2. STUDY SYNOPSIS

Name of Sponsor Company NeuroSearch Sweden AB	Individual Study Table Referring to Part of the Dossier Volume Page	(For National Authority Use Only)
Name of Finished Product Huntexil		
Name of Active Ingredient Pridopidine (ACR16)		
SPONSOR TRIAL CODE: ACR16C008	EudraCT Number: 2007-004988-22	
Title of Study: A multicentre, multinational, randomised, double-blind, parallel-group study comparing ACR16 45mg once-daily or twice-daily versus placebo for the symptomatic treatment of Huntington's Disease		
Principal Co-ordinating Investigator: [redacted]		
Study Centre(s): 32 centres in Austria, Belgium, France, Germany, Italy, Portugal, Spain, UK		
Publication Reference: Not Applicable		
Study Period (years): 1.5 Date of first enrolment: 24 April 2008 Date of last completed patient (randomised phase): 19 November 2009	Phase of Development: Phase III	
Objectives: Primary objective: The primary objective was to assess the effects of pridopidine on voluntary motor function in Huntington's Disease (HD) patients, defined as the sum score of items 4-10 and 13-15 of the UHDRS motor assessment (a modified motor score mMS) at 26 weeks of treatment. Secondary objectives: Secondary objectives were to assess the effects of pridopidine on CGI, cognitive function, behaviour and symptoms of depression and anxiety at 26 weeks of treatment and to assess the safety and tolerability of pridopidine from the adverse event profile.		
Methodology: Multicentre, multinational, randomised, double blind, parallel-group study comparing pridopidine 45mg once-daily or twice-daily versus placebo. Patients were stratified by their use or non-use of antipsychotic medication. All patients that completed the 26-week randomised-phase on study treatment were invited to participate in the 26-week open-label phase (pridopidine 45mg twice-daily).		
Number of Patients/Subjects (planned and analysed): 420 patients were planned. 499 were screened and 437 enrolled. All enrolled patients qualified for the Full Analysis Set (FAS) and 82% (357 patients) for the per protocol (PP) evaluation.		
Diagnosis and Main Criteria for Inclusion: Written informed consent obtained prior to any study related procedure. Huntington's disease diagnosed with the aid of clinical features and a positive family history and/or the presence of ≥ 36 CAG repeats in the Huntington gene. Male or female age ≥ 30 years.		

Ambulatory, being able to travel to the assessment centre, and judged by the Investigator as likely to be able to continue to travel for the duration of the study. Availability of a caregiver or family member to accompany the patient to visit 1 and visit 7. Willing and able to take oral medication and able to comply with the study specific procedures. A sum of ≥ 10 points on the mMS at the screening visit. For patients taking allowed antipsychotic, antidepressant or other psychotropic medication, the dose of medication should have been kept constant for at least 6 weeks before randomisation.
Study Product, Dose, Mode of Administration, Batch Numbers: Capsules containing 45mg of pridopidine (ACR16). Oral administration. Capsules were swallowed whole with water. For the first four weeks, one capsule was to be taken early in the morning before food. After four weeks, one capsule was to be taken early in the morning before food and one in the early afternoon at least one hour after food. Batch No: 2197740
Duration of Treatment: 26 weeks' double-blind treatment. Randomised phase - Week 1-4: pridopidine 45mg once-daily. Week 5-26: pridopidine 45mg once-daily or twice-daily. Dose de-escalation to once-daily dosing was allowed.
Comparator Product, Dose, Mode of Administration, Batch Numbers: Capsules containing 0mg (placebo) of pridopidine (ACR16). Oral administration. Batch No: 2197447
Criteria for Evaluation: The primary efficacy variable was the change in modified motor score (mMS, sum score of items 4-10 and 13-15 of the UHDRS motor assessments) from baseline to the week 26 assessment.
Statistical Methods: The primary efficacy variable was the change in mMS (sum of score of items 4-10 and 13-15 of the UHDRS motor assessments) from baseline to the week 26 assessment. The null hypothesis was that there was no difference in treatment effect between pridopidine 45mg once-daily and placebo or between pridopidine 45mg twice-daily and placebo. The alternative hypothesis was that there was a difference between respective treatment and placebo. Each of the two null hypotheses was to be tested at the 2.5% significance level using analysis of covariance (ANCOVA). In addition to the randomised treatment, the following covariates were to be included in the ANCOVA model: baseline mMS, gender and use of antipsychotic medication. Statistical significance was to be declared at the 5% level if either p-value was 2.5% or less. The primary analysis was to be performed on the full analysis set using the LOCF values for patients with missing values at the week 26 assessment.
Results and Conclusions: Four hundred and ninety-nine (499) patients with Huntington's disease were screened for the study, and of these, 437 were randomised to treatment. Of these, 247 (57%) patients were not taking antipsychotic medication and 190 (43%) patients were on allowed antipsychotic medication. 403 (92%) patients completed the study schedule, 386 (88%) patients completed on study medication, and 357 (82%) did so without protocol violations (PP cohort). Withdrawals from study and from study medication, as well as de-escalations were evenly distributed between the treatment groups including placebo. The

mean (median) treatment duration (169.4 (182) days) was similar in all treatment groups, including placebo.

Treatment with pridopidine 45mg twice-daily (90mg) showed an improvement in the modified motor score (mMS), after 26 weeks of treatment when compared to placebo (-0.99, p=0.042.). Due to the adjustment required for multiplicity, this difference was not statistically significant at the p≤0.025 level. The improvement in mMS was higher, and statistically significant, in the per-protocol population (-1.29, p=0.014). There was no significant difference between pridopidine 45mg once-daily and placebo in either the FAS or PP analysis.

There was no statistical significant difference between pridopidine and placebo in any of the secondary efficacy variables for either of the pridopidine doses in the FAS group. Of the tertiary variables the UHDRS Total Motor Score (TMS) showed a statistically significant difference (p=0.012), with a treatment-effect of -2.96 (p=0.004) for 45mg twice daily compared to placebo. The observed improvement in the TMS spans multiple motor domains including hand movement, balance and gait, eye movements as well as dystonia. There was no effect, either improvement or deterioration, observed with pridopidine on chorea. The effect of pridopidine was similar in patients with and without antipsychotics.

Both doses of pridopidine were generally well tolerated with adverse event profiles similar to placebo. The most commonly reported Adverse Events (AEs) were fall, Huntington's chorea (mostly reported as worsening of an existing condition), diarrhoea, dizziness, nausea, nasopharyngitis, depression, fatigue and insomnia. A slightly higher reporting frequency was observed for psychiatric, gastrointestinal and nervous system disorders in the highest dose group compared to placebo and pridopidine 45mg daily. The most commonly reported AEs considered related were Huntington's chorea, nausea, dizziness and fatigue.

Three cases of death were reported, one in each dose group. None of them were considered attributable to pridopidine. [redacted] The overall safety-related withdrawal rate was approximately 11%, and was similar for both active and placebo groups. The most frequently reported AEs that led to withdrawal were psychiatric disorders. Pridopidine was well tolerated in both poor and extensive CYP2D6 metabolisers and the AE profiles were comparable in patients with and without antipsychotic medications. Analysis of vital signs, ECG and laboratory parameters did not reveal any clinically significant pattern in patients treated with pridopidine.

In conclusion, the present study indicates that pridopidine 45mg twice-daily improves motor function in HD patients. Though the primary hypothesis was not met, due to the adjustment for multiplicity, the effect of treatment with pridopidine 45mg twice-daily on the mMS was significant in the per-protocol population. The observed improvement in the more comprehensive motor assessment (TMS) spans over multiple motor domains including voluntary movements, eye movements as well as dystonia. Pridopidine did not affect chorea and did not worsen any aspect of the multifaceted HD phenotype. For the dose levels used, no safety related issues were identified and the adverse event profile was comparable with that of placebo.

Date of Report: 31 January 2011