The secondary safety endpoints for this study include the following:

- clinical laboratory test results
  - hematology and chemistry results at baseline and at weeks 4 (chemistry only), 8, 24, and 36 or early withdrawal visit
- local tolerability at the injection site at approximately 1 hour after study drug administration every 4 weeks throughout the study (see Protocol Section 7.8)
- vital signs measurements every 4 weeks throughout the study
- concomitant medication usage every 4 weeks throughout the study

The **secondary objective** of this study is to evaluate the efficacy of reslizumab 110 mg administered sc once every 4 weeks in patients 12 years of age and older with severe eosinophilic asthma that is inadequately controlled on standard-of-care treatment.

The secondary efficacy endpoints for this study include the following:

- clinical asthma exacerbation (CAE) and healthcare utilization (HCU)-related endpoints
  - frequency of CAEs
  - frequency of asthma-specific hospital admissions
  - length of hospital stay and number of intensive care unit (ICU) days
  - frequency of asthma-specific emergency department visits
  - frequency of school/work days missed due to asthma
- change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1) measured using spirometry at weeks 0, 8, 24, and 36 or early withdrawal visit
- change in daily morning ambulatory FEV_1 from baseline at each week through week 36 or early withdrawal, as measured by the handheld spirometry device
- absolute and percent reduction in the daily oral corticosteroids (OCS) dose at weeks 20 and 36 or early withdrawal visit as compared with the dose at baseline (for patients on daily OCS at baseline)
- change from baseline in total inhalations of reliever bronchodilator medication (eg, short-acting beta-agonist [SABA]) measured using weekly averages until week 36 or early withdrawal visit
- change from baseline in Asthma Control Questionnaire (ACQ-6) score performed at weeks 0, 8, 24, and 36 or early withdrawal visit
- change from baseline in Asthma Quality of Life Questionnaire (AQLQ12+) score performed at weeks 0, 8, 24, and 36 or early withdrawal visit

[redacted]

Abbreviation	Term
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
iv	intravenous
LABA	long-acting beta-agonist
LPLV	Last Patient Last Visit
LSO	local safety officer
MA	Marketing Authorisation
mAb	monoclonal antibody
n	number
OCS	oral corticosteroid
OL	open-label
PD	pharmacodynamics
PEF	peak expiratory flow
PFS	pre-filled syringe
PI	principal investigator
PK	pharmacokinetics
RSI	reference safety information
SABA	short-acting beta-agonist
sc	subcutaneous
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential

Objectives	Endpoints
	weeks 20 and 36 or early withdrawal visit as compared with the dose at baseline (for patients on daily OCS at baseline) • change from baseline in total inhalations of reliever bronchodilator medication (eg, short-acting beta-agonist) measured using weekly averages until week 36 or early withdrawal visit • change from baseline in ACQ-6 score performed at weeks 0, 8, 24, and 36 or early withdrawal visit • change from baseline in AQLQ12+ score performed at weeks 0, 8, 24, and 36 or early withdrawal visit
	[redacted]
	The immunogenicity assessments for this study include the following: • ADA measurement at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the long-term immunogenicity of sc reslizumab • ADA measurement at the EOS visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout
No tertiary or exploratory objectives.	No tertiary or exploratory endpoints.

ACQ-6=Asthma Control Questionnaire; ADA=anti-drug antibody; AQLQ12+=Asthma Quality of Life Questionnaire; EOS=end of study; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ICU=intensive care unit; OCS=oral corticosteroids; [redacted]; SABA=short-acting beta-agonist; sc=subcutaneous

2.1.1. Justification of Primary Endpoint

The primary objective of this study is to support and obtain additional long-term safety data for sc administration of reslizumab treatment administered at a fixed dose of 110 mg in patients 12 years of age and older with severe eosinophilic asthma. The primary endpoint is the frequency of all adverse events including serious adverse events experienced in patients administered sc reslizumab. The study design includes standard assessments that will help inform the overall safety profile of reslizumab, as well as adverse events of interest including systemic reactions (including anaphylaxis and administration site reactions), malignancy, infections (including parasitic helminthic and opportunistic infections), ADA, and musculoskeletal/CPK abnormalities. This comprehensive data collection methodology will allow for a robust analysis of patient safety during the study.

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

This is a global, multicenter, OL extension study to obtain additional long-term safety data of reslizumab treatment administered sc at a fixed dose of 110 mg in patients 12 years of age and older with severe eosinophilic asthma.

The study consists of a screening/baseline visit (V1; seamless rollover patients; conducted on the same day as the end-of-treatment [EOT, week 52 or week 24, respectively] visit for patients who finished either Study 30025 or 30027) or a standalone screening visit (V0) for patients who did not seamlessly rollover from Study 30025 or 30027 (had a gap between placebo-controlled study EOT and start of OLE; Section 4.1 and Appendix B.1), followed by an OL treatment period, an EOT visit (V_{EOT}), a follow-up telephone call (V_{FU}) at 12 weeks after the EOT visit, and an EOS visit (V_{EOS}) for immunogenicity testing 19 weeks after the final dose of study drug administration. The duration of the OL treatment period will be 9 months (36 weeks).

Study patients will be deemed eligible only if they meet all inclusion criteria and no exclusion criteria are fulfilled. Patients currently enrolled in Studies 30025 and 30027 will be required to complete their respective treatment periods to be eligible for this study. In addition, adolescents (patients 12 through <18 years of age) from Study 30025 must also complete the 12-week early follow-up visit (off study drug) before transferring to this OL study.

There may be a gap in study drug administration for some patients due to completion of Study 30025 or 30027 before the initiation of the OL extension study (non-seamless rollover). Patients with a gap between the EOT visit for Study 30025 or 30027 will complete a V0 screening visit. Adolescents (a patient 12 through <18 years of age) from Study 30025 can complete the V0 screening visit of Study 30066 the same day as the 12-week early follow-up visit for Study 30025. Any blood tests completed by adolescents at the 12-week early follow-up visit for Study 30025 can be used for the V0 screening visit of Study 30066 and do not need to be repeated. Any patient who did not rollover seamlessly from Study 30025 or 30027 will participate in a 7-day run-in period where baseline measures for asthma control and spirometry will be established. This screening assessment and run-in period will be completed within the 2 weeks prior to visit 1.

During screening/baseline, informed consent (and assent for patients under 18 years of age according to local Institutional Review Board/Independent Ethics Committee [IRB/IEC] requirements) will be obtained. This will be conducted at the EOT visit of Study 30025 or 30027 (seamless rollover patients) or at the standalone screening visit (V0) for non-seamless rollover patients with a gap in study drug administration (those who have previously completed Study 30025 or 30027, but are not screened on the same day as the EOT visit.

During the treatment period, patients will receive reslizumab by sc injection at a dosage of 110 mg every 4 weeks (28 days ±7 days) for 32 weeks in the study center. Patients will return to the study center every 4 weeks relative to baseline during OL treatment.

After study drug administration, each patient will remain at the study center for a minimum of 1 hour for observation. If during post-study drug observation the patient develops clinical symptoms, vital signs should be collected and the patient should be assessed for anaphylaxis/hypersensitivity reactions as detailed in Section 7.1.6.1.1.

After each administration, the patient will be required to use a study-provided handheld electronic diary (eDiary)/spirometry device that will ask questions post-injection to evaluate for any new symptoms that may have developed during the 24-hour period after investigational medicinal product (IMP) administration. The patient will complete a question regarding new symptoms on the eDiary device the evening after the IMP administration and the following morning. This is in addition to the peak expiratory flow (PEF; AM and PM), FEV_1 measurements (AM only), and recording of rescue inhaler use that are performed every day during the treatment period.

A full physical examination will be completed at screening and at EOT. Other safety evaluations will be performed at every visit when the study drug is administered: adverse event inquiry, vital signs measurement, assessment of injection site, concomitant medication use, and urine pregnancy test. Additional evaluations, including clinical chemistry, hematology, and ADA measurements, will be performed throughout the study according to the schedule of procedures and assessments (Table 1). Patients will also be monitored for asthma exacerbations throughout the study (Section 6.1.1).

Asthma control measures will be assessed as part of this OL extension study to evaluate the long-term effect of sc reslizumab. These will include CAE assessment (including healthcare utilization [HCU]), pre-bronchodilator spirometry, questionnaires (including ACQ-6 and AQLQ12+), and change in OCS dose for those on maintenance therapy. Asthma control including asthma exacerbations and related HCU will be assessed at every study visit during the treatment period. Spirometry will be performed daily through the use of a handheld spirometry device. Concomitant medications will be recorded at all visits during the treatment period and will include OCS dose if participants are on maintenance corticosteroids (Appendix I). For those patients previously enrolled in Study 30027, maintenance prednisone will no longer be provided by the sponsor. In an effort to standardize a patient's maintenance therapy, it is encouraged that the investigators prescribe prednisone/prednisolone as the maintenance corticosteroid preparation if deemed necessary.

Patients will have final procedures and assessments performed at the EOT visit. Patients who withdraw before the completion of the study will have EOT procedures and assessments performed at their early withdrawal visit. All patients will have a follow-up telephone assessment 12 weeks after the EOT visit. The EOT visit includes home pregnancy testing, adverse event assessment, and concomitant medication inquiry. There will then be an EOS visit for immunogenicity testing 19 weeks after the final dose of study drug.

Measurement of ADAs will be performed on samples collected at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the potential long-term immunogenicity of sc reslizumab, and on samples collected at the EOS visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout. A blood sample will also be collected in the event of withdrawal from the study or upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). An unscheduled sample can also be drawn after a serious adverse event if the investigator or sponsor considers appropriate. Drug levels may be measured in the serum samples collected for ADAs to help inform ADA analysis. If a patient is found to have a positive ADA status after at least 2 doses of study drug in this OL study, the patient may be scheduled to complete an EOT visit. This testing may be done to enhance early data collection on potential washout samples. A summary of ADA results in previous clinical experience is outlined in Section 1.2.2.4.

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from

EOS visit (week 51) will be considered as having completed the study. See Section 3.6 for the definition of the end of the study.

3.6. End of the Clinical Study

Last Patient Last Visit (LPLV) of the treatment period is defined as the EOT. The EOS visit for immunogenicity testing only will be performed 19 weeks (±2 weeks) after the final dose of study drug (approximately week 51). This will be considered the end of the trial for the purposes of end of trial notification.

3.7. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (other assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 1: Study Procedures and Assessments

Study period	**Screening**		**Open-label treatment period**											
Visit number	**V0[a] Screening for non-seamless enrollees**	**Run-in for non-seam-less enrollees**	**V1[a] Screening /baseline**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V_{EOT} EOT or early with-drawal**	**V_{FU} Follow-up telephone assessment**	**V_{EOS} EOS**
Procedures and assessments	**W-2 -14d to ≤-7d**	**-7d to 0d**	**W0**	**W4 ±7d**	**W8 ±7d**	**W12 ±7d**	**W16 ±7d**	**W20 ±7d**	**W24 ±7d**	**W28 ±7d**	**W32 ±7d**	**W36 ±7d**	**W48 (EOT +12W) ±14d**	**W51 (V9 +19W) ±14d**
Informed assent/consent	X		X											
Medication history	X		X											
Inclusion and exclusion criteria	X		X											
Pregnancy testing	X[b]		X[c]	X	X	X	X	X	X	X	X	X	X	
Hematology (CBC with differential) (prior to IMP administration)	X		X[c]		X				X			X		
Serum chemistry tests with CPK[d] (prior to IMP administration)	X		X[c]	X	X				X			X		
Blood for ADA[e]			X[c]		X				X			X		X
Full physical examination[f]	X		X[c]									X		
ECG[f]	X		X[c]									X		
Vital signs[f]	X		X[c]	X	X	X	X	X	X	X	X	X		
Height and weight	X											X		
Pre-bronchodilator spirometry[g]			X[c]		X				X			X		
ACQ-6			X[c]		X				X			X		
AQLQ12+			X[c]		X				X			X		

Table 1: Study Procedures and Assessments (Continued)

Study period	**Screening**		**Open-label treatment period**											
Visit number	**V0[a] Screening for non-seamless enrollees**	**Run-in for non-seam-less enrollees**	**V1[a] Screening /baseline**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V_{EOT} EOT or early with-drawal**	**V_{FU} Follow-up telephone assessment**	**V_{EOS} EOS**
Procedures and assessments	**W-2 -14d to ≤-7d**	**-7d to 0d**	**W0**	**W4 ±7d**	**W8 ±7d**	**W12 ±7d**	**W16 ±7d**	**W20 ±7d**	**W24 ±7d**	**W28 ±7d**	**W32 ±7d**	**W36 ±7d**	**W48 (EOT +12W) ±14d**	**W51 (V9 +19W) ±14d**
Assess asthma control including asthma exacerbations and related HCU: step-down background medication (eg, OCS) if clinically appropriate[h]	X		X[c]	X	X	X	X	X	X	X	X	X		
Provide/collect handheld electronic diary/spirometry device; reinforce diary and PEF/spirometry compliance	X		X	X	X	X	X	X	X	X	X	X		
Patient daily use of handheld electronic diary/spirometry device		X →												
Adverse event inquiry	X		X[c]	X	X	X	X	X	X	X	X	X	X	
Concomitant medication inquiry[i]	X		X[c]	X	X	X	X	X	X	X	X	X	X	
IMP administration			X	X	X	X	X	X	X	X	X			
Injection site assessment[j]			X	X	X	X	X	X	X	X	X			

[a] Visit 1 (screening/baseline) will take place at the EOT visit for patients seamlessly rolling over from Studies 30025 and 30027. Any patient who did not rollover seamlessly from Study 30025 or 30027 will be seen first at an earlier screening visit (V0) in order to complete informed consent and eligibility criteria procedures before completing all other procedures and IMP administration at V1. Adolescents (a patient 12 through <18 years of age) from Study 30025 can complete the V0 screening visit of Study 30066 the same day as the 12 week early follow up visit for Study 30025. Additionally, any patient who did not rollover seamlessly from Study 30025 or 30027 will participate in a 7-day run-in period where baseline measures for asthma control and spirometry will be established. The screening period (including run in) will be up to a maximum of 14 days. Patients who complete the screening assessments of informed assent/consent, medication history, and inclusion and exclusion criteria at V0 do not need to repeat them at V1. Any assessments that are performed at V0 do not need to be repeated at V1 if completed within the previous 14 days (including blood tests completed by adolescents at the 12 week early follow up visit for Study 30025).

6.1.3. PEF Monitoring

PEF will be measured twice daily in the morning and evening with the use of a handheld spirometry device that has combined spirometry and eDiary capabilities. PEF is the maximum speed of exhalation.

6.1.4. Asthma Rescue Medication Use

The number of times asthma rescue medication (number of inhalations/puffs) is used will be assessed by reviewing the eDiary that will be maintained by the patient (Appendix J).
Note: SABA therapy used for exercise pretreatment should not be recorded.

6.1.5. Asthma Control Questionnaire

The ACQ-6 is a validated asthma assessment tool that has been widely used (Juniper et al 1999). There are 6 self-assessment questions. Each item on the ACQ-6 has a possible score ranging from 0 to 6, and the total score is the mean of all responses (Appendix K).

6.1.6. Asthma Quality of Life Questionnaire for Patients 12 Years and Older

The AQLQ12+ is a modified version of the standardized AQLQ (AQLQ[S]), which was developed to measure functional impairments experienced by adults ≥17 years of age. The AQLQ12+ is valid for patients 12 to 70 years of age and includes 32 questions in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli) [Juniper et al 1992, Wyrwich et al 2011]. Patients will be asked to recall their experiences during the previous 2 weeks and score each of the questions on a 7-point scale, where 7=not at all limited and 1=totally limited (Appendix L).

6.1.7. Target Biomarker Measures

Eosinophil counts will be monitored throughout as a biomarker for reslizumab activity.

7. ASSESSMENT OF SAFETY

In this study, safety and tolerability of reslizumab sc administration will be assessed by qualified study personnel by evaluating the following:

- frequency of all adverse events, including serious adverse events
- clinical laboratory test results
  - hematology and chemistry results at baseline and at weeks 4 (chemistry only), 8, 24, and 36 or early withdrawal visit
- local tolerability at the injection site at approximately 1 hour after study drug administration every 4 weeks throughout the study
- vital signs measurements every 4 weeks throughout the study
- concomitant medication usage every 4 weeks throughout the study

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily require a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to reslizumab. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant

(Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

- events associated with study procedure (eg, clinically significant adrenal insufficiency)

Asthma exacerbation is an efficacy variable for this study and should be captured on the asthma exacerbation CRF. Accordingly, asthma exacerbations should not be recorded as adverse events unless assessed as more severe than the patient's usual disease course. In this case, the investigator should determine if the adverse event is nonserious or serious based on seriousness criteria, as defined in Section 7.1.5. All asthma exacerbations should be recorded on the asthma exacerbation CRF, regardless of severity or whether it meets adverse event criteria.

7.1.2. Recording and Reporting of Adverse Events

For recording of an adverse event, the study period is defined for each patient as the time period from signature of the informed consent form to the end of the follow-up period. The follow-up period of recording of adverse events is defined as 12 weeks after the last dose of IMP. The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered and until the EOT visit.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the test IMP. For serious adverse events, the serious adverse event form must be completed and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period. Serious adverse events that occur to a patient after the end of the study should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; until the patient is referred for continued care to a healthcare professional; or until a determination of a cause unrelated to the test IMP or study procedure is made.

The onset and end dates, action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF. The approximate time of onset for each adverse event will also be recorded.

The relationship of each adverse event to the IMP and study procedures and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are provided in the Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as one of the following:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Test Investigational Medicinal Product

The relationship of an adverse event to the IMP is characterized in Table 3:

Table 3: The Relationship of an Adverse Event to the Study Drug

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

For recording of serious adverse event, the study period is defined for each patient as that time period from signature of the informed consent form to the end of the follow-up period (follow-up telephone assessment at week 48). Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is a life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event that hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

  Hospitalizations scheduled before study entry will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study. Note: Hospitalizations due to asthma exacerbation will be reported as serious adverse events if the presentation or outcome is more severe than the patient's known course of asthma.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, may not be life-threatening, or may not require hospitalization but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  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 the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below occurring together, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3× the upper limit of normal (ULN)
- total bilirubin increase of >2× ULN

- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study may be found in the IB. For the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting, the version of the IB at the time of occurrence of the SUSAR applies. All serious adverse events will be evaluated for expectedness by the sponsor's Global Patient Safety and Pharmacovigilance (GPSP) department.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the test IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a contract research organization [CRO] in a country without a sponsor LSO) [contact information is in the Clinical Study Personnel Contact Information section]; the LSO will forward the report to the sponsor's GPSP. Further details regarding this process can be found in the Safety Monitoring Plan.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the test IMP (no reasonable possibility, reasonable possibility)

Additional information includes the following:

- age and sex of patient
- date of first dose of IMP

- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the test IMP, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences form/Extensible Markup Language file to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator must ensure that the IRB is also informed of the event, in accordance with national and local regulations.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the test IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in the sponsored clinical studies of reslizumab and the appropriate competent authorities (and IEC/IRB, as appropriate).

7.1.6.1.2. Creatine Phosphokinase/Muscular Adverse Events Case Report Form

Potentially clinically significant CPK elevations (with or without associated symptoms) or myalgia/muscle symptoms will be recorded as an adverse event and documented using the potentially clinically significant CPK/myalgia CRF. A potentially clinically significant CPK is defined as ≥3.1× ULN (grade 3 based on the FDA "Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials").

If a potentially clinically significant CPK level (≥3.1× ULN) occurs, the patient should attend an unscheduled visit for a physical examination as well as additional testing, if indicated per investigator judgement. CPK levels will be retested at a minimum of every 7 to 10 days until the elevation is resolved or if agreed with the medical monitor that no further testing is indicated. For ≥10× ULN elevations in CPK, repeat CPK level, urinalysis (including microscopy), serum electrolytes, blood urea nitrogen (BUN), and creatinine will be performed as soon as possible after receipt of the CPK result. Further testing of CPK levels should be undertaken as frequently as needed to manage patient care per investigator judgment but should be at a minimum of every 7 to 10 days as above. Need for repeat urinalysis, serum electrolytes, BUN, and creatinine testing should be determined by the investigator. In addition, need for treatment (eg, administration of iv fluids and urine alkalinization) should be considered by the investigator.

In cases deemed by the investigator to be treatment-related elevations in CPK ≥10× ULN (eg, potentially rhabdomyolysis), study drug discontinuation should occur at least until CPK normalization or longer based on investigator clinical assessment in collaboration with the sponsor.

7.1.7. Withdrawal Due to an Adverse Event

Any patient who will experience an adverse event may be withdrawn from the study at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and the termination page of the CRF will be completed at that time.

The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a healthcare professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the medical monitor as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that, in the opinion of the investigator, is not severe enough to warrant discontinuation but requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be the need to take a prohibited medication, not the adverse event.

7.1.8. Overdose of Study Drug

Any dose of study drug, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. Medication errors will be captured as protocol violations or deviations depending on the error.

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Pregnancy

Administration of IMP will be discontinued for any female patient who becomes pregnant during the study.

All pregnancies of women participating in the study that occur during the study, or within at least 5 months after the last IMP injection, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

All female patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the woman participating in the study does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event
- For an elective abortion due to developmental anomalies, report as a serious adverse event
- For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an adverse event

7.3. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol

(Appendix C), or as a deviation in the patient's source documents, regardless of whether or not an adverse event occurs as a result. When meeting protocol violation criteria, all instances of incorrect IMP administration should be categorized on the CRF as "Noncompliance to investigational medicinal product (IMP)."

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used (not in accordance with the authorized product information).
4. Abuse: Persistent or sporadic, intentional excessive use of IMP that is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or nonprofessional occupation.
7. Breastfeeding: Suspected adverse reactions that occur in infants after exposure to a medicinal product from breast milk.

7.4. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and on the CRF as an adverse event and will be monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic workup. (Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

In addition, potentially clinically significant values will be predefined by the sponsor for selected laboratory parameters and will be detailed in the statistical analysis plan.

Aliquot set B samples will either be sent to the same laboratory as that for aliquot set A on a later day by next-day courier or be retained at the investigational center until the study is completed (unless shipment to another facility is requested by the sponsor).

Samples from reslizumab-treated patients will be analyzed for ADA using appropriately validated methods. The ADA serum samples may be used to measure serum drug concentration if necessary to help ADA analysis. Timing of the initiation of sample analysis will be determined by the Teva Pharmaceuticals bioanalytical department representative responsible for the bioanalysis. The bioanalytical team will not be blinded for this analysis.

Additional details regarding the collection, handling, and shipment of samples for measurement of ADAs are provided in the investigator laboratory manual and its associated specimen collection summary. Further details can be found in Appendix P.

8.2. Pharmacokinetic Assessment

Pharmacokinetic parameters will be assessed in the context of ADA samples in this study.

8.3. Pharmacodynamics Assessment

See below in “Assessment of Biomarker” section.

8.4. Assessment of Biomarkers

Biomarker measures will include blood eosinophil data, measured at the time points indicated in Table 1. Details of blood sampling and preparation are described in the Laboratory Manual provided in the study file documents. Summaries will be provided, if appropriate.

the study. Summaries will be presented for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

For continuous variables of safety measures, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will be provided.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with reslizumab.

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the CSR.

9.7. Immunogenicity Analysis

The immunogenicity assessments for this study include the following:

- ADA measurement at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the long-term immunogenicity of sc reslizumab
- ADA measurement at EOS visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout

ADA status will be listed. ADA status will be correlated with variables of safety, if appropriate.

9.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be assessed in the context of ADA samples in this study.

9.9. Pharmacodynamics Analysis

See below in “Biomarker Analysis” section.

9.10. Biomarker Analysis

Biomarker results (eosinophil counts) will be summarized using descriptive statistics.

9.11. Planned Interim Analysis

There will be a planned data cut with statistical output produced before the supplemental Biologics License Application submission.

9.12. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in the protocol amendments, the statistical analysis plan, the CSR, or any combination of these, as appropriate and in accordance with applicable national, local, and regional requirements and regulations.

- Assess asthma exacerbations and related healthcare utilization (HCU).
- Perform adverse event inquiry.
- Perform concomitant medication inquiry (includes assessment of oral corticosteroid (OCS) dose if participants are on maintenance corticosteroids).
- Provide handheld electronic diary (eDiary)/spirometry device.

The following procedures will be performed from day -7 through day 0 (run-in period):

- Patients will use the handheld eDiary/spirometry device daily to obtain obtain peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) measurements, and record rescue inhaler use. (This will provide those patients with a gap in study drug administration baseline measures for asthma control and spirometry assessments.)

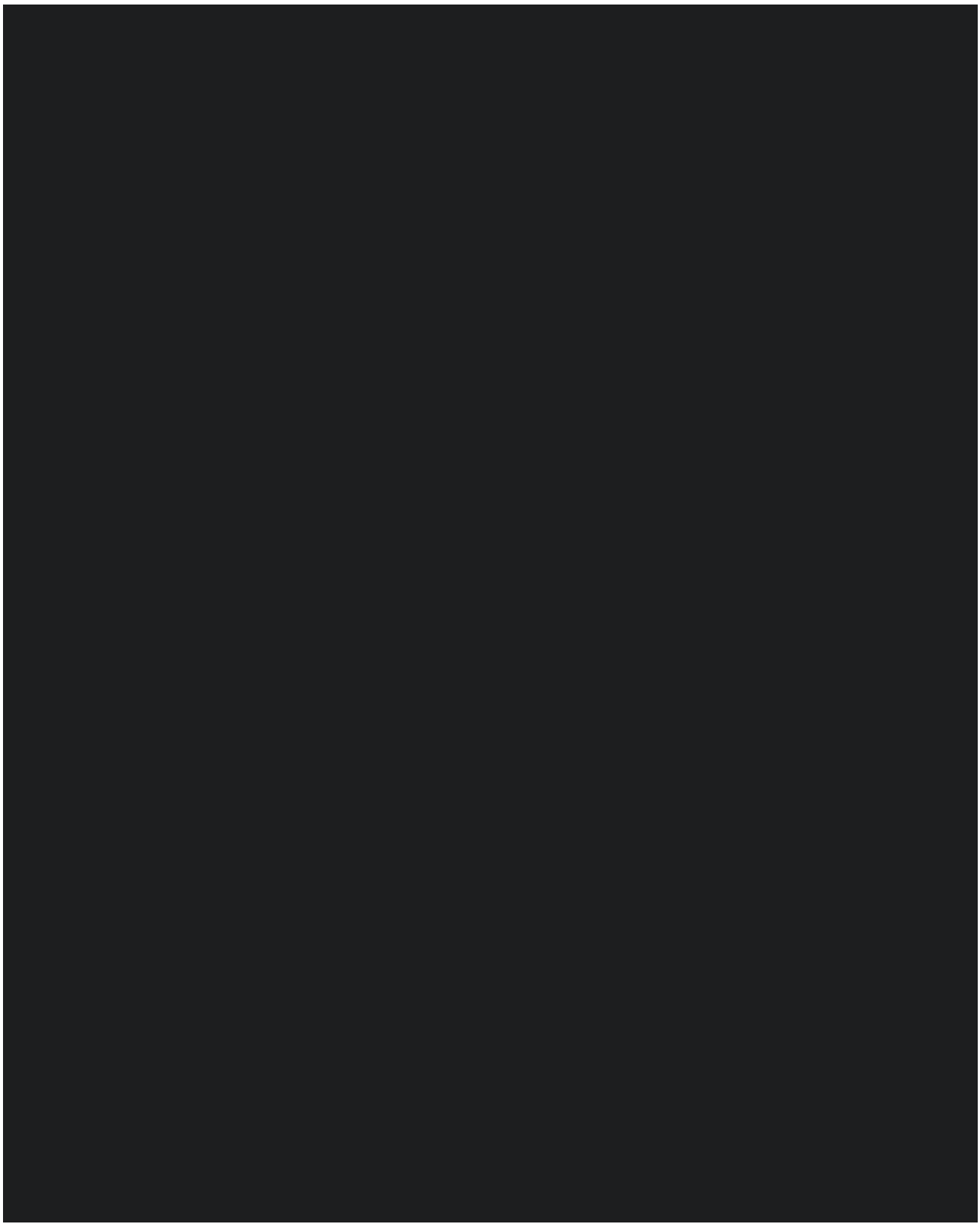
2. **Procedures at Screening/Baseline (Visit 1, Week 0)**

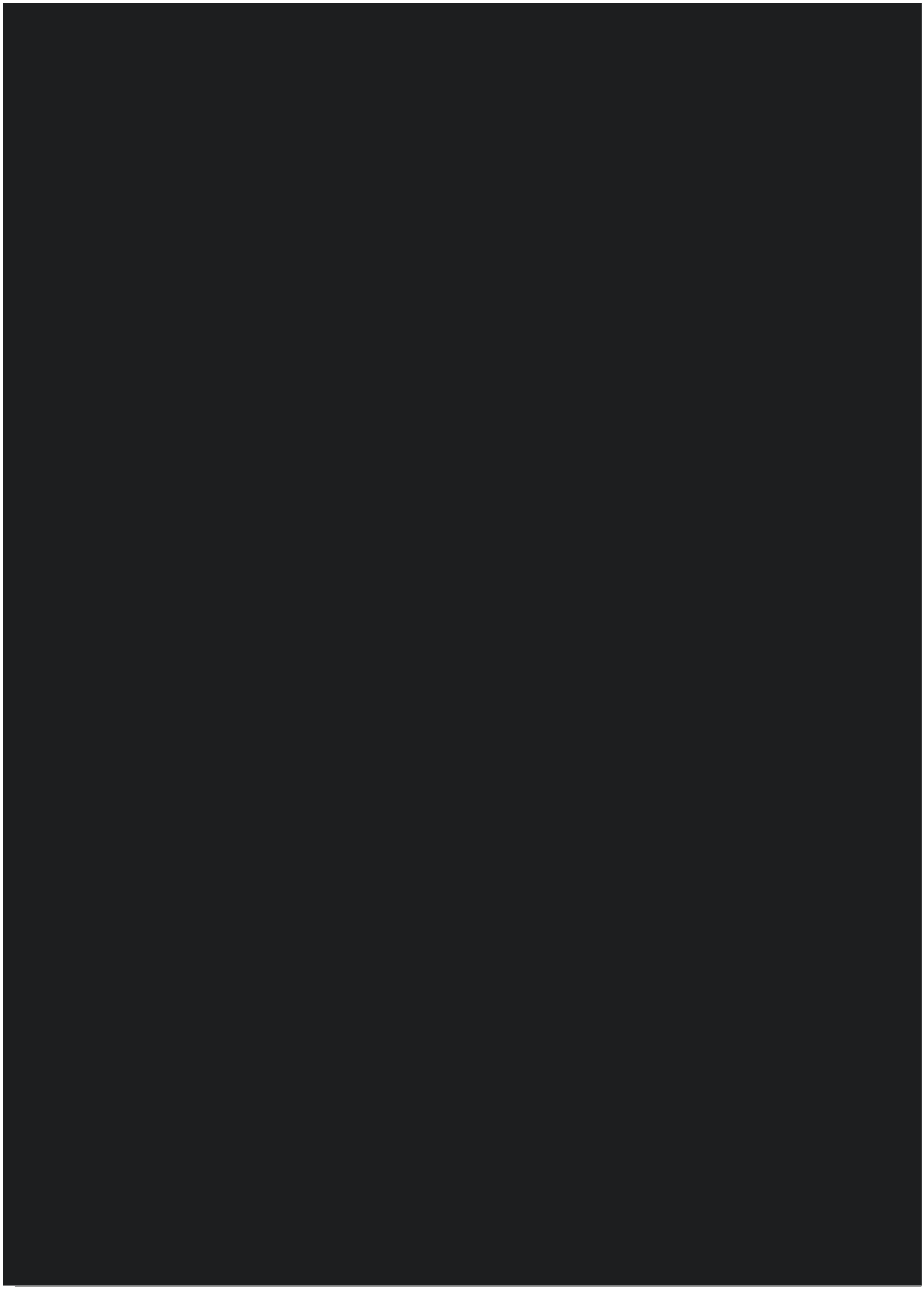
All patients will be required to attend visit 1 at week 0. The following procedures will be performed at visit 1 at week 0 (or as part of the EOT visit of the preceding Teva-sponsored double-blind study of reslizumab for patients who seamlessly rollover) for all patients:

Patients who complete the screening assessments of informed assent/consent, medication history, and inclusion and exclusion criteria at V0 (standalone screening visit) do not need to repeat them at V1 (screening/baseline visit). Any assessments that are performed at V0 do not need to be repeated at V1 if completed within the previous 14 days.

NOTE: the assessments noted with ***** may have been done as part of the EOT visit of Study 30025 or 30027 if a patient seamlessly enters this open-label study.

- Obtain written informed assent/consent before any other study-related procedures are performed.
- Review medication history.
- Review inclusion/exclusion criteria.
- Perform urine pregnancy testing (for female patients who are not postmenopausal or surgically sterile only).*****
- Perform hematology tests.*****
- Perform serum chemistry tests with CPK and follicle stimulating hormone (FSH) (Note: FSH only as required to assess postmenopausal status).*****
- Collect blood sample for immunogenicity (anti-drug antibody [ADA]) assessment. *****
- Perform full physical examination (should include the following organ systems: general appearance, HEENT, chest and lung, heart, abdomen, musculoskeletal, skin, lymph nodes, and neurological).*****
- Perform ECG.*****





APPENDIX S. PRODUCT COMPLAINTS

Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

1. **Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No

The immunogenicity assessments for this study include the following:

- anti-drug antibody (ADA) measurement at baseline and at weeks 8, 24, and 36 or early withdrawal visit to evaluate the long-term immunogenicity of sc reslizumab
- ADA measurement at the end of study (EOS) visit (19 weeks after the final dose) to evaluate immunogenicity after study drug washout

Tertiary Objectives and Endpoints: No tertiary endpoints

Exploratory Objectives and Endpoints: No exploratory endpoints

General Design: This is a global, multicenter, OL extension study to obtain additional long-term safety data for sc administration of reslizumab treatment administered at a fixed dose of 110 mg in patients 12 years of age and older with severe eosinophilic asthma. The study consists of a screening/baseline visit (V1; seamless rollover patients; conducted on the same day as the end-of-treatment [EOT, week 52 or week 24, respectively] visit for patients who finished either Study 30025 or 30027) or a standalone screening visit (V0) for patients who did not seamlessly rollover from Study 30025 or 30027 (had a gap between placebo-controlled study EOT and start of OLE), followed by an OL treatment period, an EOT visit (V_{EOT}), a follow-up telephone call (V_{FU}) at 12 weeks after the EOT visit, and an EOS visit (V_{EOS}) for immunogenicity testing 19 weeks after the final dose of study drug administration. The duration of the OL treatment period will be 9 months (36 weeks).

Study patients will be deemed eligible only if they meet all inclusion criteria and no exclusion criteria are fulfilled. Patients currently enrolled in Studies 30025 and 30027 will be required to complete their respective treatment periods before being eligible for this study. In addition, adolescents (a patient 12 through <18 years of age) from Study 30025 must also complete the 12-week early follow-up visit (off study drug) before transferring to this OL study.

There may be a gap in study drug administration for some patients due to completion of Study 30025 or 30027 before the initiation of the OL extension study (non-seamless rollover). Patients with a gap between the EOT visit for Study 30025 or 30027 will complete a V0 screening visit. Adolescents (a patient 12 through <18 years of age) from Study 30025 can complete the V0 screening visit of Study 30066 the same day as the 12-week early follow-up visit for Study 30025. Any patient who did not rollover seamlessly from Study 30025 or 30027 will participate in a 7-day run-in period where baseline measures for asthma control and spirometry will be established. During screening/baseline, informed consent (and assent for patients under 18 years of age according to local Institutional Review Board/Independent Ethics Committee requirements) will be obtained. Any blood tests completed by adolescents at the 12-week early follow-up visit for Study 30025 can be used for the V0 screening visit of Study 30066 and do not need to be repeated.

During the treatment period, patients will receive reslizumab by sc injection at a dosage of 110 mg every 4 weeks (28 days ±7 days) for 32 weeks in the study center. Patients will return to the study center every 4 weeks relative to baseline during OL treatment.

After study drug administration, each patient will remain at the study center for a minimum of 1 hour for observation.

After each administration, the patient will be required to use a study-provided handheld electronic diary (eDiary)/spirometry device, which will ask questions post-injection to evaluate for any new symptoms that may have developed during the 24-hour period after IMP administration. The patient

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Asthma is a common chronic lung disorder characterized by inflammation and narrowing of the airways. Symptoms of asthma include cough, breathlessness, and wheezing. The most recent estimates suggest that as many as 334 million people in the world have asthma (Global Asthma Network 2014).

Currently, inhaled corticosteroids (ICSs) are the most effective treatment agents for the long-term control of asthma (EPR-3 2007, GINA 2016). For patients whose asthma is not adequately controlled on daily ICS alone, the addition of long-acting beta agonists (LABAs) and/or other controller therapies often provides additional control. There are currently very few options for patients whose asthma is inadequately controlled on ICS/LABA. The most severely affected patients with asthma may require daily oral corticosteroid (OCS) doses to maintain asthma control (GINA 2016). Long-term use of daily OCS may be associated with the severe adverse effects of an iatrogenic Cushing's syndrome, including increased risk of infections, impaired growth in children, hyperglycemia, low bone density, elevated blood pressure, cataracts, and adrenal insufficiency (Stanbury and Graham 1998, Walsh et al 2001). Risk may be decreased by maintaining patients on the lowest possible dose of OCS and utilization of corticosteroid-sparing strategies.

Interleukin (IL)-5 is the prototypic maturation and survival factor for eosinophilic granulocytes, which has been strongly implicated in asthma pathogenesis (Wardlaw et al 2000). Eosinophils are major effector cells involved in the initiation and propagation of diverse inflammatory responses. A high blood eosinophil count is a risk factor for increased future asthma exacerbations and excessive short-acting beta-agonist (SABA) use after adjustment of potential confounders in adults with persistent asthma, which suggests a higher disease burden in patients with asthma and high blood eosinophil counts (Tran et al 2014, Zeiger et al 2014).

Therapies directed against IL-5 or its receptor (mepolizumab, reslizumab, and benralizumab) work by reducing eosinophil counts in the circulation and in the airway and have recently met a clinical proof of concept (reduction in asthma exacerbations, improved Asthma Control Questionnaire [ACQ-6] scores, or improved lung function) in Phase 2 and Phase 3 studies in primarily adult populations with asthma and elevated sputum or blood eosinophils (Castro et al 2011, Haldar et al 2009, Molfino et al 2012, Nair et al 2009, Ortega et al 2014, Pavord et al 2012).

Reslizumab is a humanized anti-human IL-5 monoclonal antibody (mAb) of the immunoglobulin G4/κ isotype being developed for the treatment of asthma in patients with elevated blood eosinophils. Confirmatory Phase 3 safety and efficacy studies for administration of reslizumab by the intravenous (iv) route have concluded the clinical portion; results are notable for a significant reduction in clinical asthma exacerbations (CAEs) as well as improved lung function. Reslizumab by the iv route has been approved by the following Health Authorities: Food and Drug Administration (FDA) approval date: 23 March 2016; European Medicines Agency Summary of Opinion date: 23 June 2016; and Health Canada Notice of Compliance Letter date: 20 July 2016.

The safety profile accumulated throughout the clinical development of reslizumab has demonstrated that reslizumab has a favorable benefit-risk profile in treating patients with asthma and elevated blood eosinophils. Studies 30025 and 30027 are being conducted to further investigate the safety and

procedures or tests) will be recorded on the case report form (CRF) and noted within the patient's source notes.

Study procedures and assessments with their time points are shown in Table 1.

The study schematic diagram is presented in Figure 1.

[b] Beta-human chorionic gonadotropin serum pregnancy tests will be performed at V0 for patients who did not seamlessly rollover (female patients who are not postmenopausal or surgically sterile only). Urine pregnancy testing will be performed at all other visits for all female patients who are not postmenopausal or surgically sterile only. Note: FSH level will be obtained from serum chemistry test as required to determine postmenopausal status. Please see the Laboratory Manual for further information.
[c] These assessments may have been done as part of the EOT visit of Study 30025 or 30027 if patient seamlessly enters open-label study.
[d] If a potentially clinically significant CPK level (≥3.1× ULN) occurs, please refer to Protocol Section 7.1.6.1.2 for further management.
[e] For ADA collection, a blood sample will also be collected in the event of withdrawal from the study or upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). An unscheduled sample can also be drawn after a serious adverse event if the investigator or sponsor considers appropriate. When applicable, blood samples for ADA should be taken before drug administration. Reslizumab concentration data will be assessed from the ADA blood samples.
[f] The "full" physical examination should include the following organ systems: general appearance; head, eyes, ears, nose, and throat; chest and lung; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Physical examination, ECG, and vital signs (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate) should be obtained before spirometry procedures and IMP administration. If screening occurs over multiple visits, vital signs at minimum should be performed at the initial screening visit and repeated on the day of V1.
[g] Pre-bronchodilator spirometry assessments at designated clinic visits (weeks 0, 8, and 24, and EOT) should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.
[h] Investigators can reduce maintenance OCS as clinically indicated.
[i] Inquiry will include assessment of OCS dose if participants are on maintenance corticosteroids.
[j] Assessment should be made approximately 1 hour after study drug administration.

ACQ-6=Asthma Control Questionnaire; ADA=anti-drug antibody; AQLQ12+=Asthma Quality of Life Questionnaire; CBC=complete blood count; CPK=creatine phosphokinase; d=day; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH= follicle stimulating hormone; FU=follow-up; HCU=healthcare utilization; HCG= human chorionic gonadotropin; IMP=investigational medicinal product; OCS=oral corticosteroid; PEF=peak expiratory flow; PI=principal investigator; ULN=upper limit of normal; V=visit; W=week

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to reslizumab

7.1.6. Protocol-Defined Adverse Events of Special Interest

For the purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's GPSP for evaluation:

- systemic reactions, including anaphylaxis
- administration site reactions
- newly diagnosed malignancy
- infections, including parasitic helminth infection and opportunistic infections

A list of potential opportunistic infections is found in Appendix M.

Information on data collection for all suspected anaphylaxis events is discussed in Section 7.1.6.1.1.

The process for reporting a protocol-defined adverse event of interest is the same as that for reporting a serious adverse event (Section 7.1.5.3). An adverse event of special interest does not necessarily need to be defined as a serious adverse event. Protocol-defined adverse events of special interest to be reported to GPSP can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.1.6.1. Specific Adverse Event Case Report Form Capturing

Additionally, the following specific adverse events will have specific CRFs for capturing the events.

7.1.6.1.1. Anaphylaxis/Hypersensitivity Reactions Case Report Form

Information about all suspected anaphylaxis events will be recorded on the Suspected Anaphylaxis/Hypersensitivity Reactions CRF, which is based on the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson et al 2006; Appendix N). The Anaphylaxis/Hypersensitivity Reactions CRF should be initiated in real time (along with vital sign assessment) for events occurring after study drug administration in the clinic or as soon as possible for suspect events outside the clinic. These events can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

7.4.1. Serum Chemistry and Hematology

Clinical laboratory tests (serum chemistry and hematology) will be performed before IMP administration at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided below and in Appendix H.

7.4.1.1. Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphorus
- sodium
- potassium
- chloride
- CPK (at scheduled visits as noted in Table 1)
- bicarbonate or carbon dioxide
- glucose
- BUN
- creatinine
- ALT
- AST
- ALP
- total protein
- albumin
- total bilirubin
- direct bilirubin
- indirect bilirubin
- follicle stimulating hormone (FSH) level, as required

7.4.1.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- platelet count
- absolute neutrophil count

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report (CSR).

9.1. Sample Size and Power Considerations

The sample size for this OL extension study is not based on power considerations. The sample size is determined by the number of patients anticipated to rollover from the 2 double-blind, placebo-controlled, Phase 3 studies of reslizumab sc (Studies 30025 and 30027).

Approximately 360 patients will be enrolled in this OL extension study. The objective of this study is primarily safety oriented; therefore, no formal hypothesis testing is planned. Patients completing at least the full treatment periods of Studies 30025 and 30027 (or through at least the early follow-up visit for adolescents from Study 30025) and meeting the protocol's inclusion criteria and none of the exclusion criteria are eligible for enrollment in this study. It is estimated that the majority of patients enrolled in eligible reslizumab safety and efficacy studies will rollover to this OL extension study.

9.2. Analysis Sets

9.2.1. Enrolled Analysis Set

The enrolled analysis set will include all enrolled patients, regardless of whether or not a patient took any dose of reslizumab. A patient is considered enrolled according to the status reported in the database. The set of enrolled patients will be used for study population summaries.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who received at least 1 dose of reslizumab in this study. The primary analysis population for both safety and efficacy summaries will be the safety analysis set.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses; that is, there is no plan to estimate missing data.

9.3.1. Handling Withdrawals and Missing Data

Missing data will not be imputed, unless otherwise specified.

9.4. Study Population

The enrolled analysis set (Section 9.2.1) will be used for all study population summaries, unless otherwise specified. Summaries will be presented for all patients. For continuous variables,

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix C for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations and violations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement by the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study and with the properties of the IMP as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix T for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

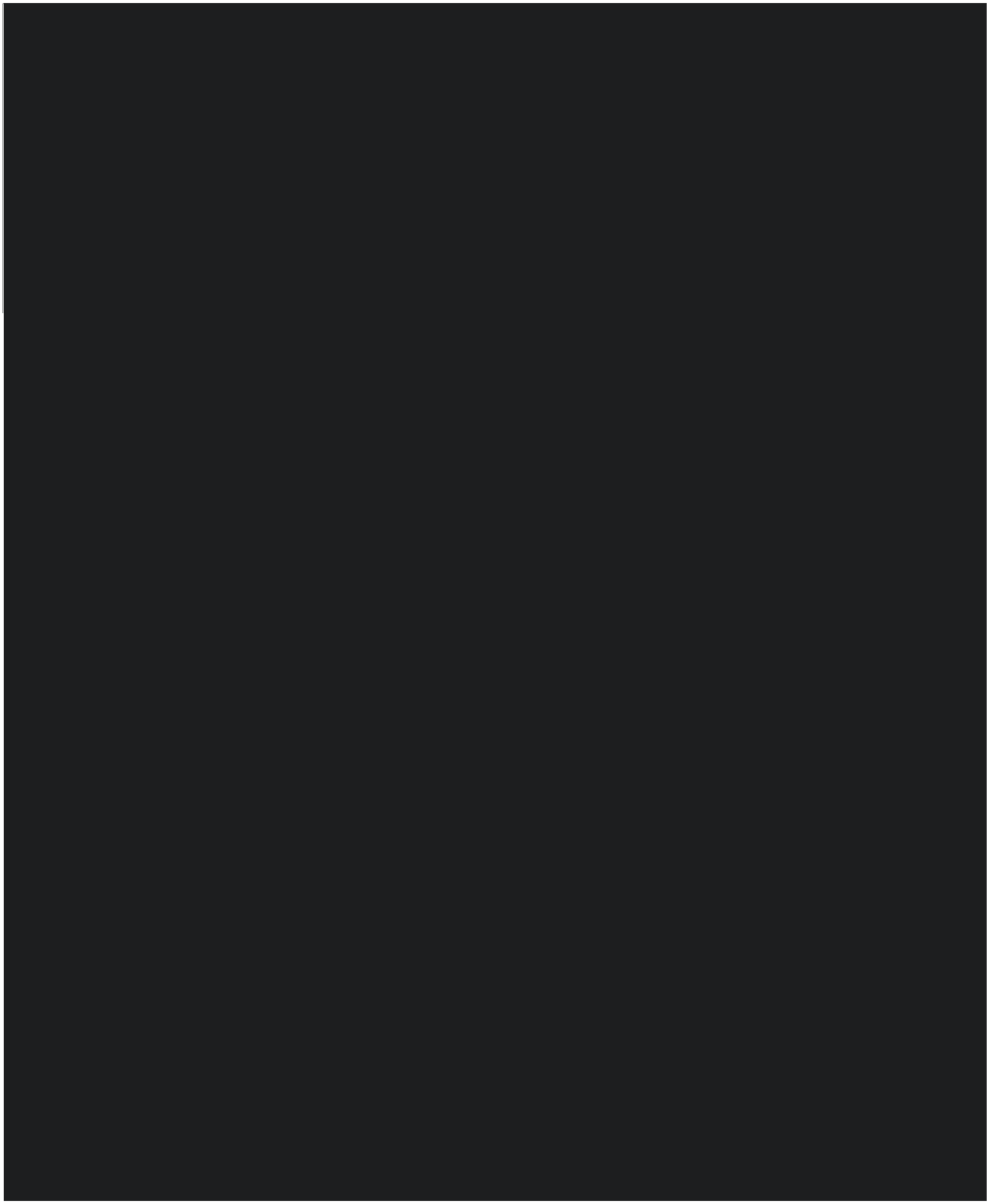
- Perform vital sign measurements (includes systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate). *****
- Provide handheld eDiary/spirometry device (if not provided at V0).
- Perform pre-bronchodilator spirometry (FEV_1). Patients will perform spirometry using the centralized spirometry if rolling over seamlessly from the previous double-blinded studies (Studies 30025 or 30027). If there is a gap between the EOT visit of Studies 30025 or 30027 and Visit 1 of this study, the spirometry will be performed using the handheld spirometry device. *****
    - Pre-bronchodilator spirometry assessments should only be performed after withholding short-acting bronchodilators (ie, inhaled short-acting beta-adrenergic agonists and/or short-acting anticholinergics) for at least 6 hours and long-acting bronchodilators (ie, inhaled long-acting beta-adrenergic agonists and long acting anticholinergic agents) for at least 12 or 24 hours, according to their labeled dose schedule.
- Reinforce eDiary, PEF/spirometry compliance, and rescue medication use.
- Complete asthma-specific tests (Asthma Control Questionnaire [ACQ-6] and Asthma Quality of Life Questionnaire [AQLQ12+]).*****
- Assess asthma exacerbations and related HCU. *****
- Perform adverse event inquiry. *****
- Perform concomitant medication inquiry (includes assessment of OCS dose if participants are on maintenance corticosteroids). *****
- Perform IMP administration.
- Observation at the study center for 1 hour after IMP administration
- Vital sign assessment for any reported symptoms during 1-hour observation.
- Assessment of injection site by study personnel approximately 1 hour after IMP administration.

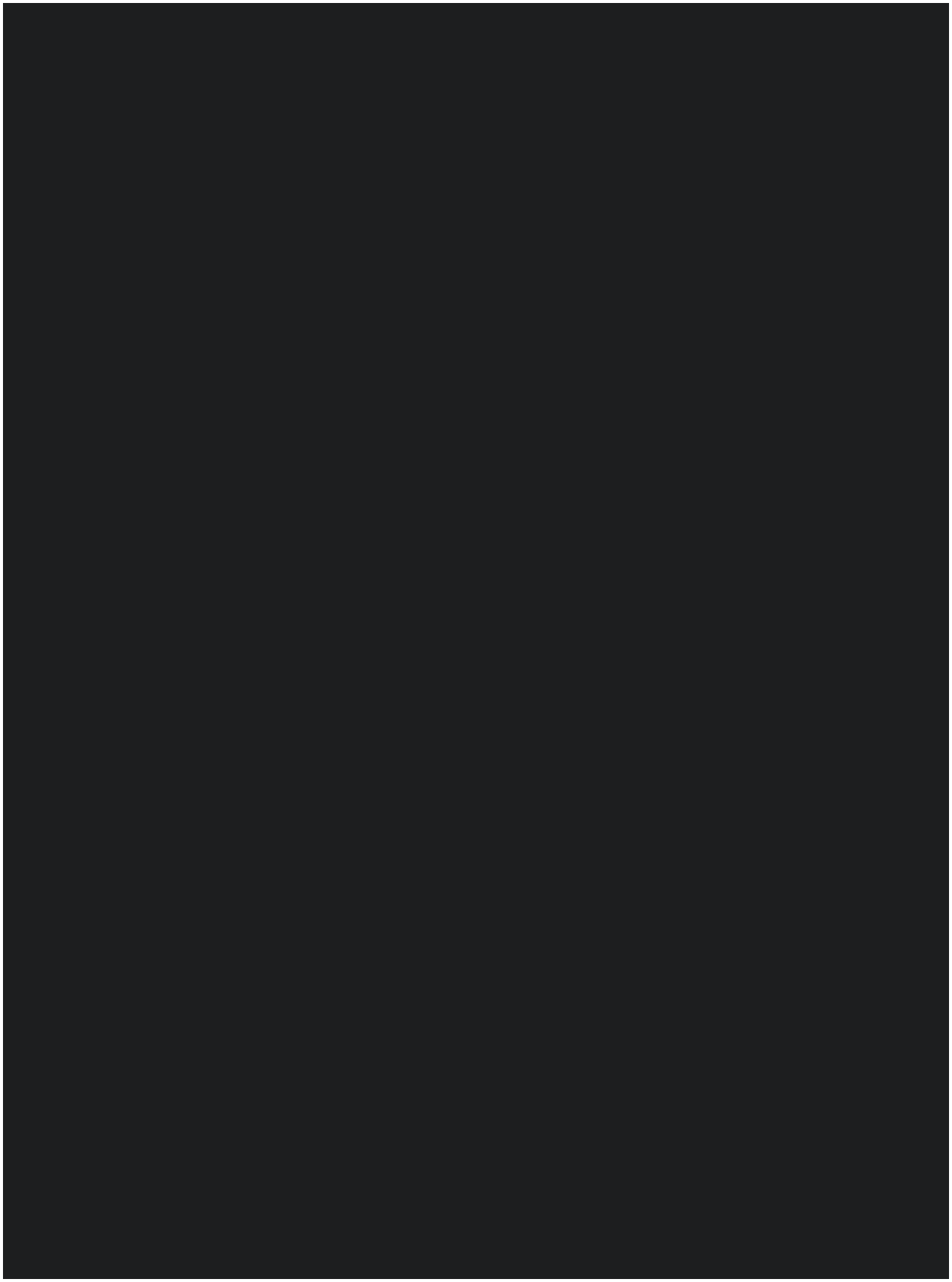
Additionally, patients will complete a question regarding new symptoms on the handheld eDiary/spirometry device the evening after the IMP administration and the following morning as well as obtain PEF and FEV_1 measurements, and record rescue inhaler use.

3. **Procedures During Administration of Investigational Medicinal Product (Open-Label Treatment Period, Visit 2 through Visit 9)**

During the OL treatment period, patients will return to the study center once every 4 weeks (±7 days) and thereafter (relative to baseline) for administration of study drug and assessments until week 32 or early withdrawal.

The following procedures/assessments will be performed before the administration of study drug at each of these visits, unless otherwise indicated:





- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

2. **Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP, the sponsor will provide the information needed to handle the return.

3. **Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

4. **Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.