2. SYNOPSIS

Name of Company: PARI Pharma GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: NA	Volume:	
Name of Active Ingredient: Aerosolised liposomal ciclosporin A (L-CsA)	Page:	

Title of Study:

A long-term safety follow-up study of L-CsA therapy for patients who participated in study 12011.201 and volunteered to continue or to cross-over to L-CsA inhalation therapy

Principal Investigator:

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Study Centre(s):

Approximately 18 centres previously participating in study 12011.201 were planned.

However, only 5 of the 18 centres in 4 European countries enrolled patients.

Publication (Reference):

- Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002; 21:297-310.
- Hachem RR, Trulock EP. Bronchiolitis obliterans syndrome: pathogenesis and management. Semin Thorac Cardiovasc Surg 2004;16:350-355.
- Halloran PF, Homik J, Goes N, et al. The "injury response": A concept linking nonspecific injury, acute rejection, and long-term outcomes. Transplant Proc 1997; 29:79-81.
- Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005; 26:153-161 (a).
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26:319-338 (b).
- Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26:948-968.
- Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005; 26:511-522.

Phase of Development:

Phase 2/3 Extension Study

Studied Period (years):

Date of First Enrolment: 16 Mar 2012

Date of Last Completed: 26 Jun 2013

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Objectives:

Safety Objective:

To evaluate long-term safety of L-CsA in prevention of bronchiolitis obliterans syndrome (BOS) following lung transplantation (LTx) in patients previously enrolled in phase 3 L-CsA clinical trial 12011.201

Efficacy Objective:

To determine the long-term efficacy outcome over a maximum of three years of patients previously enrolled in phase 3 L-CsA clinical trial 12011.201

Methodology:

This was a Phase 2/3, multicentre, non-randomised, open-label, uncontrolled extension study of clinical trial 12011.201.

Independent of former (study 12011.201) treatment allocation, each patient received as add-on L-CsA therapy consisting of:

- Twice daily 10 mg aerosolised L-CsA for double lung transplant (DLT) recipients
- Twice daily 5 mg aerosolised L-CsA for single lung transplant (SLT) recipients

L-CsA was administered as an aerosol using the eFlow® device that has been optimized for use with this particular L-CsA formulation.

Patients originally randomised to receive placebo in study 12011.201 had to remain in the clinic for at least 2 hours for observation after the first inhalation and were to be watched carefully for indications of intolerance.

Each patient received two IMP administrations per day; one in the morning and one in the evening. The inhalations should be taken 12 h apart, e.g. at 8:00 and 20:00 each day.

A patient might be excluded from the clinical trial by the Investigator, if the IMP treatment compliance was less than 75% according to the eFlow® monitoring system.

If at any time the patient did not have the ability to inhale due to e.g. SAEs or other hospitalizations this was not considered in the compliance calculation. The reason for non-compliance should be documented accordingly in the eCRF.

All participants received Standard of Care basic immunosuppression as a triple drug therapy (TDT) consisting of tacrolimus, prednisone, and mycophenolate mofetil (MMF).

Duration of Treatment:

Maximum duration of patient treatment was planned for three years. Due to early termination, the total study duration was only approx. 15 months.

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Number of Patients:

Planned:

A formal sample size calculation for statistical significance was not applicable for the following reasons:

- Uncontrolled design
- Sample size depends on the willingness of patients to continue or cross-over

A total of approximately 75 patients were expected to roll-over from the ongoing controlled core study 12011.201 to participate in the extension study 12011.203. Participation was limited by the number of patients completing 12011.201 who volunteered to participate in 12011.203.

Analysed:

Due to the premature study termination, only 14 patients rolled over to the extension study and 12 patients provided enough data for analysis (Full Analysis Set, FAS).

Diagnosis and Main Criteria for Inclusion:

Patients who met the following criteria were included in the study:

- Completed the L-CsA clinical trial 12011.201
- Capable of understanding the purpose and risks of the follow-up study, has been fully informed and has given written informed consent to participate in the study
- Female patients of child bearing potential must test negative on standard urine pregnancy test prior to continuation and must agree to practice effective birth control during the study (contraceptive implant, injectable or patch hormone therapy, combined oral contraceptives and barrier methods, intrauterine device (IUD), sexual abstinence, surgical sterilisation of the female or male partner)
- Estimated life expectancy > 6 months
- Capable of self-administration of medications
- Stable creatinine levels

Investigational Medicinal Product:

Aerosolised L-CsA was supplied in glass vials of 1.25 ml/5 mg (SLT recipients) and 2.5 ml/10 mg (DLT recipients) using PARI Pharma's eFlow® vibrating membrane nebuliser device for inhalation.

Dose, Mode of Administration:

The study drug was administered twice daily by inhalation (morning/evening). Total treatment period was planned for 3 years. The daily dose was 10 mg L-CsA in SLT patients and 20 mg L-CsA in DLT patients. At every visit, one inhalation cycle was to be monitored by the clinical trial

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centre personnel. The patient remained in the clinic for at least 2 h for observation after the first inhalation. Treatment compliance was to be verified with the eFlow® MS.

L-CsA Batch Number(s): 100304, 100305, 100306, 100307, 104696, 104697, 108377, 108378.

Reference Therapy:

Not applicable.

Criteria for Evaluation:

Safety Endpoints:

Safety was assessed using the following parameters (from inclusion into the 12011.203 study until end of study):

- Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Laboratory evaluations (chemistry, haematology and urinalysis) were performed as scheduled by the local institution. Only abnormal and clinically relevant values were recorded whenever reported
- Overall rate of mortality
- Vital signs
- Trough L-CsA and tacrolimus blood levels

Efficacy Endpoints:

Efficacy was assessed using the following parameters:

- Bronchiolitis obliterans syndrome (BOS):
  - BOS-free survival
  - Incidence of BOS
  - Pulmonary function
- Time to occurrence of BOS (≥ grade 1), respectively BOS progression over the following time period
  - Period of time starting from inclusion into study 12011.201 (Phase III) until occurrence of BOS ≥ grade 1, or death, or re-transplantation
- Incidence of BOS (until end of study):
  - Number and severity of BOS episodes from inclusion until end of study 12011.203 (Safety follow-up)
- Pulmonary Function Tests (PFT) (at each clinic visit):
  - Forced Expiratory Volume in one second (FEV_1)
  - Forced Midexpiratory Flow (FEF_{25-75})

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Statistical Methods:

In this long-term safety follow-up study, only descriptive statistical analyses were performed.

To determine the safety profile of L-CsA the above safety endpoints were tabulated.

The following analyses were provided in order to determine the efficacy of L-CsA:

- Kaplan–Meier estimates of duration of the BOS-free survival were reported along with 95% confidence intervals
- The number and severity of BOS progression events were analysed descriptively
- Pulmonary Function Tests (PFT) (at each clinic visit) were analysed descriptively

All results were presented by original treatment assignment; hence, the following two groups were compared:

- Patients who received placebo in core study, which is equivalent to a delayed treatment onset for the overall study
- Patients who received active treatment in the core study

Interim Analysis:

An interim analysis was planned when at least 20 subjects have been enrolled in 12011.203 and at least 16 months have passed after First Patient In, but was not performed due to premature termination of the study.

SUMMARY – CONCLUSIONS

SAFETY RESULTS:

The majority of the AEs were mild and moderate in severity and mostly not related to study drug administration.

No AE required a withdrawal of a patient from the study or a permanent discontinuation of treatment. No AE resulted in a fatal outcome.

The few SAEs were reported in the SOCs ‘Investigations’, ‘Infections and infestations’ and ‘Respiratory, thoracic and mediastinal disorders’, classes which would be expected in this patient population. Out of the 7 SAEs, 4 events were reported by one individual patient. All reported SAEs provided no reasonable relationship to treatment with study medication. No deterioration of renal function was documented.

Within the observation period, cough was the only ADR reported in two patients, one of the former L-CsA group and one of the former Placebo group.

No SUSAR was reported during the course of the study.

Death was reported in one patient during the course of the study. However, this patient was

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excluded from the safety analysis because never receiving study medication.

Due to the premature termination of the Core Study 12011.201, only few patients completed the two-year study period. Out of these, 12 patients volunteered to participate in the Long-Term Safety Follow-up Study 12011.203 and were actively treated with L-CsA. The decision of the sponsor to terminate the Core Study consequently affected also the Follow-up Study. This circumstance did not allow for a sufficient number of patients and hence for a statistical analysis leading to a conclusive statement regarding the long-term treatment of recipients of a pulmonary allograft with L-CsA.

However, the prolonged treatment with L-CsA did not result in the occurrence of serious adverse events of new quality other than observed already in the core study. Events were limited to the SOCs 'Investigations', 'Infections and infestations' and 'Respiratory, thoracic and mediastinal disorders' which represent expected system organ classes in such a study population. Half of the SAEs accumulated within one individual patient.

Patients received study medication (L-CsA) for a maximum of 10 months in the follow-up study; thus, patients formerly allocated to L-CsA treatment were exposed to study drug for a minimum of 24 months in the core study and for maximum 34 months overall. For said reasons, the long-term safety profile of the drug could not be established. However, the additional 10-month period of L-CsA administration suggests that L-CsA was not harmful for the patients.

EFFICACY RESULTS:

The FAS included 12 patients, 7 patients of the former L-CsA and 5 patients of the former Placebo group, respectively. The premature discontinuation of the study resulted in censoring 11 of the 12 FAS patients for the main efficacy parameter, time of BOS-free survival, hence not allowing for estimation of median time to event. As a result of the early termination of the study the efficacy results obtained are difficult to interpret due to the limited patient numbers.

From the limited data available, it seems that in patients who continued with L-CsA after receiving this treatment already in the core study lung function parameters were further stabilised and thus the observed positive treatment effect of L-CsA during the core study could be sustained. In contrast, in formerly Placebo-treated patients, lung function parameters continued to deteriorate. On the other hand, this impression has to be relativized because the one patient with a remarkable loss of lung function leading to BOS grade 2 at the end of study was a patient in the former Placebo-group. As of the low patient number, such a sharp decrease in FEV_1 of a single patient pulls down also the mean of the total group.

Thus, no conclusive statements regarding long-term efficacy can be drawn.

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CONCLUSION:

The long-term safety profile of L-CsA could not be established for reasons of premature termination of the core and extension study. However, the limited additional data of the follow-up study were not contradictive to the beneficial treatment effect of L-CsA in preventing the occurrence of BOS after lung transplantation as suggested by the results of the core study. As currently no therapeutic alternatives to reduce the incidence of BOS following lung transplantation or satisfying therapeutic armaments to treat BOS are available, the use of inhaled L-CsA in the prophylaxis of BOS may offer an advantageous, at least not harmful therapeutic opportunity for lung transplant recipients.

Date of the report: 25 July 2014