EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Zerit

(Stavudine)

Procedure No. EMEA/H/C/000110/P46/059

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Rapporteur's Preliminary Assessment Report for paediatric studies submitted in accordance with Art 46 of Regulation (EC) No1901/2006, as amended

P46 059

Protocol AI455120: Observational Protocol for AI455094 Late Outcomes.
This was an observational study designed to provide long-term safety monitoring of infants who were born during the conduct of the AI455094 study. The children were followed for late outcomes that might be uniquely related to perinatal antiretroviral interventions. This study was terminated by the sponsor for business reasons.

Zerit

(stavudine)

EMEA/H/C/110

Marketing Authorisation Holder: Bristol-Myers Squibb Pharma EEIG

Rapporteur:	Bengt Ljungberg
Start of the procedure:	24 February 2013
Date of the Final report:	12 August 2013

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Zerit
INN (or common name) of the active substance:	Stavudine
MAH:	Bristol-Myers Squibb Pharma EEIG
Currently approved Indication:	Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected adult patients and paediatric patients (over the age of 3 months) only when other antiretrovirals cannot be used. The duration of therapy with Zerit should be limited to the shortest time possible.
Pharmaco-therapeutic group (ATC Code):	J05AF04
Pharmaceutical form(s) and strength(s):	Capsule, hard, 15 mg

I. INTRODUCTION

The MAH has submitted a completed paediatric study for Zerit (stavudine) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Zerit (stavudine) and that there is no consequential regulatory action.

The Rapporteur has asked for another presentation of the data given that it is difficult to draw overall conclusions from the presentation in the current submission.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study

Stavudine (BMY-27857; d4T) is a nucleoside reverse transcriptase inhibitor (NRTI) used in combination with other antiretroviral (ARV) medications in the treatment of human immunodeficiency virus (HIV) infection.

This was a long-term observational study of children who received NRTI during the perinatal and newborn period during the conduct of the MTCT Study AI455094.

Therefore, no study medication was administered during Study AI455120.

II.2 Clinical aspects

II.2.1 Introduction

The MAH submitted a final report for AI455120 was an observational study designed to provide long-term safety monitoring of infants who were born during the conduct of Study AI455094. The children were followed for late outcomes that might have been uniquely related to perinatal ARV interventions.

Study AI455120 was a Phase 3b uncontrolled, observational study designed to provide long-term safety monitoring of infants who were born during the conduct of the AI455094 study at 1 study site in South Africa. The children were followed for late outcomes that might be uniquely related to perinatal ARV interventions. Two cohorts of children were evaluated: 1) those who were HIV negative and 2) those who were HIV positive at the final study visit in Study AI455094.

The first assessment of data occurred when the children were 5 years of age, and was included in the first interim CSR. The second interim CSR summarized the assessment and analysis of the data collected when all the children reached the age of 10 years. The second interim assessment was submitted to European Medicines Agency (EMA) in January 2011 and to the United States Food and Drug Administration (FDA) in April 2011. The EMA and FDA concurred that Study AI455120 could be terminated, as it was unlikely to expose any additional safety signals not already evident after the 10-year observational period. Consequently, this study was terminated, and the final CSR includes the final data on these children.

Objectives

The primary objective was to describe and assess the long-term health and development of children who received ARV therapy in utero and during the newborn period for prophylaxis of mother-to-child-transmission of HIV during the conduct of the AI455094 study.

The secondary objective was to assess the occurrence of the following categories of medical events that have been identified in the literature and by Health Authorities as being of specific interest with respect to the long-term follow-up of NRTI-exposed neonates. Occurrences of these events are being assessed for the cohorts of HIV-negative and HIV-positive children.

- Neurologic Events: including seizures, developmental delay, speech disorder, tremor, movement disorder, abnormal motor strength
- Hepatic Events: events of clinical hepatitis, hepatic steatosis, or hepatomegaly
- Pancreatic Events: events of pancreatitis
- Metabolic Disorders: elevated blood lactate and elevated triglycerides; clinical diagnoses of diabetes mellitus
- Hematologic Disorders: anemia, macrocytosis and neutropenia
- Neoplastic Events: pathologically confirmed cases of benign and non-benign neoplasms; in addition, categories of benign lesions that are normally assessed and diagnosed by physical examination documentation alone
- Other: cardiomyopathy and clinical syndrome of myopathy.

Methodology

All subjects evaluated annually, on or around their birth date. Yearly evaluations included physical (including neurologic) examinations; growth measurements; hospitalizations;

Denver Development Tests (until 7 years of age); medical diagnoses; procedural/surgical interventions; concomitant medications; clinical laboratory tests (hematology and serum chemistries); CD4 cell count; plasma HIV-1 ribonucleic acid for HIV-positive subjects, and HIV enzyme-linked immunosorbent assay for HIV-negative subjects. The following tests were to be conducted once by the age of 5 years, then whenever clinically indicated: audiometry; echocardiogram (ECHO); ophthalmic examinations (every 2 years for children receiving didanosine; and special chemistries (triglycerides, lipase, and lactic acid). Female subjects were to receive a pelvic examination annually when sexually active.

Statistical Considerations

For the final CSR, all analyses were descriptive, and were presented by cohorts (HIV positive and HIV negative). Categorical variables were tabulated with counts and proportions. Continuous variables were summarized with univariate statistics.

Results

Disposition

A total of 147 subjects who completed Study AI455094 were included in the database used for this final analysis (10 HIV positive and 137 HIV negative).

Disposition is summarized in Table 5.1. The most common reason for discontinuation was lost to follow up.

Table 5.1: Subject Disposition - Study AI455120 Enrollment

	Number of Subjects (%)		
	HIV Infection Status		
	Positive (N = 10)	Negative (N = 137)	Total (N = 147)
Enrolled in AI455120	10 (100)	137 (100)	147 (100)
Discontinued	10 (100)	137 (100)	147 (100)
Administrative Reason by Sponsor	3 (30)	52 (38)	55 (37)
Death	1 (10)	2 (1)	3 (2)
Lost to Follow-up	6 (60)	77 (56)	83 (56)
Subject Withdrew Consent	0	6 (4)	6 (4)

Source: Table 1 of the AI455120 final CSR[1]

All 147 children enrolled were from South Africa, and all were Black. The mean age of the children was 4.8 years, with an even distribution of male and female subjects. Ten subjects were HIV positive.

Overall exposure to ARVs in Study AI455094 is summarized in Table 5.3. No study medication was administered during Study AI455120.

Table 5.3: Enrollment by Treatment Groups in Study AI455094

	Number of Subjects (%)		
	HIV Infection Status		
Treatment in Study AI455094	Positive (N = 10)	Negative (N = 137)	Total (N = 147)
Stavudine	3 (30)	37 (27)	40 (27)
Stavudine + Didanosine	0	34 (25)	34 (23)
Didanosine	3 (30)	33 (24)	36 (24)
Zidovudine	4 (40)	33 (24)	37 (25)

Source: Table 3 of the AI455120 final CSR[1]

Deaths

Three subjects died (1 HIV-positive subject due to tuberculosis meningitis with increased intracranial pressure, 1 HIV-negative subject due to a motor vehicle accident, and 1 HIV-negative subject due to

natural causes). The first 2 deaths were reported in the first interim CSR when all children reached the age of 5 years. The third death was reported in the final analysis. Subject AI455120-1-1284, a 10-year-old HIV-negative boy with cerebral palsy, died in his sleep due to natural causes. No post-mortem was conducted, and no further information is available.

Medical Events

Twenty-one children (14%) reporting medical events since they were enrolled in the study (Table 5.4 below and Appendix 12H of the AI455120 final CSR1). This total includes 1 HIV-negative subject (AI455120-1-1284) with cerebral palsy reported in the first interim analysis, who had subsequent convulsions in the second interim analysis, and whose death was reported in the final analysis. None of these medical events was likely related to NRTI therapy.

Table 5.4: Medical Events Reported in Study AI455120

Subject ID	Treatment in AI455094	HIV Status	Medical Event (Preferred Term)	Grade
AI455120-1-1034	ddI	Positive	Hepatitis A	3
			Transaminases Increased	2
AI455120-1-1070	ZDV	Positive	Humerus Fracture	3
			Hepatitis C	2
AI455120-1-1317	ddI	Positive	Groin Abscess	3
			Abscess Limb	3
AI455120-1-2504	ZDV	Positive	Febrile Convulsion	NS
AI455120-1-1003	ZDV	Negative	Speech Disorder	1
AI455120-1-1009	ddI	Negative	Epilepsy	2
AI455120-1-1016	ddI	Negative	Upper Limb Fracture	1
AI455120-1-1020	d4T+ddI	Negative	Pneumonia	3
AI455120-1-1109	d4T+ddI	Negative	Asthma	4
AI455120-1-1133	d4T+ddI	Negative	Bronchitis	3
			Attention Deficit/Hyperactivity Disorder	2
AI455120-1-1145	ddI	Negative	Pulmonary Tuberculosis	3
AI455120-1-1160	d4T+ddI	Negative	Attention Deficit Hyperactivity Disorder	2
AI455120-1-1170	ZDV	Negative	Neurofibroma	3
AI455120-1-1182	d4T	Negative	Tuberculosis	1
AI455120-1-1278	ddI	Negative	Fetal Alcohol Syndrome	NS
AI455120-1-1282	d4T	Negative	Febrile Convulsion	2
AI455120-1-1284	d4T+ddI	Negative	Cerebral Palsy	3
			Convulsion	3
			Convulsion	3
AI455120-1-1311	d4T	Negative	Hepatitis A	3
AI455120-1-1505	d4T+ddI	Negative	Tuberculosis	2
AI455120-1-1510	d4T	Negative	Convulsion	3
AI455120-1-1514	d4T+ddI	Negative	Tibia Fracture	3

Source: Table 4 of the AI455120 final CSR[1]

NS = Not specified; ddI = didanosine; ZDV = zidovudine; d4T = stavudine.

Clinical Laboratory Evaluations

No new safety issue associated with laboratory evaluation has been observed since the first interim analysis in 2005. Several subjects had Grade 3/4 laboratory data reported since the first interim analysis. These were transient elevations that were generally improved or normal on subsequent testing.

Assessor's comment: Appropriate appendices from the CSR have been reviewed. Review was difficult, given that there is no easily obtained information noting the number of subjects for which information was available, and the number of results for subjects varied, from as few as 2 to as many as < 10

(depending on the type of test). Abnormalities in haemoglobin/hematocrit were infrequent and only of 1-2 grade severity: Abnormalities in white count indices were slightly more frequent with deviations in neutrophils and eosinophils predominating; abnormalities were of 1-2 grade severity. Liver function abnormalities appear to be primarily of increased ALT and alkaline phosphatase at a greater frequency than increased AST. Abnormalities (grade 1-2) of CPK were the most common chemistry findings (creatnine, urea, lipase). Abnormalities of triglycerides and lactic acid were less frequent. There was no consistent pattern of abnormalities that would indicate any relationship to exposure to stavudine.

Vital signs and physical findings

No new safety issue associated with blood pressure measurements, physical measurements, and physical examination results has been observed since the first interim analysis in 2005.

Assessor's comments: The appropriate appendix from the CSR have been reviewed. Review was difficult, given that there is no easily obtained information noting the number of subjects for which information was available and the number of results for subjects varied. It is noted that the most common physical finding was cervical lymphadenopathy which did not appear to be persistent over several examinations.

Neurologic Examinations

Neurological examination results were normal except for 2 subjects:

- Subject AI455120-1-1284 had increased reflexes, tone, and power. This subject has had cerebral palsy and convulsion episodes
- Subject AI455120-1-1531 had depressed reflexes only on 1 neurological examination, and the subsequent neurological examinations were normal.

Assessor's comment: The appropriate appendix from the CSR have been reviewed. Review was difficult, given that there is no easily obtained information noting the number of subjects for which information was available, and the number of results for subjects varied,

Audiometic evaluations

Audiometric evaluations were to be done at study entry and once at 5 years, and then repeated based on the results and the investigators' decisions. Four subjects had the audiometric evaluation repeated after the 5-year test:

- Subject AI455120-1-1132 had a moderate conductive hearing loss
- Subject AI455120-1-1218 had a moderately severe right sensorineural hearing loss
- Subject AI455120-1-1510 had no significant hearing impairment
- Subject AI455120-1-1325 had an initial conductive hearing loss that was not found at the second evaluation.

Assessor's comment: The appropriate appendix from the CSR have been reviewed. Review was difficult, given that there is no easily obtained information noting the number of subjects for which information was available, and the number of results for subjects varied

Denver Development Test

When all children had reached the age of 7 years, approximately half of them had a suspect result on at least 1 of the individual components of the Denver Developmental Test, and the most common suspect results were in the language test.

Assessor's comment: The appropriate appendix from the CSR have been reviewed. Review was difficult, given that there is no easily obtained information noting the number of subjects for which information was available, and the number of results for subjects varied. Individual components of the test were personal-social, fine motor, language, and gross motor. MAH reporting of the results endorsed.

Echocardiograms

Echocardiograms were normal in almost all subjects, and no evidence of cardiomyopathy was observed in any child. Six of 7 subjects who had abnormal ECHO results at study entry had normal results on repeat testing; the results were unchanged in 1 subject who had a mild mitral valve prolapsed (AI455120-1-1008).

Assessor's comment: The appropriate appendix from the CSR have been reviewed. Review was difficult, given that there is no easily obtained information noting the number of subjects for which information was available, and the number of results for subjects varied.

Ophthalmologic Examinations:

Results of ophthalmologic examinations were normal in most children.

Assessor's comment: The appropriate appendix from the CSR have been reviewed. Review was difficult, given that there is no easily obtained information noting the number of subjects for which information was available, and the number of results for subjects varied.

MAH Assessment and Conclusion

Overall, the results obtained in this study did not identify clinical evidence of long-term, NRTI-related toxicity in children after receiving NRTIs in utero and in the first 6 weeks of life.

The overall benefit-risk profile of stavudine remains favorable for patients with limited alternative ARV treatment options. No changes to the Summary of Product Characteristics are required.

II.2.2 Discussion on clinical aspects

The MAH submitted a completed paediatric study for Zerit (stavudine) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Zerit (stavudine) and that there is no consequential regulatory action.

A concern of the submitted report is that the presentation of the data make it difficult to draw overall conclusions. It is noted in table 5.1 that a total of 147 subjects were enrolled; however, 83 subjects (56%) were lost to follow-up. It is unclear from the data when these subjects were lost to follow-up over the time of observation. Furthermore, for each of the measured variables, the MAH has provided only line listings of results, so it is difficult to get an overview of the actual number of subjects (of the total of 147) who had the evaluations performed and how many of the subjects completed the entire course of planned observations. Another issue is that subjects had different numbers of

observations/evaluations which is not clearly explained (it is assumed that it is related to different durations of follow up).

The MAH is therefore requested to make another presentation of the data to allow for a clarified overview of the results. The MAH should focus on clarifying the total of number of subjects who completed all the planned observations/evaluations as well as noting the proportions of enrolled subjects who had results for each of the planned observations/evaluations.

It is acknowledged that this study was requested at a time which Zerit was routinely used to prevent perinatal transmission of HIV which is no longer recommended. However, given that the study has been completed and data are available, it seems justified that they should be reviewed appropriately.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

It is difficult to draw conclusions from the data based upon the current presentation of the data.

Recommendation

Not fulfilled: Based on the data submitted, the MAH should provide a clarified presentation of the data as part of this procedure P46 059. (see section IV "Additional clarifications requested")

IV. ADDITIONAL CLARIFICATIONS REQUESTED

The MAH is requested to make another presentation of the data to allow for a clarified overview of the results. The MAH should focus on clarifying the total of number of subjects who completed all the planned observations/evaluations as well as noting the proportions of enrolled subjects who had results for each of the planned observations/evaluations.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION ON THE RESPONSES

Background and Scope of RSI:

Study AI455120 was an observational study, designed to provide long-term safety monitoring of infants who were born during the conduct of studyAI455094 (which concerned perinatal antiretroviral interventions, which included stavudine). Study AI455120 was planned to be a roll-over study, and to follow the children up to 16 years of age. Study initiation was delayed for administrative reasons, and was started in June 2004, at a time when the mean age of the children included was around 4.5 years. It was terminated earlier than planned, in April 2012.

In the first review of AI455120, no particular safety issued were seen. However, a concern of the submitted report was that the presentation of the data made it difficult to draw overall conclusions. Of the total of 147 subjects enrolled; 83 subjects (56%) were lost to follow-up in the final analysis. It was unclear from the data when these subjects were lost to follow-up over the time of observation. Only line listings of results were presented, so it was difficult to get an overview of the actual number of

subjects (of the total of 147) who had the evaluations performed, and how many of the subjects completed the entire course of planned observations.

The MAH was therefore requested to make another presentation of the data to allow for a clarified overview of the results. The MAH should focus on clarifying the total of number of subjects who completed all the planned observations/evaluations as well as noting the proportions of enrolled subjects who had results for each of the planned observations/evaluations.

Summarized response

Study AI455120 was conducted at 1 study site in South Africa. All subjects were to be evaluated annually, on or around their birth date. Data to be collected are shown below. Due to administrative delays in starting the study, the children were approximately 4 to 5 years of age when they were enrolled. Therefore, a decision was made to perform the first interim analysis when all participating children reached approximately 5 years of age.

Procedures	Screen	Annually to age 16	By 5 years of age, then only as clinically indicated	Annually beginning when sexually active
Signed Informed Consenta	X			
History	X			
Physical Exam		X		
(including neurologic exam)				
Growth measurements		X		
Hospitalizations		X		
Denver Developmental Testc		X		
Vaccinations and HIV therapy				
Audiometry, echocardiogram, ophthalmic examsd			X	
Routine Chemistries		X		
Special Chemistries			X	
Hematology		X		
CD4 Cell Count		X		
Plasma HIV RNA		X		
HIV-ELISA	X	X		
Pap smear (female subjects)				X

Of the 350 eligible subjects from study AI455094, 42% (147/350) enrolled in Study AI455120.

The most common reason that eligible subjects did not enroll was inability to locate the subjects (48%, 167/350), followed by refusal to consent (9%, 31/350) and subject death (1%, 5/350).

5-Year Interim Analysis

The first interim analysis was conducted when all subjects had reached 5 years of age; at this time 144 (98%) were continuing the study. Of the 3 subjects who discontinued, 2 withdrew study consent and 1 died.

10-Year Interim Analysis

The second interim analysis was conducted when all subjects had reached 10 years of age; now with 118 subjects (80%) still in study. Of the 29 subjects who discontinued, 20 were lost to follow up, 6 withdrew study consent, 2 died, and 1 for other reasons (i.e., mother had died/no stable home)

Final Analysis

The final analysis included all available data as of 10-Aug-2012 (study stopped by the sponsor)

83 subjects (56%) had been lost to follow up, 55 subjects (37%) were discontinued for this administrative reason, 6 subjects (4%) had withdrawn consent, and 3 subjects (2%) had died.

Once the decision was made in January 2012 to terminate the study, the investigator asked subjects to come in by April 2012 for a final visit. The sponsor gave site personnel the following guidance regarding case report form status page completion:

- "Administrative reason by sponsor" was to be selected for subjects who had study visits completed since the last database lock on 23-Sep-2010. This reason was entered for 55 subjects (37%) in the final analysis.

- "Lost to follow up, death, or withdrew consent," whichever was most appropriate, was to be selected for subjects who did not have a study visit since the last database lock on 23-Sep-2010. The reason "lost to follow up" was entered for 83 subjects (56%) in the final analysis.

Table 3.2-1: Number of Subjects Assessed at Each Year - Enrolled Subjects

	Number of Subjects with Assessment (%)
Timepoint	Pooled N=147
Entry	146 (99.3)
Year 1	134 (91.2)
Year 2	104 (70.7)
Year 3	105 (71.4)
Year 4	107 (72.8)
Year 5	108 (73.5)
Year 6	78 (53.1)
Year 7	61 (41.5)

This ad hoc analysis showed that although a significant number of subjects (56%) were designated as "lost to follow up," compliance with the annual visits for these subjects was in line with the subjects who were designated as "discontinuing due to study termination." The majority of the subjects who were lost to follow up were followed for at least 5 years

Assessor's conclusion: The company has shown that a majority of patients were followed up to the age of 10 years of age. Hence, the previously reported data (no safety signals) would therefore seem more valid. The main problem with this study would be the delayed start, and the fact that only around 50% of the children in the prior study were included. This only shows the difficulties in performing studies in these settings.

Issue resolved. The final report of study AI455120 does not call for any changes in the SmPC or RMP of Zerit.