# SUMMARY OF PRODUCT CHARACTERISTICS

# 1 NAME OF THE MEDICINAL PRODUCT

CINQAERO 10 mg/mL concentrate for solution for infusion

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 10 mg of reslizumab (10 mg/mL).

Each vial of 2.5 mL contains 25 mg of reslizumab.

Each vial of 10 mL contains 100 mg of reslizumab.

Reslizumab is a humanised monoclonal antibody produced in mouse myeloma cells (NS0) by recombinant DNA technology.

Excipient with known effect

Each vial of 2.5 mL contains 0.05 mmol (1.15 mg) of sodium.

Each vial of 10 mL contains 0.20 mmol (4.6 mg) of sodium.

For the full list of excipients, see section 6.1.

# 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly hazy opalescent, colourless to slightly yellow solution with pH 5.5. Proteinaceous particles might be present.

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

CINQAERO is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment (see section 5.

## 4.2 Posology and method of administration

CINQAERO should be prescribed by physicians experienced in the diagnosis and treatment of the above-mentioned indication (see section 4.1).

Posology

CINQAERO is given as intravenous infusion once every four weeks.

*Patients **below** 35 kg or **above** 199 kg*

The recommended dose is 3 mg/kg body weight. The volume (in mL) required from the vial(s) should be calculated as follows: 0.3 x patient body weight (in kg).

*Patients **between** 35 kg and 199 kg*

The recommended dose is achieved using the vial-based dosing scheme in Table 1 below. The recommended dose is based on patient body weight and should only be adjusted for significant changes in body weight.

**Table 1: Vial-based dosing scheme* for patients with body weight between 35 kg and 199 kg**

| Body weight (kg) | Reslizumab total dose (mg) | Numbers of each vial** | |
|---|---|---|---|
| | | Vials with 10 mL concentrate (100 mg reslizumab) | Vials with 2.5 mL concentrate (25 mg reslizumab) |
| 35-41 | 100 | 1 | 0 |
| 42-49 | 125 | 1 | 1 |
| 50-58 | 150 | 1 | 2 |
| 59-66 | 175 | 1 | 3 |
| 67-74 | 200 | 2 | 0 |
| 75-83 | 225 | 2 | 1 |
| 84-91 | 250 | 2 | 2 |
| 92-99 | 275 | 2 | 3 |
| 100-108 | 300 | 3 | 0 |
| 109-116 | 325 | 3 | 1 |
| 117-124 | 350 | 3 | 2 |
| 125-133 | 375 | 3 | 3 |
| 134-141 | 400 | 4 | 0 |
| 142-149 | 425 | 4 | 1 |
| 150-158 | 450 | 4 | 2 |
| 159-166 | 475 | 4 | 3 |
| 167-174 | 500 | 5 | 0 |
| 175-183 | 525 | 5 | 1 |
| 184-191*** | 550 | 5 | 2 |
| 192-199*** | 575 | 5 | 3 |

* This dosing scheme is based on a maximum dose of 3 mg/kg.

** The nominal volume of the vials (10 mL or 2.5 mL for each vial) has to be used.

*** Patients weighing more than 188 kg were not studied.

*Treatment duration*

CINQAERO is intended for long-term treatment.

A decision to continue the therapy should be made at least annually based on disease severity and level of exacerbation control.

*Missed dose*

If a reslizumab infusion is missed on the planned date, dosing should resume as soon as possible on the indicated dose and regimen. A double dose must not be administered to make up for a missed dose.

*Special populations*

*Elderly*

There are limited data available on the use of reslizumab in patients older than 75 years of age. Based on the similar reslizumab exposure observed in patients older than 65 years of age as compared to patients 18 to <65 years of age, no dose adjustment is recommended (see section 5.2).

*Renal impairment*

No dose adjustment is required in patients with renal impairment (see section 5.2).

*Hepatic impairment*

No dose adjustment is required in patients with hepatic impairment (see section 5.2).

*Paediatric population*

The safety and efficacy of CINQAERO in children and adolescents aged up to 17 years have not been established.

No data are available for children aged up to 11 years. Currently available data in adolescents from 12 to 17 years are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Intravenous use.

This medicinal product is for intravenous infusion only. It must not be administered by the subcutaneous, oral or intramuscular route.

The appropriate volume of concentrate should be dispensed into an infusion bag containing 50 mL sodium chloride 9 mg/mL (0.9%) solution for infusion.

This medicinal product must not be administered as a bolus injection or as undiluted concentrate.

The infusion must be discontinued immediately if the patient experiences a hypersensitivity reaction to reslizumab or to any of the excipients (see section 4.4).

*Instructions for administration*

1. CINQAERO should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis (see section 4.4). The patient has to be observed over the duration of the infusion and for an appropriate period afterwards. Patients should be instructed on how to recognise symptoms of serious allergic reactions.
2. If the solution for infusion has been stored in a refrigerator, allow it to reach room temperature (15 °C-25 °C).
3. The solution for infusion should be infused intravenously over 20 – 50 minutes. Infusion time may vary depending on the total volume to be infused.
4. The solution for infusion should not be infused concomitantly in the same intravenous line with other medicinal products. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of reslizumab with other medicinal products.
5. An infusion set with an in-line, sterile, non-pyrogenic, single-use, low-protein-binding filter (pore size of 0.2 µm) should be used for infusion. CINQAERO is compatible with polyethersulfone (PES), polyvinylidene fluoride (PVDF), nylon, cellulose acetate (CA) low protein binding in-line infusion filters.
6. Upon completion of the infusion, flush the infusion set with sterile sodium chloride 9 mg/mL (0.9%) solution for infusion to ensure that all of the CINQAERO solution for infusion has been administered.

For instructions on dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Reslizumab should not be used to treat acute asthma exacerbations.

Asthma-related symptoms or exacerbations may occur during treatment. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number

of the administered product should be clearly recorded.

Hypersensitivity and administration-related reactions

Acute systemic reactions, including anaphylactic reactions, have been reported in association with reslizumab (see section 4.8). These adverse reactions were observed during or within 20 minutes after completion of the infusion. Patients should be monitored during and for an appropriate time after administration of reslizumab. If an anaphylactic reaction occurs,

administration of reslizumab should be stopped immediately and appropriate medical treatment should be provided; reslizumab must be discontinued permanently (see section 4.3).

Parasitic (helminth) infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting reslizumab therapy. If patients become infected whilst receiving treatment with reslizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

Sodium content

This medicinal product contains 4.6 mg sodium per vial of 10 mL (1.15 mg sodium per vial of 2.5 mL), equivalent to 0.23% (0.06%) of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical interaction studies have been performed with reslizumab. *In vitro* data indicate that IL-5 and reslizumab are unlikely to affect CYP1A2, 3A4 or 2B6 activity. Based on the characteristics of reslizumab, interactions are not expected. Results of population pharmacokinetic analysis confirm that concomitant use of either leukotriene antagonists or systemic corticosteroids does not affect the pharmacokinetics of reslizumab (see section 5.2).

Reslizumab has not been studied in patients concurrently taking immunosuppressant medicinal products other than oral corticosteroids (OCS); therefore, the safety and efficacy profile of reslizumab in these patients is unknown.

Reslizumab has not been studied in patients receiving live vaccines. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving reslizumab or the response to new immunisations in patients receiving reslizumab.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of reslizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of CINQAERO during pregnancy. Reslizumab has a long half-life (see section 5.2). This should be taken into consideration.

Breast-feeding

It is unknown whether reslizumab is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of reslizumab in milk.

In humans, during the first few days after birth antibodies may be transferred to the newborns through milk. In this short period, a risk to the suckling child cannot be excluded. Afterwards, CINQAERO could be used during breast-feeding if appropriate.

Fertility

There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility.

## 4.7 Effects on ability to drive and use machines

CINQAERO has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are increased blood creatine phosphokinase (approximately 2% of patients) and anaphylactic reaction (see section 4.4) less than 1% of patients).

During controlled clinical studies, the proportion of patients who discontinued due to any adverse reaction was 1% for both the 3 mg/kg reslizumab and placebo groups.

Tabulated list of adverse reactions

.The following adverse reactions have been reported with reslizumab during placebo-controlled asthma studies for up to 52 weeks of treatment with a 3 mg/kg dose given intravenously. Adverse reactions are listed below in Table 2 by system organ class and frequency (frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

**Table 2: Adverse reactions**

| **System organ class** | **Frequency** | **Adverse reaction** |
|---|---|---|
| *Immune system disorders* | Uncommon | Anaphylactic reaction* |
| *Musculoskeletal and connective tissue disorders* | Uncommon | Myalgia* |
| *Investigations* | Common | Blood creatine phosphokinase increased* |
| *See subsection "Description of selected adverse reactions" below | | |

Description of selected adverse reactions

*Anaphylactic reaction*

The serious adverse reaction of anaphylactic reaction was reported and considered related to reslizumab in 3 patients (0.19%) during placebo-controlled and open-label asthma studies. These reactions were observed during or within 20 minutes after completion of the reslizumab infusion and were reported as early as the second dose of reslizumab. They were fully resolved with standard treatment with no residual effect. Manifestations included skin or mucosal involvement, dyspnoea, wheezing, gastrointestinal symptoms and chills. These cases resulted in the discontinuation of treatment. Due to an overlap in signs and symptoms, it was not possible to distinguish between an anaphylactic reaction, another hypersensitivity reaction and an infusion-related reaction in all cases (see section 4.4).

*Myalgia*

Myalgia was reported in 0.97% of patients (10 out of 1,028) in the 3 mg/kg reslizumab group of the placebo-controlled asthma studies compared with 0.55% of patients (4 out of 730) in the placebo group.

*Blood creatine phosphokinase increased*

Blood creatine phosphokinase elevations were transient and asymptomatic, and did not lead to treatment discontinuation.

Malignancies

In placebo-controlled clinical studies, 6 out of 1,028 patients (0.6%) receiving 3 mg/kg reslizumab had at least one malignant neoplasm reported compared to 2 out of 730 patients (0.3%) in the placebo group. The malignancies observed in reslizumab-treated patients were diverse in nature and without clustering of any particular tissue type.

Paediatric population

Experience in paediatric patients is limited (see section 5.1). The data did not indicate a difference in the safety profile of reslizumab in paediatric patients compared with that in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

The highest single dose administered intravenously was reported at 12.1 mg/kg and had no clinical consequences for the patient. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases; ATC code: R03DX08

Mechanism of action

Reslizumab is a humanised monoclonal antibody (IgG4, κ) against the human interleukin-5 (IL-5). Reslizumab binds specifically to IL-5 and interferes with IL-5 binding to its cell-surface receptor. IL-5 is a key cytokine responsible for the differentiation, maturation, recruitment and activation of human eosinophils. Reslizumab binds human IL-5 with picomolar affinity blocking its biological function; consequently survival and activity of eosinophils are reduced.

Pharmacodynamic effects

*Effect on sputum eosinophils*

The effect of reslizumab in patients with asthma and elevated sputum eosinophil counts (at least 3%) was evaluated in a 15-week, phase 2, randomised, double-blind, placebo-controlled clinical study with reslizumab 3 mg/kg. Sputum eosinophils were measured in a subset of 38 adult patients at the end of therapy. In this study, the percentage of sputum eosinophils was reduced from a mean baseline value of 17.4% (standard deviation: 15.9%) by 82% at end of therapy in the reslizumab group.

*Effect on blood eosinophils*

In clinical studies I and II with reslizumab 3 mg/kg, decreases in blood eosinophil counts were seen following the first dose and maintained through 52 weeks of treatment with no signs of tachyphylaxis. In pooled data, mean eosinophil counts were 655 $\mu L^{-1}$ (n=476) and 654 $\mu L^{-1}$ (n=477) for the placebo and reslizumab treatment groups at baseline and were 514 $\mu L^{-1}$ (n=405) and 61 $\mu L^{-1}$ (n=407) at week 52. Eosinophils began to return towards baseline in those reslizumab patients completing a 90-day follow-up assessment (394 $\mu L^{-1}$, n=36). Decreases in blood eosinophils were related to reslizumab levels.

The reduction in blood eosinophil counts by reslizumab in anti-reslizumab antibody-positive patients was not different from patients who were anti-reslizumab antibody-negative.

Clinical efficacy and safety

*Overview of clinical efficacy*

The efficacy of reslizumab in eosinophilic asthma (blood eosinophils ≥400 $\mu L^{-1}$) was evaluated in three randomised, double-blind, placebo-controlled studies (studies I to III) from 16 to 52 weeks' duration involving 1268 patients with moderate to severe asthma

inadequately controlled on medium- to high-dose inhaled corticosteroids (ICS) (at least 440 μg of fluticasone propionate daily or equivalent) with or without other controllers; prior stable allergen immunotherapy was allowed.

Studies I and II were 52-week, randomised, placebo-controlled studies in patients who had at least one asthma exacerbation requiring systemic corticosteroid use over the past twelve months. Maintenance OCS (up to 10 mg per day prednisone equivalent) were allowed. The patients received either 13 doses of placebo or reslizumab 3 mg/kg administered once every 4 weeks.

Study III was a 16-week, randomised, placebo-controlled study. There was no prior asthma exacerbation requirement for this study. Maintenance OCS was not allowed. The patients received either four doses of placebo or reslizumab 0.3 mg/kg or 3 mg/kg administered once every 4 weeks.

Table 3 presents the demographics and baseline characteristics of studies I, II and III.

**Table 3: Demographics and baseline characteristics of asthma studies I - III**

| Demographic or baseline characteristic | Study I (n=489) | Study II (n=464) | Study III (n=315) |
|---|---|---|---|
| **Demographics** | | | |
| Age, mean in years | 46.65 | 46.97 | 43.89 |
| Asthma duration, mean in years | 19.28 | 18.41 | 20.35 |
| **Pulmonary function tests** | | | |
| Pre-bronchodilator $FEV_1$[a], mean % predicted | 64.31 | 69.21 | 70.14 |
| **Eosinophil counts** | | | |
| Baseline mean blood eosinophil count, $\mu L^{-1}$ | 660 | 649 | 614 |
| **Exacerbation history** | | | |
| Mean number of exacerbations in previous year | 1.99 | 1.94 | 2.03 |
| **Proportions of patients in GINA steps 4 and 5[c]** | | | |
| GINA 4, % | 68 | 70 | 79 |
| GINA 5, % | 13 | 9 | <1 |
| **Patients with refractory asthma[d]** | | | |
| % | 34 | 31 | NA[b] |

[a] $FEV_1$=forced expiratory volume in 1 second
[b] NA=not available
[c] The GINA classification is based on the Global Initiative for Asthma (GINA) definition:
GINA step 4 patients received medium- to high-dose ICS plus another controller.
GINA step 5 patients received in addition, as an add-on, maintenance OCS.
[d] The percentage of patients with refractory asthma (based on the American Thoracic Society [ATS]/European Respiratory Society [ERS] 2000 workshop definition for refractory asthma) from studies I and II was analysed post hoc.

*Studies I and II*

The primary efficacy measure for both studies I and II was the frequency of asthma exacerbations for each patient during the 52-week treatment period. In both studies, an asthma exacerbation was defined as a worsening of asthma that required the following medical intervention:

1) use of systemic corticosteroids or an increase in the use of ICS treatment for 3 or more days, and/or
2) asthma-related emergency treatment including at least one of the following: an unscheduled visit to their healthcare professional for nebuliser treatment or other urgent treatment to prevent worsening of asthma symptoms; a visit to the emergency room for asthma-related treatment; or asthma-related hospitalisation.

*Overall population*

In studies I and II, patients receiving reslizumab 3 mg/kg had significant reductions in asthma exacerbations (50% and 59%, respectively) compared to placebo (see Table 4). The overall reduction was 54%.

**Table 4: Frequency of asthma exacerbations during the 52-week treatment period – studies I and II, integrated data (studies I and II) for the overall population and subgroup GINA 4 and 5**

| | **Treatment arms (n)** | **Asthma exacerbation rate[a]** | **% reduction** |
|---|---|---|---|
| **Data by study** | | | |
| **Study I** | Reslizumab 3 mg/kg (n=245) | 0.90 | 50% (p<0.0001) |
| | Placebo (n=244) | 1.80 | |
| **Study II** | Reslizumab 3 mg/kg (n=232) | 0.86 | 59% (p<0.0001) |
| | Placebo (n=232) | 2.12 | |
| **Integrated studies I and II** | | | |
| **Overall population** | Reslizumab 3 mg/kg (n=477) | 0.84 | 54% (p<0.0001) |
| | Placebo (n=476) | 1.81 | |
| **Subgroup GINA 4 and 5** | Reslizumab 3 mg/kg (n=383) 95% CI[b] | 0.85 (0.64, 1.12) | 56% |
| | Placebo (n=380) 95% CI | 1.95 (1.50, 2.53) | |

[a] Rate adjusted for stratification factors (baseline usage of OCS and geographical region).

[b] CI = Confidence interval

In the subset of patients requiring courses of OCS treatment for management of their asthma exacerbation, reslizumab was shown to reduce the frequency of asthma exacerbations by 56% ($p<0.0001$) and 60% ($p<0.0001$) in study I and study II, respectively. A reduction in asthma exacerbations resulting in hospitalisation or an emergency room visit was observed with reslizumab 3 mg/kg that was not statistically significant (34% [p=0.2572] and 31% [p=0.4020] in study I and study II, respectively).

The proportion of patients who did not experience an asthma exacerbation during the 52-week treatment period was higher in the reslizumab 3 mg/kg group (62% and 75%) compared with the placebo group (46% and 55%), in studies I and II, respectively.

*Patients with severe eosinophilic asthma*

In studies I and II, severe eosinophilic asthma is defined as any patients falling into GINA steps 4 and 5 (medium- to high-dose ICS [≥ 440 µg fluticasone propionate] plus another controller, with or without maintenance OCS) with a blood eosinophil count of ≥400 $\mu L^{-1}$ at start of treatment. A cohort of 763 patients within studies I and II met this criterion; the primary efficacy outcome is presented in Table 4. In integrated studies I and II, patients receiving reslizumab 3 mg/kg had significant reductions in asthma exacerbations (56% for subgroup GINA 4 and 5) compared to placebo.

The effect of reslizumab 3 mg/kg administered once every 4 weeks on secondary endpoints, including $FEV_1$, Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Questionnaire (ACQ) and Asthma Symptom Utility Index (ASUI), further supports the efficacy of reslizumab 3 mg/kg compared to placebo. Improvements were observed as early as 4 weeks following the first dose of reslizumab (AQLQ at 16 weeks) and sustained through week 52.

Results for $FEV_1$, ACQ and AQLQ are shown in Table 5 below for the overall population, and subgroup GINA 4 and 5.

**Table 5: Treatment difference in mean change from baseline for selected secondary efficacy variables – Integrated data (studies I and II) for the overall population and subgroup GINA 4 and 5**

| | Overall population | | Subgroup GINA 4 and 5 | |
|---|---|---|---|---|
| **Efficacy variable[a]** | **Over 16 weeks** | **Over 52 weeks** | **Over 16 weeks** | **Over 52 weeks** |
| $FEV_1$ (mL) | | | | |
| Mean diff (95% CI[b]) (p-value) | 117 (73, 160) (p<0.0001) | 110 (66, 154) (p<0.0001) | 143 (94, 192) | 129 (80, 179) |
| ACQ | | | | |
| Mean diff (95% CI) (p-value) | -0.232 (-0.325, -0.139) | -0.250 (-0.343, -0.156) | -0.321 (-0.424, -0.218) | -0.330 (-0.433, -0.226) |
| AQLQ | | | | |
| Mean diff (95% CI) (p-value) | 0.226 (0.094, 0.359) (p<0.0001) | 0.272 (0.155, 0.388) (p<0.0001) | 0.295 (0.151, 0.438) | 0.346 (0.219, 0.473) |

[a] The values represent the treatment difference between placebo and reslizumab 3 mg/kg based on adjusted means over the specified time period for each treatment group, except for the change to week 16 for AQLQ, which was the first timepoint where AQLQ was assessed.

[b] CI = Confidence interval.

*Patients with severe refractory eosinophilic asthma*

Reslizumab produced significant reductions in asthma exacerbations relative to placebo in the refractory population (59%) and non-refractory population (49%). Results were supported by the secondary efficacy endpoints and were in line with the overall population.

*Study III*

The primary endpoint was the change from baseline over 16 weeks in $FEV_1$. In study III, patients receiving reslizumab 3 mg/kg had significantly larger increases in $FEV_1$ from baseline compared to placebo (treatment difference: 160 mL, p=0.0018). Improvements were noted in $FEV_1$ at 4 weeks following the first dose of reslizumab.

*Immunogenicity*

In phase 3 placebo-controlled studies with a duration of 16 to 52 weeks, low-titre, frequently transient anti-reslizumab antibodies were detected in 53 out of 983 asthma patients (5%) receiving reslizumab at 3 mg/kg. In an open-label phase 3 extension study, low-titre, frequently transient anti-reslizumab antibodies were detected in 49 out of 1,014 asthma patients (5%) who received 3 mg/kg reslizumab for up to 36 months. Systemic exposure to reslizumab appears to be unaffected by anti-reslizumab antibodies. The antibodies had no impact on clinical pharmacodynamics, efficacy or safety.

*Ethnicity*

Population pharmacokinetic analyses indicated that the pharmacokinetics of reslizumab is not significantly different between ethnic groups (white, black and Asian). There are limited safety data in non-white ethnic populations.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with CINQAERO in one or more subsets of the paediatric population in asthma (see section 4.2 for information on paediatric use).

39 paediatric asthma patients from 12 to 17 years were randomised to reslizumab 0.3 mg/kg, reslizumab 3 mg/kg or placebo as part of two 52-week exacerbation studies (studies I and II) and one 16-week lung function study (study III). In studies I and II only, patients were required to have at least one asthma exacerbation requiring systemic corticosteroid use in the year prior to study entry. Asthma exacerbations were evaluated only in the exacerbation studies (studies I and II: reslizumab 3 mg/kg [n=14] and placebo [n=11]). No treatment effect on asthma exacerbations was observed for this age group (asthma exacerbation rate ratio [reslizumab/placebo] of 2.09). Given the small sample size and baseline imbalances resulting from subgroup analysis, no conclusion can be drawn regarding asthma efficacy in the paediatric population.

## 5.2 Pharmacokinetic properties

Peak serum concentrations of approximately 80 µg/mL are typically observed at the end of the infusion. Serum reslizumab concentrations generally decline from peak in a biphasic manner. Following multiple doses, serum concentrations of reslizumab accumulate approximately 1.5- to 1.9-fold. No apparent deviation from dose-proportional reslizumab pharmacokinetics was noted over the dose range of 0.3 mg/kg to 3.0 mg/kg. Inter-individual variability in peak and overall exposure is approximately 20-30%

Based on population pharmacokinetic analysis, systemic exposure to reslizumab appears to be unaffected by circulating anti-reslizumab antibodies.

Distribution

Reslizumab has a volume of distribution of approximately 5 L, suggesting minimal distribution to the extravascular tissues.

Biotransformation

In common with other monoclonal antibodies, reslizumab is believed to be degraded by enzymatic proteolysis into small peptides and amino acids. As reslizumab binds to a soluble target, linear non-target-mediated clearance is expected.

Elimination

Reslizumab clearance is approximately 7 mL/hour. Reslizumab has a half-life of about 24 days.

Special populations

*Elderly*

The pharmacokinetics of reslizumab was similar in adults (18-65 years of age; n=759) and elderly patients (greater than 65 years of age; n=30).

*Paediatric population*

The range of systemic exposures in patients from 12 to less than 18 years of age (n=15) overlapped that in the other groups although the median value was slightly lower than in adult patients (18-65 years of age; n=759) and elderly patients (greater than 65 years of age; n=30).

*Gender*

The pharmacokinetics of reslizumab was not significantly different between males and females.

*Ethnicity*

Population pharmacokinetic analyses indicated that the pharmacokinetics of reslizumab is not significantly different between ethnic groups (white, black and Asian).

*Hepatic impairment*

Reslizumab has not been studied in patients with hepatic impairment. No direct effect of hepatic function on the pharmacokinetics of reslizumab is expected because antibodies are principally cleared by catabolism. In a population pharmacokinetic analysis, patients were classified by baseline liver function levels. Most patients had normal liver function tests (n=766, approximately 95%) or mildly increased liver function tests (either, in the first case, total bilirubin above the upper limit of normal [ULN] but less than or equal to 1.5 times the ULN or, in the second case, aspartate aminotransferase greater than the ULN and total bilirubin less than or equal to the ULN; n=35, approximately4%). No significant difference in the pharmacokinetics of reslizumab was observed across these groups.

*Renal impairment*

Reslizumab is an antibody with a molecular mass of 147 kDaltons and is therefore not expected to be excreted in urine. Most patients in the population pharmacokinetic analysis had normal renal function (estimated glomerular filtration rate [eGFR]) greater than or equal to 90 mL/min/1.73 $m^2$; n=294, approximately 37%), mild renal impairment (eGFR 60-89 mL/min/1.73 $m^2$; n=446, approximately 56%), or moderate renal impairment (eGFR 30-59 mL/min/1.73 $m^2$; n=63, approximately 8%). No noteworthy differences in the pharmacokinetics of reslizumab were observed across these renal function groups. Reslizumab has not been studied in patients with severe renal impairment or end stage renal disease.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium acetate trihydrate

Acetic acid glacial

Sucrose

Water for injections

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

4 years

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated at 2 °C-8 °C and at 25 °C in sodium chloride 9 mg/mL (0.9%) solution for infusion protected from light for up to 16 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 16 hours at 2 °C-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.

## 6.5 Nature and contents of container

2.5 mL of concentrate in a clear type I glass vial closed by a poly(ethylene-co-tetrafluoroethylene)-coated butyl rubber stopper covered with a crimped-on aluminium ring and a white plastic flip-off cap.

10 mL of concentrate in a clear type I glass vial closed by a poly(ethylene-co-tetrafluoroethylene)-coated butyl rubber stopper covered with a crimped-on aluminium ring and a blue plastic flip-off cap.

Pack sizes:

1 vial of 2.5 mL

2 vials of 2.5 mL

1 vial of 10 mL

2 vials of 10 mL

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

CINQAERO is provided as a concentrate for solution for infusion in a single-use vial. The solution for infusion is intended only for intravenous use after dilution and should be prepared using aseptic technique as follows:

Preparation of solution for infusion

1. Remove CINQAERO from the refrigerator. Do not shake the vial.
2. The medicinal product should be inspected visually before use. The concentrate is clear to slightly hazy opalescent, colourless to slightly yellow. Proteinaceous particles may be present in the concentrate that appear as translucent to white, amorphous particles, some of which may look fibrous. This is not unusual for proteinaceous solutions. The concentrate must not be used if coloured (except slightly yellow) or if foreign particles are present.
3. A suitable injection syringe should be used to withdraw the needed amount of the concentrate from the vial(s) (see section 4.2).
4. Slowly dispense the contents of the syringe(s) into an infusion bag containing 50 mL of sodium chloride 9 mg/mL (0.9%) solution for infusion. Gently invert the bag to mix the solution. This medicinal product must not be mixed with other medicinal products except sodium chloride 9 mg/mL (0.9%) solution for infusion.
5. Any concentrate remaining in the vial must be discarded.
6. It is recommended that the solution for infusion be administered immediately after preparation. Solutions of CINQAERO diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion may be stored refrigerated at 2 °C-8 °C (or not above 25 °C if dilution has taken place in controlled and validated aseptic conditions), protected from light for up to 16 hours.
7. CINQAERO is compatible with polyvinylchloride (PVC) or polyolefin (PO) infusion bags.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

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