and communicated to UCB Clinical Supply Unit (CSU) only. Neither the subject nor any of the investigator or sponsor staff (except CSU) will be aware of the treatment received during the first 18-month treatment period (trial A00309) or the additional 18-month treatment period (trial A00384) as long as
the A00309 database is blind. This, in order to protect the double-blind character of the first trial (A00309).

The procedure to unblind trial A00309 while keeping the second trial A00384 blind will be fully described in a separate document.

8.4 Trial Duration

For each subject, the trial will last 18 months. After the first 18-month treatment period of the previous protocol (A00309), at V9 B, there will be a treatment allocation for the additional 18-month treatment period, then, the following 3 visits will be scheduled every 6-months, ± 3 weeks, during 18-months (V10 B, V11 and V12).

In the case of a postponed visit, the next visit will be scheduled based on the randomization visit, V2 of A00309, (and not on the postponed visit) in order to maintain a total of 36 months of treatment for each patient. (A00309 followed by A00384).

The clinical part of the trial is planned to start in Q1 2004, with the last subject inclusion in Q3 2005 and to finish in Q1 2007 approximately, 3 years after the target number of subjects is reached for the first 18-month treatment period (A00309).

This time schedule is consistent with the expected duration of the treatment and the declared potential rate of entry of eligible subjects by the Investigator(s).
9. **SELECTION AND WITHDRAWAL OF SUBJECTS**

Before any trial procedures are initiated for any subject in this trial, an Independent Ethics Committee (IEC) approved written informed consent form will be properly executed and documented.

### 9.1 Subject Inclusion Criteria

Inclusion criteria which must be verified at visit 9 to allow subjects entering the new protocol with the additional 18-month treatment period:

#### 9.1.1 Inclusion criterion for the site:
- Site having randomized at least 2 subjects from the previous trial (A00309)

#### 9.1.2 Inclusion criteria for the patient:
- Having completed the previous 18-month treatment period of the EPAAC trial
- Written informed consent signed for the additional 18-month treatment period and dated by parent(s)/legally acceptable representative(s) according to local regulations.

### 9.2 Subject Exclusion Criteria

Not applicable.

### 9.3 Subject Withdrawal Criteria

Investigators should attempt to minimize the number of losses to follow-up and to obtain a maximum of information on such subjects. In case of withdrawal or discontinuation, the Investigator should make every effort, and document his/her effort, to complete the final evaluation (end of treatment visit – V12). All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents and in the CRF.

#### 9.3.1 Withdrawal criteria

Withdrawal criterion after treatment allocation for the additional 18-month treatment period (V9 B):
- Safety laboratory results are not within the normal range of the central laboratory and are considered as clinically significant by the Investigator unless trial disease related or part of usual and benign pathology for this age group
Other withdrawal criteria

- Withdrawal of consent by the parent(s) or legally acceptable representative for any reason, at any time
- Withdrawal for safety reasons by the Investigator (AE)
- Protocol violation that could invalidate the interpretation of the results e.g. intake/use of prohibited medication (Class D corticosteroids, systemic tacrolimus or ciclosporin).

9.3.2  Follow-up of Withdrawn Subjects

If the reason for withdrawal is an AE, the Investigator will follow the case up to resolution and provide the Sponsor with a final report of this AE or justify why no final report will be provided.
10. TREATMENT OF SUBJECT (INVESTIGATIONAL PRODUCTS AND CONCOMITANT MEDICATIONS)

10.1 Trial Investigational Products

10.1.1 Description of all Investigational Products

The active investigational product and placebo will be supplied under the responsibility of the UCB Clinical Supply Unit:
- levocetirizine 5 mg/mL oral drops - 20 mL bottles with childproof caps
- placebo oral drops - 20 mL bottles with childproof caps

All drops will be identical in aspect to allow a double blind design.

Subjects will receive drops of either levocetirizine or placebo in 2 administrations per day. The quantity needed for one administration, according to weight is as follows:

<table>
<thead>
<tr>
<th>Body Weight between:</th>
<th>Single dose (mg) to be taken twice a day</th>
<th>Number of drops to be taken twice a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1 and 9 kg</td>
<td>1.00 mg</td>
<td>4</td>
</tr>
<tr>
<td>9.1 and 11 kg</td>
<td>1.25 mg</td>
<td>5</td>
</tr>
<tr>
<td>11.1 and 13 kg</td>
<td>1.50 mg</td>
<td>6</td>
</tr>
<tr>
<td>13.1 and 15 kg</td>
<td>1.75 mg</td>
<td>7</td>
</tr>
<tr>
<td>15.1 and 17 kg</td>
<td>2.00 mg</td>
<td>8</td>
</tr>
<tr>
<td>17.1 and 19 kg</td>
<td>2.25 mg</td>
<td>9</td>
</tr>
<tr>
<td>19.1 and 21 kg</td>
<td>2.50 mg</td>
<td>10</td>
</tr>
<tr>
<td>21.1 and over</td>
<td>2.75 mg</td>
<td>11</td>
</tr>
</tbody>
</table>

The dose will not be changed in the interval between 2 visits. At each visit, the Investigator will adapt the dose according to the actual weight of the subject.

The caring person should pour the appropriate number of drops into water or another liquid and administer the mixture to the child. The caring person should also check that the whole dose is actually swallowed. Doses must be administered twice daily: once at breakfast and once during the evening meal.

If a child has not received his dose within 2 hours after the scheduled time, or has vomited, the study medication should not be (re-)administered before the next scheduled time.
10.1.2 Packaging

Three visit boxes (V9B, V10B, V11) will be prepared to cover the 18-month treatment period. They will each contain 14 bottles of 20 mL of levocetirizine 5 mg/mL or placebo oral drops.

The caring person will be informed that excess is present in the investigational product package.

The same randomization number as for the first 18-month treatment period (trial A00309) will be used for this trial.

Visit boxes will be grouped in subject boxes (all 3 visits or less if necessary). They will be sent to each individual center according to the planned Visit 9 B of the subjects in each center and according to the expiry date of the investigational product.

10.1.3 Labeling

The label of the visit box consists of two parts. The first is a tear-off sticker which must be attached to the Case Report Form at the time of dispensing/administration and the second remains fixed to the investigational product package.

Each bottle will bear a simple label.  
A model of label (English version) is as follows:

<table>
<thead>
<tr>
<th>Levocetirizine 5 mg/mL/ placebo</th>
<th>Levocetirizine 5 mg/mL/ placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mL oral drops</td>
<td>20 mL oral drops</td>
</tr>
<tr>
<td>Protocol RPCE04B0203</td>
<td>Protocol RPCE04B0203</td>
</tr>
<tr>
<td>Dosage 0,125 mg/kg/body weight b.i.d.</td>
<td>Dosage 0,125 mg/kg/body weight b.i.d.</td>
</tr>
<tr>
<td>…… drops in the morning</td>
<td>…… drops in the morning</td>
</tr>
<tr>
<td>…… drops in the evening</td>
<td>…… drops in the evening</td>
</tr>
<tr>
<td>Subject no:</td>
<td>Subject no:</td>
</tr>
<tr>
<td>Dr....</td>
<td>Dr....</td>
</tr>
<tr>
<td>Visit no:</td>
<td>Visit no:</td>
</tr>
<tr>
<td>Batch no:</td>
<td>Batch no:</td>
</tr>
<tr>
<td>Exp.:</td>
<td>Exp.:</td>
</tr>
<tr>
<td>For clinical trial use only</td>
<td>For clinical trial use only</td>
</tr>
<tr>
<td>Keep out of reach of children</td>
<td>Keep out of reach of children</td>
</tr>
<tr>
<td>No particular storage conditions</td>
<td>No particular storage conditions</td>
</tr>
<tr>
<td>UCB SA Pharma Sector</td>
<td>UCB SA Pharma Sector</td>
</tr>
<tr>
<td>chemin du Foriest – B-1420 BRAINE-L'ALLEUD</td>
<td>chemin du Foriest – B-1420 BRAINE-L'ALLEUD</td>
</tr>
</tbody>
</table>

Subject boxes will bear a simple label.

The label will be adapted to local regulatory requirements and to the size of the investigational product package, and translated as appropriate.
10.1.4 Storage requirements

Investigational product packages should be stored in a secured limited access area. There are no particular temperature storage conditions.

The Investigator or the hospital pharmacist is responsible for the appropriate storage of investigational product packages at the research site. No other special storage conditions are required.

The Investigator will instruct the caring person to store the medication in a secure place out of the reach of children.

10.1.5 Monitoring of Subject Compliance

At each visit after drug is dispensed, subjects must return all unused, in-use medication and empty medication containers. Drug reconciliation must be done in the caring person’s presence in order to obtain explanations regarding discrepancies in the compliance with regards to the dosing regimen.

The number of bottles returned and the date must be recorded on the CRF and on the Drug Accountability Form. Explanations of non-compliance must also be recorded in the CRF.

Compliance with trial medication will be measured by the weight of the visit boxes (including all bottles with the cap) measured before the shipment to the investigator site and after retrieval from site.

10.1.6 Investigational Products Accountability

Each Investigator will receive numbered treatments and each subject will receive the same treatment number as in the A00309.

The Sponsor will supply a drug accountability form, to be kept up-to-date. After completion of the trial, all used (including empty bottles) and unused investigational bottles must be returned to the Sponsor, preferably in their original box.

10.1.7 Maintenance of Trial Treatment Randomization Codes and Procedures for Blind Breaking.

The identification of investigational products for this additional 18-month treatment period will be contained in sealed envelopes that will bear a colored label to be easily differentiated from the envelopes of A00309. They will carry a label with the protocol number, subject
identifier and investigator's name with the instruction: “To be opened only in case of an emergency”.

**Under normal circumstances, the blinded treatment must not be revealed.** In the case of a medical emergency UCB or its representative must be contacted. If UCB or its representative cannot be contacted, the blind may be broken if doing so will aid in a decision as to the subject’s treatment or clinical intervention. The blind may be broken by following the directions provided. If the blind is broken, the date, the reason for breaking the blind, and person doing so must be recorded on the envelope with name, date and signature and in the appropriate section of the CRF. UCB or its representative must be notified immediately, if the blind is broken.

These envelopes should be kept in a secure place with restricted access and returned to the Sponsor at the end of the trial.

**10.2 Concomitant Treatments and Rescue Medications**

Should any treatment other than the investigational product be used, an accurate record must be kept in the clinic chart (source documentation) and the Case Report Form. This record should include the name of the drug, the dose, the date(s) of administration, and the indication for use.

**10.2.1 Rescue Medication**

All caring persons must be given recommendations in order to practice allergen avoidance. The investigator will give specific advice adapted to each case. Levocetirizine is an antihistamine medication. The use of any other antihistamine should be avoided. The possibility of overdose should be considered before initiating any antihistamine treatment judged necessary by the clinician.

For the sake of homogeneity in the trial population, it is requested that the following medications should be used in the case of atopic dermatitis or asthma, according to the clinical judgment of the investigator.
10.2.1.1 Atopic dermatitis

10.2.1.1.1 Topical medication:

We advise to use only creams or ointments but no gel.

Please use the following medication:

- **First line therapy:** topical emollient
- **Second line:** nonsteroidal anti-inflammatory drug/topical corticosteroids (class A-B)
- **Third line:** topical corticosteroids (class C)
- **Fourth line:** in the case of non-response to those treatments alone or in combination, the clinician should administer any drug he finds suitable, such as topical tacrolimus or pimecrolimus excepted highly potent corticosteroids (class D), systemic tacrolimus or ciclosporin.
Table 10:1  Table summarizing the topical corticosteroids:

<table>
<thead>
<tr>
<th>Anti inflammatory potency</th>
<th>Generic Name</th>
<th>Trade name (example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Slightly potent</td>
<td>Hydrocortisone acetate 1%</td>
<td>Hydracort®</td>
</tr>
<tr>
<td></td>
<td>Flumetasone-pivalate</td>
<td>Locacorten®</td>
</tr>
<tr>
<td>B. Moderately potent</td>
<td>Triamcinolone acetonide 0.1%</td>
<td>Tibicorten®</td>
</tr>
<tr>
<td></td>
<td>Clobetasone butyrate 0.05%</td>
<td>Eumovate®/Emovate®</td>
</tr>
<tr>
<td></td>
<td>Desonide</td>
<td>Sterax®</td>
</tr>
<tr>
<td>C. Potent</td>
<td>Betamethasone dipropionate 0.05%</td>
<td>Diprosone®</td>
</tr>
<tr>
<td></td>
<td>Halometasone 0.05%</td>
<td>Sicorten®</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone 17-butyrate 0.1%</td>
<td>Locoid® / Alfason®</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate</td>
<td>Ecural®</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone 0.25%</td>
<td>Topicorte® / Ibaril®</td>
</tr>
<tr>
<td></td>
<td>Betamethasone 17 valerate 0.1%</td>
<td>Betnelan® / Celestoderm®</td>
</tr>
<tr>
<td></td>
<td>Fluocinonide 0.05%</td>
<td>Topsyn®</td>
</tr>
<tr>
<td></td>
<td>Halcinonide 0.1%</td>
<td>Halciderm®</td>
</tr>
<tr>
<td></td>
<td>Amcinonide 0.1%</td>
<td>Amicla® / Cycloderm</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate 0.05%</td>
<td>Florone® / Dermaflor®</td>
</tr>
<tr>
<td>D. Highly potent</td>
<td>Clobetasol propionate</td>
<td>Dermoval® / Dermovate®</td>
</tr>
<tr>
<td></td>
<td>Betamethasone dipropionate in propylene glycol 0.05%</td>
<td>Diprolene®</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
<td>Preferid®</td>
</tr>
</tbody>
</table>

Antibiotics or antiseptics for topical use:

When there is a clinically relevant infection with Staphylococcus aureus, the use of a bacteriostatic agent like chlortetracycline-HCL (Aureomycin®) or mupirocine (Bactroban®) or fucidic acid (Fucidine®) is recommended. Other compounds such as chlorhexidine (Hibitane®) or hexomedine (Hexomedine®) can be used if necessary.

10.2.1.1.2 Systemic antibiotic:

If necessary any systemic antibiotic could be used.
10.2.1.2 Asthma

For the treatment of asthma episode, in the framework of this protocol, it is asked to follow the Treatment Guidelines issued by the Pediatric Asthma Consensus Group for the treatment of asthma:\(^{(46)}\):

**Level 1**
Infrequent episodic asthma (i.e. less than 1 episode per month with no chest signs or symptoms between episodes).
Inhaled \(\beta_2\)-agonists and/or inhaled parasympathomimetics as required. If used consistently more frequently than 3 times per week, except for predosing before exercise, proceed to level 2.

**Level 2**
Frequent episodic asthma (episodes more frequently than once per month but less than once per week with no symptoms or signs between episodes).
Regular sodium cromoglicate or low dose inhaled corticosteroids \(\leq 200\ \mu g/day\) of beclometasone dipropionate or equivalent and inhaled \(\beta_2\)-agonists as necessary.

**Level 3**
Persistent asthma (episodes more frequently than once a week, exercise-induced symptoms not completely prevented by \(\beta_2\)-agonist predosing).
Low to moderate dose inhaled corticosteroids up to 400 \(\mu g/day\) of beclometasone dipropionate or equivalent, inhaled \(\beta_2\)-agonists as required.

**Level 4**
Continuing symptoms despite 400 \(\mu g/day\) of inhaled corticosteroids.
Add either a leukotriene-receptor antagonist (e.g. montelukast), an inhaled long-acting \(\beta_2\)-agonist or slow-release theophylline.

**Level 5**
Continuing problems despite the above.
Increasing dose titrated inhaled corticosteroids.

**Level 6**
Continuing problems with relative corticosteroids insensitivity.
Consider use of oral corticosteroids, methotrexate, ciclosporin\(^{(a)}\) or continuous subcutaneous \(\beta_2\)-agonist infusion.

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\(^{(a)}\) Not permitted concomitant treatments (see section 10.2.2), if used the child should be withdrawn from the trial.
10.2.2 Not Permitted Concomitant Treatments (Medications and Therapies)

For the whole duration of the trial, the use of cetirizine (Zyrtec®) is forbidden for more than 8 days (cumulatively) in order to avoid the introduction of a major bias within the trial. The possibility of overdose should be considered before initiating any antihistamine treatment judged necessary by the clinician.

Highly potent corticosteroids (class D), systemic tacrolimus and ciclosporin will not be allowed.
Potent corticosteroids (class C) will be allowed with a maximum of 1 month of use, cumulatively, for the whole study period.
Topical tacrolimus (e.g. Protopic®) or pimecrolimus (e.g. Elidel®) could be used for a maximum treatment period of 20 days (in 1 or 2 courses) over the 36-month treatment period, taking into account the quantity already used during the first 18-month treatment period (i.e. treatments are allowed after the first 6 months of the first 18-month treatment period (after V5) of the A00309).
11. **TRIAL PROCEDURES**

11.1 **Subject Identifier**

Each subject will be identified by 4 initials (only letters, without spaces or any punctuation signs such as coma, slash, hyphen …) and subject identifier, consisting of trial number (A00384), center number and a sequential randomization number (001-nnnn). The randomization number of the first 18-month treatment period will be kept for this additional 18-month treatment period, so that the randomization number will remain the same during both trials (A00309 and A00384),

11.2 **Description of Procedures**

11.2.1 **Urticaria**

Urticaria episodes having occurred during the trial will be collected with localization, onset, evolution, duration, concomitant symptoms (pruritus, diarrhea, vomiting, other) and provoking factors, if known (infection; medication: antibiotics, other; food: peanuts, tree nuts, cow’s milk, egg, fish, other; allergen inhalation or contact: grass pollen, animal dander, insect bite or sting, other)

11.2.2 **Atopic Dermatitis**

A weekly evaluation of the severity and pruritus related to AD will be recorded on the diary card. Each Sunday, the caring person will have to answer the following 2 questions:

<table>
<thead>
<tr>
<th>Over the last week, how severe do you think your child’s eczema (dermatitis) has been? i.e. how red, scaly, inflamed or widespread?</th>
<th>Extremely severe</th>
<th>Severe</th>
<th>Average</th>
<th>Fairly good</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over the last week, how much has your child been itching and scratching?</td>
<td>All the time</td>
<td>A lot</td>
<td>A little</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

(Reproduced with permission of M.S. Lewis-Jones and A.Y. Finlay)
11.2.3 Nocturnal cough episodes and wheezing episodes

The caring person will note on the diary card each nocturnal cough event with sleep disturbances occurring from 19:00 to 7:00 and each wheezing event occurring at any time together with the treatment for these symptoms. Each nocturnal cough episode defined as any episode of nocturnal cough with sleep disturbances lasting at least 3 consecutive nights and each wheezing episode will be reviewed and validated by the investigator and transcribed in the CRF at the next visit. For each of them the start and end dates, intensity and pattern of the symptom, the use of any therapy and their occurrence with a concomitant disease / infection will be specified.

11.2.4 Direct medical cost parameters

Direct medical costs parameters will consider the resources used linked to the child's asthma. The direct medical costs parameters measured will be the additional physician visits, medications, emergency room visits, hospitalizations and medical procedures related to child's asthma. The relationship to asthma and the specific reason for the use of resources will be collected. For the physician (health care provider) visits, the information to collect includes the type of provider and the site of care. For the hospitalizations, the information to collect includes the admission date, the discharge date, the type of unit visited (including duration of stay), the reason of the hospitalization and the associated medications and medical procedures. For the emergency visits, the information to collect includes the duration of stay in the emergency room for medical purpose (excluding time spent in the waiting room) and the associated medications and medical procedures.

11.2.5 Psychomotor assessment

11.2.5.1 Global psychomotor development questionnaire

Questions on the global psychomotor development will be asked to the caring person at each visit in all countries adapted to the age of the child in this additional 18-month treatment period on the following items:

- Gross motor development: pedal tricycle, balance on one foot (10 sec), hop on one foot, can consistently catch a football.
- Fine motor assessment: copy circle, copy cross, draw a man; including 3 items.
- Personal-Social: play interactive games, dress with supervision, without supervision
- Speech & language: give first and last name, understand prepositions (under/on/behind/in front of), point to colors on request (red/blue/yellow/green).
11.2.5.2 Behavioral assessment

In the United Kingdom and Australia, the behavioral assessment will be evaluated, before each scheduled visit (from V9 to V12), by the caring person.

The Behavioural Checklist (BCL)\(^{(48,49,52)}\) will be used to measure the presence of behavior problems. The BCL is a parent/caring person completed checklist of 12 main items of behavior: fears, eating, sleep, hyperactivity, relationship, attention seeking, soiling, concentration, management, tantrums, moods and worries.

11.3 Description Visit by Visit

The trial will be carried out as described below:

11.3.1 Visit 9 B

To be performed at the same time as the V9 of the first 18-month treatment trial

- Dated and signed written Informed Consent by the parent(s)/ legally acceptable representative(s)
- Demographic data (date of birth, gender, racial group)\(^{(b)}\)
- Medical /Surgical history \(^{(b)}\)
- Verification of eligibility
- Physical examination \(^{(c)}\)
- Body mass (weight, height, percentiles) \(^{(c)}\)
- Recording of Nocturnal cough episodes \(^{(c)}\)
- Recording of Wheezing episodes \(^{(c)}\)
- Recording of Urticaria episodes \(^{(c)}\)
- Recording of medications/procedures \(^{(c)}\)
- Recording of Adverse Events \(^{(c)}\)
- Recording of Direct Medical Cost parameters \(^{(c)}\)
- Psychomotor assessment: Behavioral questionnaire \(^{(c)}\)
- Blood sampling: IgE, Safety, Pop-PK \(^{(c)}\)
- Daily record cards booklet management
- Study drug management
- Treatment allocation status

\(^{b}\) Those data are the same as in the A00309 trial and do not need to be collected again.

\(^{c}\) Those data are already recorded at Visit 9 (V9) of the A00309 trial
11.3.2 Visit 10 B (V10 B) and Visit 11 (V11)

- Withdrawal criteria
- Physical examination
- Body mass (weight, height)
- Recording of nocturnal cough episodes
- Recording of wheezing episodes
- Recording of urticaria episodes
- Daily record card management
- Study drug management
- Recording of medications and procedures
- Recording of adverse events
- Recording of direct medical cost parameters
- Updated Global Psychomotor Development Questionnaire for all subjects
- Behavioral questionnaire only for subjects from the United Kingdom and Australia

11.3.3 Visit 12 (V12) End of trial Visit or early discontinuation visit

- Withdrawal criteria (only if early discontinuation visit)
- Physical examination
- Body mass (weight, height)
- Recording of nocturnal cough episodes
- Recording of wheezing episodes
- Recording of urticaria episodes
- Blood sampling: IgE + safety parameters + population PK, (no sample for biobank )
- Daily record card management
- Study drug management
- Recording of medications and procedures
- Recording of adverse events
- Recording of direct medical cost parameters
- Updated Global Psychomotor Development Questionnaire for all subjects
- Behavioral questionnaire only for subjects from the United Kingdom and Australia
- Final evaluation with:
  - randomization code (blind broken Yes/No) for the additional 18-month treatment period
  - subject’s status evaluation for the additional 18-month treatment period
  - follow-up of adverse events if any.
11.4 Handling of Biological Samples

A central laboratory will be in charge of processing of all biological samples. One blood sample will be collected during the trial, at the end of the additional 18-month treatment period (V12, i.e. 18 months later or at early discontinuation visit - ca 8 mL). This amount corresponds to less than 1% of the total blood volume of the children of this trial. Additional blood tests could be performed if judged required by the investigator (for safety reasons).

Blood samples will be collected for the following:

- Efficacy parameters
  - Total IgE and specific IgE by RAST (Grass Pollen, House Dust Mite, Egg, Cat, Peanuts, Cow’s milk, Alternaria and one center specific aeroallergen).

- Safety parameters
  - Hematology: Hemoglobin, Hematocrit, Erythrocytes, white blood cells total + differentiation count and Platelets
  - Chemistry: Total bilirubin, SGPT, SGOT, Total proteins, C-RP and Creatinine

If subject's data are recorded in an electronic CRF, the results from the central lab will be electronically injected in the electronic CRF. The investigator will then be prompted to comment all results out of the reference range as follows:

1: Not clinically significant
2: Clinically significant
3: Clinically significant but chronically typical for this subject
4: Not assessable

In parallel the central lab will also fax to the investigator a paper version of the laboratory results. The laboratory results should be within the normal range of the central laboratory or considered as not clinically significant (code 1) or study disease related (code 3) by the investigator.

If the status assessed is clinically significant (code 2), the abnormal laboratory value should be reported in the “Adverse Events” section of the CRF. And according to the withdrawal criteria, if necessary, the patient should be withdrawn from the trial.

If the status is not assessable, the parameter(s) should be retested and re-evaluated by the investigator.
If subject's data are recorded in a paper CRF, certified copies of the faxed printouts from the central laboratory, signed by the Investigator with the results of all tests cited above will be attached to the paper CRF. All results out of the reference range will be commented by the Investigator as mentioned above (from 1 to 4).

- Population Pharmacokinetic analysis.
  - An aliquot of the laboratory sample collected at the last visit (normally at V12 after the additional 18 months of treatment, or earlier in case of early discontinuation), will be used for the population pharmacokinetic analysis. A serum subsample (ca 0.500 mL) will be stored at -20°C at least until completion of the trial.

The exact times of the blood sample withdrawal (date, hour, minute) and the exact time of the preceding medication intake (date, hour, minute) should be accurately recorded. The time elapsed between last medication intake and blood sample withdrawal should preferably not exceed 12 hours.

After database lock and opening of the randomization code, the samples of subjects in the levocetirizine treatment arm will be submitted to analysis for determination of levocetirizine concentration, using a validated, specific and sensitive analytical method. The details of the analytical procedures will be described in a separate analytical study plan, and will be reported separately.

Blood samples will be drawn by direct venipuncture using disposable pediatric needles. If necessary, local anesthetic (e.g. Emla® ointment) may be used in order to decrease local pain.

Blood will be drawn into several properly identified evacuated tubes:
  - EDTA tube for hematology.
  - Dry tube for biochemistry, IgE’s, C-RP, population pharmacokinetic.

Details for the handling and shipment of samples can be found in the Operating Laboratory Manual.
12. ASSESSMENT OF EFFICACY

12.1 Specifications of Efficacy Variables

The procedures for obtaining the data of the efficacy variables are found in section 11.2. The complete list of variables to be analyzed is found in sections 14.1.2.1, 14.1.2.3.

12.2 Methods and Timing for Assessing, Recording, and Analyzing the Efficacy Variables

The methods and timing for assessing and recording the efficacy variables are found in sections 5.1 and 11.3. The analysis methods are found in 14.1.4.1, 14.1.4.3 and 14.1.4.4.
13. ASSESSMENT OF SAFETY

13.1 Specifications of Safety Variables

The Safety Variables are Adverse Events (AE), Serious Adverse Events (SAE), data from the Physical Examination assessments, laboratory results, body mass parameters and psychomotor evaluation.

The procedures for obtaining the data of the safety variables are found in section 11.2.

The complete list of variables to be analyzed is found in section 14.1.2.2.

13.2 Methods and Timing for Assessing, Recording, and Analyzing the Safety Variables

The methods and timing for assessing and recording the safety variables are found in sections 5.1 and 11.3.

The analysis methods are found in section 14.1.4.2.

13.3 Adverse Events

13.3.1 Definition of Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs or undesirable experiences occurring during the trial (i.e. after signature of the Informed Consent), including any pre- and post-treatment periods required by the protocol, must be reported even if no investigational product was taken but specific trial procedures were conducted. These include all AEs not present prior to the initial visit and all AEs which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the subject’s history or the baseline period.
13.3.2 Procedures for Reporting and Recording Adverse Events

13.3.2.1 Recording/Collection of AEs

The trial participant will be given the opportunity to report Adverse Events spontaneously. A general prompt will also be given to detect adverse events, e.g.,

“Did you notice anything unusual about the child’s health (since your last visit)?”

In addition, the Investigator should review any self-assessment procedures (e.g. diary cards) employed in the trial.

13.3.2.2 Description of AEs

The following guidelines and definitions should be used by the Investigator for the description of an AE when reporting information:

- **Nature of the AE**: Preferably an overall diagnosis or syndrome, rather than individual symptoms or signs. The Investigator must report adverse events using standard medical terminology. Any discrepancies between the subject’s own words on his/her own records (e.g. diary card) and the corresponding medical terminology should be clarified in the source documentation.

- **Date of onset**: Date the AE started.

- **Pattern**:
  - **Intermittent**: The AE recurs with the same intensity at various intervals throughout the entire time period specified. There were intervals within the specified time period when the AE was not present.
  - **Continuous**: The AE is present at the same intensity for the entire time period specified. There was no time at which the event abated or was not present during the time period specified.

- **Intensity**:
  - **Mild**: The subject is aware of the sign or symptom (*syndrome*), but it does not interfere with his/her usual activities and/or it is of no clinical consequence.
Moderate  The AE interferes with the usual activities of the subject or it is of some clinical consequence.

Severe  The subject is unable to work normally or to carry out his/her usual activities, or the AE is of definite clinical consequence.

Action taken with investigational product:

- **Not applicable**  For AEs occurring during the pre-treatment or post-treatment periods and single dose studies
- **No change**  Investigational product dosing remained the same in spite of AE being present.
- **Dosage changed**  Investigational product dose was increased or decreased because of this AE.
- **Temporarily discontinued**  Investigational product was temporarily discontinued because of this AE, either because the subject chose to discontinue the trial drug or the physician felt it was in the subject’s best interest to temporarily discontinue the investigational product.
- **Permanently discontinued**  Investigational product was permanently discontinued because of this AE, either because the subject chose to discontinue the trial drug or the physician felt it was in the subject’s best interest to discontinue the investigational product.

Other actions taken:

- **None**  No other action was taken for this AE
- **Concomitant medication**  Drug treatment: the subject took a concomitant medication (either prescription or non-prescription) specifically for this AE OR existing concomitant medication dosage was modified as a result of this AE.
- **Hospitalization or prolongation of hospitalization**  The subject was hospitalized for this AE or subject’s stay in hospital was prolonged because of this AE.
| Therapeutic or diagnostic procedure | Subject used other therapeutic measures (e.g. ice, heating pad, brace, cast, etc.) or subject underwent a diagnostic procedure (e.g., additional lab test, x-ray, etc.) for this AE. |
| Date of outcome: | Date the AE abated. If the AE consists of several signs and symptoms (syndrome), the sign or symptom with the longest duration determines the duration of the AE. If the AE is marked “ongoing”, the outcome date should be blank. |
| Outcome: | |
| Resolved | The AE is no longer present at any intensity - completely abated. |
| Resolved with sequelae | The AE is resolved but residual effects are still present. |
| Worsened | The AE is still present but at a heightened intensity. The rule of repetition of AE reporting should be applied. |
| Fatal | This AE caused or directly contributed to subject’s death. |
| Ongoing | The AE is still present at the last contact with the subject. |
| Relationship to investigational product: | |
| None | only applicable when no investigational product was taken or when the subject is taking single-blind placebo, or when the AE can be ascribed with reasonable certainty to another cause. |
| Unlikely | there are good reasons to think that there is no relationship, e.g. the AE is a known adverse drug reaction of a concomitant medication, or the same AE does not reappear after re-administration of the investigational product. |
Possible equally valid arguments can be considered for or against an implication of the investigational product, e.g. the AE:

- follows a reasonable temporal sequence from the administration of the investigational product;
- follows a known or expected response pattern to the investigational product;
- but could readily have been produced by a number of other factors.

Probable the relationship is likely, e.g. the AE:

- follows a reasonable temporal sequence from administration of the investigational product;
- follows a known or expected response pattern to the investigational product;
- is confirmed by improvement on stopping or reducing the dosage of the investigational product;
- could not be reasonably explained by the known characteristics of the subject’s clinical state.

Highly probable there is a strong relationship, e.g. the AE:

- follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissues;
- follows a known or expected response pattern to the investigational product;
- is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the AE on repeated exposure (rechallenge).

### 13.3.3 Follow-up of Adverse Events

If an AE is still ongoing at time the Electronic CRF is being locked, or, in case a paper CRF has been used, at the time, the paper CRF is collected, a follow-up report should be provided later on.

If no follow-up report is being provided, the Investigator must provide a justification.
UCB may request that the Investigator perform or arrange for the conduct of additional measurements and/or evaluations (e.g. rechallenge procedure).

A serious AE or an AE leading to premature discontinuation from the trial must always be followed up until it has resolved/has a stable level of sequelae or the Investigator no longer feels it is clinically relevant.

13.3.4 Rule for Repetition of an AE

An increase in the intensity of an AE should lead to the repetition of the AE reporting with:
• the outcome date of the first AE being the same as the start date of the repeated AE,
• the Investigator’s original description of the AE being the same for the first and repeated AE, so that they code to the same dictionary term.

13.3.5 Overdose of Investigational Product:

For this protocol, any single intake of 0.5 mg/kg will be considered as an overdose.

Symptoms associated with an overdose must be recorded as AEs.

Overdose without signs or symptoms will be documented in the “Study Medication Intake” section of the CRF.

13.4 Serious Adverse Events

13.4.1 Definition of Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence that at any dose:
• results in death,
• is life threatening,
• requires in-subject hospitalization or prolongation of existing hospitalization,
• results in persistent or significant disability / incapacity,
or
• is a congenital anomaly/birth defect.

In this context, the term life threatening refers to an event in which the subject was at immediate risk of death at the time of the event; it does NOT refer to an event which might have caused death if it would have been more severe.
Any **important medical event** that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also be reported as a SAE. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Any **event reported by the Investigator to the local authorities** will follow the same reporting procedure as a “Serious Adverse Event”.

Cases involving cancer as an Adverse Event could be reported as serious using the criterion “medically important”.

Hospitalization for diagnostic or therapeutic procedures in the absence of any associated Adverse Event will not be considered as a SAE, except when otherwise required by Regulatory Authorities. This also applies to situation of scheduled elective surgery where no AE is present.

### 13.4.2 Procedures for Reporting Serious Adverse Events (SAE)

If a SAE is reported, the Sponsor or its representative must be informed within 24 hours of receipt of this information by the site (see emergency contact numbers on front page). The Investigator must promptly forward to the Sponsor or its representative a duly completed “Investigator SAE report form” provided by the Sponsor, even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusions.

Additional information (e.g. autopsy or lab reports …) should be provided to the Sponsor in a timely fashion to ensure accurate follow-up of each case.

The Sponsor or its representatives will communicate safety information to the appropriate agency(ies) and all active Investigators, as it becomes available. The appropriate IEC will also be informed by the Investigator or by the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Investigators are to provide the Sponsor or its representatives with evidence of such IEC notification.

A copy of the Investigator SAE report form and the completion guide will be provided by the monitor.

Event leading to an SAE report should be reported in the Adverse Event (AE) section of the Case Report Form (CRF).
In case of hospitalization for a procedure such as tonsillectomy, ENT interventions, the reason for such procedure e.g. tonsillitis should be reported as AE and the procedure detailed in the medical procedure section.

If known by the Investigator, Serious Adverse Events up to 30 days after withdrawal of trial medication must be reported to the Sponsor, even if the Investigator is certain that they are in no way associated with the trial drug. Adverse Events that the Investigator thinks may be associated with the trial medication must be reported to the Sponsor regardless of the time between the event and the end of the trial.
14. STATISTICS

14.1 Statistical and Analytical Plans

14.1.1 Trial Population(s)

Two populations are defined for this trial:
• The A00309 ITT population is the ITT population as defined in trial A00309,
• The A00384 ITT population will consist of the subjects of the A00309 ITT population enrolled in trial A00384 and who took at least one dose of medication during trial A00384.

14.1.2 Efficacy and Safety Variables

14.1.2.1 Efficacy Variables

The primary efficacy variable is the time to onset of asthma evaluated during the 36-month treatment period. The time to onset of asthma is defined as the period elapsed between the randomization visit (V2 of trial A00309) and the date of onset of asthma.

The secondary efficacy variable is:
• The time to onset of asthma during the additional 18 month treatment period, defined as the period elapsed between the end of the first 18 month treatment period (V9) and the date of onset of asthma. The diagnosis of asthma will be determined using the episodes of wheezing and nocturnal cough, including those recorded during the A00309 trial. This variable is defined only for the subjects entering the A00384 trial still asthma-free after the first 18 months of treatment with LCTZ.

The exploratory variables are:
• Symptoms and use of medications for asthma (described according to the definition mentioned in section 4.5.4) during the additional 18-month treatment period, as measured by:
  • Percentage of days with symptoms of either wheezing or nocturnal cough,
  • Percentage of days with symptoms of wheezing,
  • Percentage of days with symptoms of nocturnal cough,
  • Use and percentage of days of use of asthma medication, considering the following classes: β2-agonists; cromoglicate; corticosteroids; leukotriene-receptor antagonists.
• Use and percentage of days of use of the following medications for Atopic Dermatitis during the additional 18-month treatment period: topical corticosteroids; topical tacrolimus and pimecrolimus, oral H1-antihistamines; local antibiotics or antiseptics.
• Incidence of subjects with urticaria and the number of episodes of urticaria per subject during the additional 18-month treatment period,
• The time to onset of asthma considering an alternative definition of asthma based on wheezing only and / or a new definition adopted by the scientific community. The date of onset of asthma based on wheezing only is defined as the first day of the third episode of asthmatic wheezing.
• The severity of atopic dermatitis and pruritus scores, as assessed by the caring person each week during the additional 18-month treatment period: severity of atopic dermatitis, evaluated on a 5-point scale from 0 to 4; and pruritus score, evaluated on a 4-point scale from 0 to 3
• The status of sensitization to allergens (normal/elevated) at the end of the additional 18-month treatment period (visit 12): total IgE, IgE specific to Grass Pollen, House Dust Mite, egg, cat, peanuts, cow’s milk, alternaria and one center specific aeroallergen.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IgE:</td>
<td>&lt;30 kU/L</td>
<td>≥30 kU/L</td>
</tr>
<tr>
<td>Specific IgEs:</td>
<td>&lt;0.35 kUA/L</td>
<td>≥0.35 kUA/L</td>
</tr>
</tbody>
</table>

Values under the detection limit will be considered as normal values.

Total and specific IgE values will also be analyzed as a continuous variable.

14.1.2.2 Safety Variables

Safety assessments will be made during the additional 18-month treatment period using physical examinations, adverse events, body mass parameters, laboratory test results and the psychomotor evaluation.

The Global Psychomotor Development questionnaire will be applied to all children in all countries at each visit.

The behavioral development of the child will be evaluated by the caring person at each scheduled visit, using the following questionnaire: Behavioural Checklist (BCL). This evaluation will be restricted to the United Kingdom and Australia.

14.1.2.3 Direct Medical Cost Variables

The variables for the direct medical cost are the number of additional physician visits for asthma, the number of medications for asthma, the number of emergency room visits for asthma, the length of stay in emergency room for asthma, the number of hospitalizations (and the type of unit visited) for asthma, and the length of hospitalization for asthma. These are assessed over the 36 months of treatment.
14.1.3 Criteria for a Positive Trial

Due to the specific nature of this trial, which is a follow-up to trial A00309, the notion of criteria for a positive trial is not applicable here.

14.1.4 Statistical Evaluation

Summary statistics will consist of frequency tables for binary or categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum and maximum) will be tabulated.

Selected baseline characteristics for the A00384 ITT population will be summarized descriptively. Baseline is defined as the baseline for trial A00309.

14.1.4.1 Evaluation of Efficacy

14.1.4.1.1 Primary efficacy analysis
The primary efficacy variable will be analyzed descriptively on the A00309 ITT population. This analysis will consist of the number and percentage of subjects with asthma during the 36 month treatment period and the cumulative incidence curves of asthma, estimated using the Kaplan-Meier approach. If more than half the subjects are diagnosed with asthma, the median time to onset of asthma will be estimated with its 95% confidence interval\(^{(50,51)}\).

The examination of the results of primary efficacy analysis for the treatment groups LCTZ-LCTZ and PLC-PLC will allow to evaluate the primary objective of the trial.

The primary efficacy analysis will also allow to evaluate the first two secondary objectives of the trial.

14.1.4.1.2 Secondary efficacy analysis
The analysis of the secondary efficacy variable will be performed on the subset of the A00384 ITT population, consisting of those subjects still asthma-free after the first 18 month of treatment with LCTZ. This analysis will be performed similarly to the primary efficacy variable, considering only the treatment groups LCTZ-LCTZ and LCTZ-PLC.

14.1.4.1.3 Exploratory analyses
Exploratory analysis of the time to onset of asthma based on an alternative definition of asthma will be performed similarly to the primary and secondary efficacy variables.

Other exploratory variables will be analyzed descriptively on the A00384 ITT population using summary statistics by treatment group.
The analysis of the use and percentage of days of use of medication for atopic dermatitis will be performed overall and according to the severity of AD at baseline. The severity of AD at baseline will be categorized in two classes according to the SCORAD index:

- Mild: SCORAD index < 25
- Moderate to severe: SCORAD index ≥ 25

The analysis of the incidence of subjects with urticaria and the number of episodes of urticaria per subject will be performed overall and considering the subgroups of subjects who never experienced urticaria since birth to inclusion in trial A00309 and those who experienced urticaria from birth to inclusion in trial A00309.

The severity of atopic dermatitis and pruritus, as assessed by the caring person each week, will be described graphically, by displaying the treatment means by week.

The status of sensitization to allergens (normal/elevated) will be described at visit 12, overall and broken down by the status at baseline. Total and specific IgE values will also be analyzed as a continuous variable. Summary statistics will include quantiles of the distribution (5%, 10%, 25%, median, 75%, 90%, 95%).

14.1.4.2 Evaluation of Safety

Safety variables will be listed individually for detailed clinical review, when needed. Laboratory values, body mass parameters, and changes from baseline in laboratory values and body mass parameters will be presented descriptively by treatment group. Ninety-five % confidence intervals will be calculated on the median of the difference between the on-treatment values and the baseline values. Adverse events will be summarized descriptively by treatment group, body system, and preferred term. Additional tables will summarize adverse events by severity and relationship to trial drug as well as separate tables for adverse events leading to withdrawal from the trial and SAEs.

The psychomotor assessments will be analyzed descriptively by treatment group. Safety analyses will be performed on the A00384 ITT population.

14.1.4.3 Pharmacokinetic Analyses

The individual pairs of levocetirizine concentration versus time data will be submitted to an exploratory population pharmacokinetic analysis, aimed at establishing a model of levocetirizine pharmacokinetics in the trial population as well as identifying covariates (including but not limited to age, body weight, body area, gender, creatinine, concomitant medication...) that have a significant impact on the prediction of levocetirizine pharmacokinetic parameters (clearance, half-life, distribution volume).

The analysis will be supported by previous similar work performed on population pharmacokinetics of cetirizine in pediatric populations. The detailed objectives and
methodologies of the population pharmacokinetic analysis will be described in a separate study plan. The population pharmacokinetic trial will be reported separately.

14.1.4.4 Direct medical cost parameters analyses

The direct medical costs parameters defined in section 14.1.2.3 will be presented descriptively by treatment group using summary statistics.

14.2 Determination of the Sample Size

Due to the specific nature of this trial, which is a follow-up to trial A00309, no sample size calculation has been performed. Around 300 subjects are expected to enter trial A00384.

14.3 Changes in the Conduct of the Trial or the Planned Analyses

A Statistical Analysis Plan (SAP) will be developed and approved prior to the database for trial A00309 being unblinded. The full details of the statistical analyses will be provided in the SAP. Any deviations from the final SAP as well as changes from the protocol will be discussed in Section 9.8 of the Trial Report.

14.4 Statistical and Analytical Issues

14.4.1 Adjustments for Covariates

As no statistical modeling is foreseen for the analysis of the primary efficacy variable, adjustment for baseline covariates is not applicable here.

14.4.2 Handling of Dropouts or Missing Data

The primary efficacy variable is analyzed by means of a survival analysis method: subjects who withdraw prematurely from the trial or complete the trial with no onset of asthma will be handled using censored data.

14.4.3 Interim Analysis and Data Monitoring

No formal interim analysis is planned for this trial.

A blind review will be performed after last subject last visit (visit 12) and before breaking the blind. The purpose of this blind review will be to check the quality of the data, identify outliers, and to verify that the assumptions in the primary analyses are not violated. The statistician should ensure that the results of this review is communicated to the trial team before unblinding and that the actions taken introduce no bias in the treatment comparison.
14.4.4 Multicenter Studies

This is a multi-center trial. However, as no statistical modeling is foreseen for the analysis of the primary efficacy variable, the consistency of treatment effect across trial centers (countries or regions) will not be formally assessed.

14.4.5 Multiple Comparisons / Multiplicity

As no statistical modeling is foreseen for the analysis of the primary efficacy variable, adjustment for multiple comparisons is not applicable here.

14.4.6 Use of an Efficacy Subset of Subjects

Not applicable.

14.4.7 Active Control Studies Intended to Show Equivalence

Not applicable.

14.4.8 Examination of Subgroups

An analysis of time to onset of asthma during the additional 18-month treatment period will be performed on a subset of the A00384 ITT population, consisting of those subjects still asthma-free after the first 18 month of treatment with LCTZ.

The aim of this analysis is to investigate the clinical benefit, on the time to onset of asthma, of an additional 18 month treatment period in this subset of subjects (LCTZ-LCTZ versus LCTZ -PLC).

14.5 Criteria for Unblinding the Results

A pre-analysis review will take place:

- before starting analysis,
- after all the data have been verified / coded / entered into a database,
- before requesting the codes of the administered treatments.

The review will be held to decide how to deal with problems in subject’s data (missing values, withdrawals, drop outs, protocol deviation,...).

After the pre-analysis review and documentation of all material decisions, the database will be locked.
The randomization codes will be requested and released after locking of the database and approval of the final SAP.

14.6 Unblinding Data

As described in section 10.4, a laboratory sample will be collected at the last visit and used for the population pharmacokinetic analysis. After database lock and opening of the randomization code, the samples of subjects in the levocetirizine treatment arm will be submitted to analysis for determination of levocetirizine concentration. The levocetirizine concentration levels will then be injected in the locked trial database according to the database lock/unlock/re-lock procedure.

14.7 Dictionaries

Adverse events, medical abnormalities and procedures will be coded using the MedDRA dictionary (last available version).

Medications will be coded using the WHO Drug dictionary (last available version).

Reasons for additional physician visits, medications, emergency room visits, hospitalizations, and medical procedures will be coded using the MedDRA dictionary (last available version).
15. ETHICS

15.1 Approval

When finalized, the protocol and any amendments must be signed by the principal Investigator of the center, the UCB Clinical Research Physician (CRP) and the UCB Clinical Trial Manager (CTM).

The final version must be submitted to and approved by:

a) a duly constituted Independent Ethics Committee (IEC)

b) the relevant Regulatory Authorities, according to local regulations.

If any alterations to the protocol are required by these bodies, they can be implemented only with the written agreement of the Investigator, the CRP, the CTM and the UCB approval Committee(s) and this before further submission to the requesting body.

A copy of the IEC written approval (with clear identification of the submitted document(s)) and a list of members attending the meeting (listed by title) should be forwarded by the Investigator to the CTM. The trial is not allowed to start until the protocol and related documents (informed consent, advertisements, etc …) have received written approval from the IEC and Regulatory Authorities, if applicable, as well as until other GCP prerequisites are fulfilled.

If new information becomes available, it should be communicated without delay to the subject, the Investigator and the IEC, and regulatory authorities whenever required.

15.2 Subject Information and Consent

Adequate information will be provided to the child’s parent(s)/legally acceptable representative in both oral and written form and consent will be obtained in writing prior to the subject inclusion in the trial. The content and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

The Sponsor may provide a sample informed consent form/subject information sheet. The final form must be agreed by the IEC and must contain all ICH-GCP (4.8.10) elements in a language readily understood by the subject.

If the informed consent form is amended during the trial, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended informed consent form by the IEC and use of the amended form.
15.2.1 Information

The Investigator, or a person designated by the Investigator, should fully inform the child’s parent(s)/ legally acceptable representative of all pertinent aspects of the trial.

The child’s parent(s)/ legally acceptable representative will be informed of the nature of the trial in an unambiguous language they easily understand. The participation is voluntary and they can at any time decide to stop the participation without any influence on the future care or treatment of their child. The child’s parent(s)/ legally acceptable representative must be informed about the main procedures used to guarantee their anonymity, especially during the analysis of their personal data. They should be able to ask all the questions they want about the trial and to receive relevant answers. They will receive complete written information in the “Parent(s)/ legally acceptable representative Information Sheet”.

15.2.2 Informed Consent

After having received extensive information about the nature, significance, implication and risks of the trial and having had enough time to consider, the child’s parent(s)/ legally acceptable representative must give their written consent by signing and dating the Informed Consent Form.

This form will also be dated and signed by the person who obtained the informed consent and then retained by the Investigator. Obtaining of consent will be confirmed in the subject’s medical chart and in the CRF.

Two copies of the Informed Consent Form will be signed. The child’s parent(s)/ legally acceptable representative will receive a copy and the other copy will be filed in the Investigator’s study File.

The child’s parent(s)/ legally acceptable representative may withdraw their consent to their child's participation in the trial at any time. A subject is considered as enrolled in the trial when the informed consent form has been signed. A Case Report Form must not be started, nor may any trial specific procedure be performed for a given subject, without having obtained the parent(s)/ legally acceptable representative written consent to participate in the trial.

If any new information that could influence the child’s parent(s)/ legally acceptable representative decision to stay in the trial becomes available, this will be transmitted without delay to the child’s parent(s)/ legally acceptable representative.
15.3 Subject Confidentiality

Subject confidentiality will be maintained at all times.

Personnel from the Sponsor (or its representative), from Regulatory Authorities and members of IEC may inspect medical records and case report forms for verification of accuracy of data and are obliged to respect medical secrecy and to refrain from divulging the subject's identity or any other personal information.

15.4 Informing the General Practitioner (or Pediatrician)

If the child’s parent(s)/legally acceptable representative agree, the Investigator will inform the subject’s regular physician of his/her participation in the trial, by sending him/her the “letter to the GP” prepared by the Sponsor and the Investigator.
16. TRIAL MANAGEMENT AND ADMINISTRATION

16.1 Monitoring

The monitoring of the trial is the responsibility of the Sponsor. The monitor (the individual responsible for monitoring) will advise the Investigator regarding the practical conduct of the trial and assist him/her in working according to the protocol, Good Clinical Practice (GCP), and the regulatory requirements.

The Investigator will allow the Sponsor or its representatives to periodically monitor at mutually convenient times during and after the trial has been completed, all CRFs (whether in electronic or paper form) and the corresponding source documents. Therefore, the monitor will have direct access to these records. The monitoring visits provide the Sponsor or its representatives with the opportunity to evaluate the progress of the trial, to verify the accuracy and completeness of CRFs (whether in electronic or paper form), to ensure that all protocol requirements, applicable local authority regulations and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the trial records.

Electronic Case Report Forms (e-CRF) will also be reviewed on an ongoing basis, from remote, without the monitor being physically present at the trial site at the time of review.

16.2 Direct Access to Source Data/Documents

The Investigator(s)/Institution(s) will permit trial-related monitoring, audits by or on behalf of UCB, IEC, and regulatory inspector(s), providing direct access to source data/documents.

Source documents (SD) are original records in which raw data are first recorded. These may be: hospital / clinic / General Practitioner (GP) records, charts, diaries, x-rays, laboratory results, pharmacy records, care records, completed psychometric scales, daily record cards, etc.

If they are not included in the clinical dossier/hospital file of the subjects, the following data may be written directly in the CRF and will therefore be considered as source data:

- Global Psychomotor questionnaire
- Behavioral Questionnaires (for U.K. and Australia)

The diary cards (for AD evaluation as well as nocturnal cough, wheezing and urticaria reporting) and, if used, the original lab results documents with the investigator’s comments, will be inserted in the CRF and are also to be considered as source data.

All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc).
Hospital/Clinic/Medical files that are computer generated and stored on magnetic support media must be printed. The Investigator will sign and date the print-out. The monitor will also sign and date the print-out when reviewing them. The Investigator will authorize the monitor to compare the content of the print-out and the data stored in the computer to ensure all data are consistent.

The minimum requirements for medical charts used in clinical trials are that they should contain: the identity of the subject and a trial related identifiers (such as treatment numbers, CRF numbers, or similar), the subject's participation in the trial and identification of that trial (trial title or number), the date of obtaining signed informed consent, the subject's medical history, the treatments and dates that the subject received, AEs and SAEs and the dates of the visits. The source documents should also provide evidence that inclusion/exclusion criteria were evaluated and met. Information recorded in the CRF must be consistent with entries in the source documents.

16.3 Audit and Inspection

The Investigator will permit trial-related audits by auditors mandated by UCB, and inspections by domestic or foreign regulatory authorities, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, and that all data relevant for the evaluation of the investigational product have been processed and reported in compliance with the planned arrangements, GCP and applicable regulatory requirements. The Investigator will provide direct access to all trial documents, source records and source data. If a regulatory inspection is announced, the Investigator will immediately inform UCB.

16.4 Scientific Advisory Board

In order to guarantee the high scientific and ethical standard of the protocol and of the monitoring of the trial, an independent Scientific Advisory Board (SAB) will supervise all the steps in the development of the Early Prevention of Asthma in Atopic Children project and advise the Sponsor about the preparation of the protocol, the follow-up of the trial, especially for the safety and ethical issues, and give its conclusions. Regularly, during the trial, the SAB will blindly review the safety data and advise the Sponsor accordingly. When needed, the Sponsor may organize extra meetings in order to discuss important issues arising during the trial.

16.5 Data Review Committee (DRC)

A Data Review Committee will be organized by the Sponsor in order to ensure a central review of the data related to asthma, before unblinding. For each patient, the date of onset of asthma and the number of asthma episodes will be calculated by a computerized algorithm,
according to the definition of asthma provided in section 4.5.4. The results of the review will be validated by the Scientific Advisory Board before unblinding. The DRC will develop its own operating procedures, which will be part of the trial documentation.

16.6 Research Fellow

In order to optimize the homogeneity of the data collection, it is recommended that a research fellow take care of the trial under the responsibility of the main investigator in each center: logistical aspects (biological samples handling, visits schedule...), contacts between investigator and caring persons/subjects, help in CRF completion...

The RF will receive a special training from the Sponsor for this trial and will be invited to each investigators meeting.

16.7 Case Report Forms (CRF)

Data reflecting subject experience with the drug(s) under investigation will be reported to the Sponsor. These data will be recorded in the Case Report Forms (CRF). The CRF is essentially a data entry form and may not routinely constitute the original (or source) medical record.

CRFs will be signed and dated by the Investigator as indicated. The Investigator’s signature on the CRF attests to its accuracy and completeness. Paper CRFs will be filled in black ink, and must be legible.

The Sponsor cannot interpret a blank answer as “NONE” or “N/A”, therefore, all fields must be completed. In paper CRF, if the data are not available, a straight line should be drawn through all applicable fields. In the electronic CRF, the equivalent “N/A” option should be chosen.

Data reported in the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained in these source documents.

The Investigator will keep the (A00309) subject screening log to document identification of subjects who entered pre-trial screening of A00384. The Investigator must submit to the Sponsor or its representatives a CRF (or equivalent) for each participant who signed an informed consent form (see also additional information in section 16.11).

All supportive documentation submitted to the Sponsor in addition to the Case Report Form, such as laboratory results or hospitalization records, must be clearly identified with the trial or protocol number, trial participant number, and trial participant initials; any personal
information, including the trial participant’s name, must be removed or rendered illegible to preserve individual confidentiality.

Most of subject’s data will be recorded in an Electronic Case Report Form (e-CRF). However, due to their nature, some data will always need to be recorded in an abbreviated paper CRF.

### 16.7.1 Electronic Case Report Forms

The Electronic Case Report Forms (e-CRF) are part of an Electronic Data Capture system and will be completed by the investigator or designated members of his/her team who will have access to the Electronic Case Record Forms via individually and confidentially assigned username + password combinations.

The Electronic Case Report Form is essentially a data entry tool and should not constitute the original (or source) medical record.

All entries in such e-CRFs, including changes to previously entered data, will be done under the Electronic Signature of the person performing the action. This Electronic Signature consists of the username + password combination used to access the Electronic Data Capture (EDC) system, and declared to be the legally binding equivalent of the handwritten signature.

In case previously entered data are changed, a reason for change will be provided.

The Investigator will ensure that the Electronic Case Report Forms are completed accurately and promptly. Monitors will be able to review the Electronic Case Report Forms from remote and on an ongoing basis through a monitor-specific access profile to the Electronic Data Capture System. The Investigator will attest to the accuracy and completeness of the e-CRF by personally answering under his/her Electronic Signature the referenced question in the e-CRF.

Detailed instructions for the paper use/completion of the e-CRF will be given in a separate document.

For practical issue, the e-CRF will be the amended (A00309) e-CRF allowing the continuation of recording of data. Therefore, there will be no need to reenter baseline data.

### 16.7.2 Abbreviated paper Case Report Forms

The following data will not be collected in the e-CRF, but will be recorded in the appropriate sections of an Abbreviated paper CRF:

- Study drug dispensing (including the pasting of the study medication label)
- Global Psychomotor Development Questionnaire
- Behavioral questionnaires (for U.K. and Australia)
16.7.3 Traditional, full length paper Case Report Forms

Traditional, full length paper CRFs will be available as back-up measure in case the Electronic Data Capture system fails and only after prior written permission from UCB S.A. Pharma Sector. The exact modalities regarding the use of the full length paper CRFs will be described in an ad-hoc section of an Electronic Data Capture Contingency Plan.

As in the case of the Electronic Case Report Form, the full length paper Case Report Form is essentially a data entry form and should not routinely constitute the original (or source) medical record.

In case data are recorded on paper CRFs (abbreviated or full length), the investigator will ensure that these CRFs are completed accurately and promptly and that they are available for review by the Monitor during the regular visits.

The paper CRFs will be signed and dated by the Investigator as indicated. The Investigator handwritten signature on the paper CRF attests to their accuracy and completeness.

16.8 Adherence to Protocol

The Investigator/Institution should conduct the trial in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies) and for which an approval by the IEC was given. The Investigator/Institution and the Sponsor should sign the protocol to confirm agreement.

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the trial participant from immediate hazard followed by notification of the Sponsor or its representatives and the IEC regarding the type of emergency and the course of action taken. Significant changes in or deviations from the protocol will ONLY be made as an amendment to the protocol and must be approved in writing by the Sponsor and the IEC prior to being implemented. Unless the Sponsor has consented to any such deviations or changes in writing, they cannot be implemented and the Sponsor will not assume any resulting responsibility or liability.

Any significant protocol deviation will be documented and explained by the Investigator or the person designated by the Investigator and will be included in the final Trial Report.
16.9 Termination of the Trial

Upon completion of the trial, the monitor will conduct the following activities in conjunction with the Investigator, as appropriate:

- return of all trial data to UCB or its representative
- data clarification and/or resolution
- accountability, reconciliation and arrangements for used and unused trial drugs
- review of site trial records for completeness
- return of treatment codes to UCB or its representative
- discussion/reminder on archiving responsibilities

In addition, UCB reserves the right to temporarily suspend or prematurely discontinue this trial either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues, severe non-compliance, recurrent non-compliance, or unsatisfactory enrollment with respect to quality or quantity.

If the trial is prematurely terminated or suspended, UCB will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for all unused study drugs and other material in accordance with UCB procedures for the trial.

16.10 Investigator Site File

The content of the investigator file is structured in a manner that aids in the filing, retrieval, and/or auditing of study-related documents. All documents will be filed according to Standard File Categories that identify specific aspects of the trial.

16.11 Data Handling and Record Keeping

The Sponsor will be responsible for data processing.

Subjects’s data will be either entered directly in the e-CRF or recorded on paper CRF and then entered in an electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. An electronic audit trail system will be used to track all data changes in the database subsequent to the reconciliation of the double-entered data. The SAS system will be used for the statistical analysis of the data. Regular back-ups of the electronic data will be carried out.
16.12 Clinical Trial Report

The Sponsor will prepare, in collaboration with the Scientific Advisory Board, a clinical trial report according to the relevant ICH guidelines. The report will include a thorough description of the clinical and laboratory methods, a discussion of the results and a list of all measurements.

This report may be included in submissions to government drug regulatory authorities worldwide, or used for whatever reason considered appropriate by the Sponsor. No use should be made of the report without written approval by the Sponsor. The Chairman of the Scientific Advisory Board will sign the CSR on behalf of the EPAAC Scientific Advisory Board.

16.13 Subject Insurance

The Sponsor declares that it has subscribed an insurance, for the total duration of the trial, covering the subjects, in respect of the risks involved in this trial carried out according to this protocol. In case of injury or disability deriving from participation in the trial, the subject is requested to inform without delay the treating physician responsible for the trial.

16.14 Publication and Presentation Policy

No unpublished data given to the Investigator may be transmitted to a third party without written approval of the Sponsor.

The Investigator shall not publish any research findings resulting from the trial nor any scientific work, with respect to UCB’s drug or its development, without UCB’s prior written consent on the content of the manuscript or other materials prepared for publication. UCB shall have three (3) months in which to suggest changes to the Investigator in order to preserve UCB’s intellectual property rights and major marketing interests. Should UCB decide to file a patent application, the Investigator agrees to withhold publication of any part of the manuscript or materials which UCB determines to be prejudicial to the granting of such patent for a period not exceeding twelve (12) months.

The Investigator agrees that all reasonable comments made by UCB in relation to a proposed publication by the Investigator will be incorporated by the Investigator into the publication.

The Sponsor shall not use the Investigator’s name in any publication without the prior written permission of the Investigator. The Investigator shall not use the Sponsor’s name in any publication without the prior written permission of the Sponsor.
16.15 Archiving and Data Retention

The Investigator will maintain adequate records for the trial including PDF files of the electronic CRFs that will be delivered by the Sponsor at the end of the trial, copies of paper CRFs if any were used, medical records, laboratory reports, informed consent documents, drug disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All records are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or by an agreement with the sponsor (ICH-GCP Guideline-section 4.9.5). The Investigator will contact the Sponsor for authorization prior to the destruction of any trial records or in the event of accidental loss or destruction of any trial records. The Investigator will also notify the Sponsor should he/she relocate or move the trial related files to a location other than that specified in the Sponsor’s Trial Master File.

16.16 Allocation of Responsibilities

The Investigator is responsible for the implementation of the protocol but can delegate tasks to the research team. He/she remains responsible for coordinating and informing his/her staff about the protocol and the possible changes made to it.

The Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant trial-related duties ("authorized signatures" document with name, function, signature, initials, dates of participation in the trial conduct and type of delegated tasks).

This list should be kept up to date.

16.17 Curriculum Vitae (CV)

The Investigators should supply their updated CVs (English translation), dated and signed, together with a list of their collaborators responsible for the practical conduct of the trial. These collaborators should also provide a recent English version of their CVs, dated and signed.
16.18 Financial Disclosure

A financial disclosure statement must be obtained from each Investigator participating to the trial. This will be collected before subject enrollment. The Investigator must inform the Sponsor if information related to financial disclosure changes during the course of the trial and for one year after completion of the trial.
17. REFERENCES

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