Neurophyxia

EudraCT Number 2011-002502-74

A multi-centre, randomised, double-blind, placebo-controlled Phase II study to evaluate the efficacy, safety, tolerability and pharmacokinetics of 2-Iminobiotin (2-IB) in neonates with gestational age of ≥36 weeks with moderate to severe perinatal asphyxia (NEU 01-02-01)

Abstract of results of the prematurely ended study

In the pilot stage of the NEU 01-02-01 study investigating the safety, tolerability and pharmacokinetics of 2-Iminobiotin (2-IB) after moderate to severe perinatal asphyxia in neonates not receiving therapeutic hypothermia, in total six patients were included in 2 sites. All included patients received at least one dose of study medication. This report covers the data obtained during the hospitalisation period.

The original plan for the study was to proceed with a randomised, double-blind, placebo-controlled main phase with 60 evaluable patients after the completion of the pilot phase. After 5 patients had been included in the pilot phase (March 2015) it was decided, after consultation with the DSMB, that since for some patients a considerable amount of data was lacking, the pilot phase should be extended with 3 more patients (so in total 8 patients).
In September 2014 the sponsor decided to stop further recruitment. The most important reasons for the recruitment stop were that:

- despite serious efforts of the investigators only 6 patients had been included since the first site was opened in June 2012 until September 2014.
- the site that had recruited most patients (Van), planned to introduce hypothermia as treatment (exclusion criteria).

With regard to safety and tolerability, in the six patients included no adverse events that could be attributed to 2-IB were reported, and 2-IB was well tolerated. Especially no signs of hypotension occurred and no relevant changes in haematology or biochemistry were noted, other than those that were related to the condition of perinatal asphyxia.

A total of 8 Serious Adverse Events (SAE's) were reported in 3 patients. Two of these patients died. All SAE's were evaluated by the investigators with regard to causality as not or unlikely related to the study drug.
In western countries a death rate of 1 in 3 is fairly normal for this group of patients with moderate to severe asphyxia. Also, based on aEEG at screening, 5 out of 6 patients were classified as having severe perinatal asphyxia, which indicates that the study population was significantly more severe than the general population.
In addition to the SAE's, also fourteen non-serious AE's were recorded in three patients. In all of these the investigator evaluated the causality as not or unlikely related.

The pharmacokinetic data obtained in this study were not always complete and reliable. Limited pharmacokinetic data using the data from 2 patients show the typical 2-IB PK: first a rapid decline just after the end of the 15-minute infusion and thereafter a slower terminal elimination phase. The median predose plasma concentration (185 ng/mL) just before start of the 6th infusion indicates that some degree of accumulation is present.
2-IB exposure (AUC0-4h) ranged from 566 to 712 ng.h/mL after the first infusion, which was higher than the predefined target AUC0-4h of 365 ng.h/mL. AUC0-∞ values after the first infusion were about 56% higher than AUC0-4h. Therefore, it is expected that exposure will accumulate somewhat further upon multiple administrations.

Due to the limited reliable data, conclusions should be interpreted with caution.