EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 October 2010
EMA/180593/2013
Committee for Medicinal Products for Human Use (CHMP)

Zavesca

(miglustat)

Procedure No. EMEA/H/C/000435/A46/0039

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

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

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Zavesca
INN (or common name) of the active substance(s):	Miglustat
MAH:	Actelion Registration Ltd
Currently approved Indication(s)	Zavesca is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1) Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease (see sections 4.4 and 5.1)
Pharmaco-therapeutic group (ATC Code):	A16AX06
Pharmaceutical form(s) and strength(s):	100 mg hard capsules.
Rapporteur:	Kristina Dunder

I. INTRODUCTION

On 21 July 2010, the MAH submitted a completed paediatric study for Zavesca, 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 Zavesca and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

Zavesca, with the active substance migalustat, is approved for "the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable. Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease"

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

Oral Zavesca hard capsules 100 mg authorised at present was used in the study. There was no paediatric formulation.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

AC – 056A202: A single-centre, double-blind, randomized, placebocontrolled, two period/two treatment crossover study investigating the effect of miglustat on the nasal potential difference in patients with cystic fibrosis homozygous for the F508del mutation.

The use of miglustat in cystic fibrosis (CF), the patient population in this clinical trial, is outside the approved indication for Zavesca.

2. Clinical study

➢ Description

This was a double-blind, randomized, placebocontrolled, two period/two-treatment crossover, proof-of concept, Phase 2a study performed at a single centre.

➢ Methods

- Objectives

The primary study objective was to demonstrate that miglustat restores the function of the cystic fibrosis transmembrane conductance regulator (CFTR), as reflected in nasal potential difference (NPD), in patients with CF homozygous for the F508del mutation. Secondary objectives were to investigate the effect of miglustat on the concentration of sodium and chloride in sweat, and to investigate the safety and tolerability of miglustat in the patient population.

- Study design

Patients were randomized to one of two treatment sequences (placebo/miglustat or miglustat/placebo).

- Study population /Sample size
  11 male and female patients aged 12 years or older with CF homozygous for the F508del mutation (confirmed by a genetic test).

- Treatments
  Miglustat (or matching placebo) was administered orally at a dose of 200 mg TID for 7 days and a single dose on day 8. The two treatment periods were separated by a washout period of ≤14 days.

- Outcomes/endpoints
  The primary efficacy endpoint was the change from baseline to end of treatment in total chloride secretion (TCS), defined as the sum of NPD responses after perfusion with isoproterenol and chloride-free buffer in the presence of amiloride.

  Secondary efficacy endpoints were:
  Change from baseline (pre-dose on day 1) to end of treatment in:
  - Baseline NPD response
  - NPD response after perfusion with amiloride
  - NPD response after perfusion with a chloride-free buffer in the presence of amiloride
  - Sweat sodium and chloride concentration
  - NPD response after perfusion with an ATP solution in the presence of chloride-free buffer, amiloride, and isoproterenol

  Safety endpoints were:
  - Treatment-emergent adverse events (AEs), serious adverse events (SAEs) and AEs leading to premature discontinuation of study drug.
  - Change in vital signs (supine systolic and diastolic arterial blood pressure, and heart rate) and body weight from baseline to day 8 of both treatment periods.
  - Treatment-emergent electrocardiogram (ECG) abnormalities and laboratory abnormalities in both treatment periods.

Statistical Methods

The main analysis was performed on the per-protocol analysis set. No substitution rules were applied for missing data. Student's t-test was applied to differences between treatment and placebo response for each patient. Potential carry-over and period effects were investigated using mixed modelling. Supplementary analysis (least square means, least square mean treatment effects, p-values (parametric) and p-value period effect) were carried out using a linear model with treatment, period and sequence as fixed effects and patient as random effect.

Assessor's Comment: All patients completed both treatment periods and were included in the per protocol analysis set. With a sample size of 12, it was calculated that this study had 94% power to detect a difference in means of 5.0 mV, assuming a standard deviation of 4,4 mV and using a paired t-test with a 0.05 two-sided significance level. However, based on the patients replacement policy that stated that patient would be replaced if the total of patient was less than 11 patients, the recruitment was stopped by the investigator after the randomization of 11 patients. Thus, the study may not have been statistically powered to meet the efficacy endpoints.

➢ Results

- Recruitment/ Number analysed
  Eleven patients (of 12 planned) were enrolled in the study. All patients completed both treatment periods.

- Baseline data
  Six male and 5 female patients were included. All patients were Caucasian with a mean age of 26.4 years (range 15-44). Only one patient was less than 18 years old. Baseline characteristics were similar in both treatment groups.

Table 1 Summary of demographics characteristics, all randomized set

	placebo/ miglustat N=6	miglustat/ placebo N=5	All treatments N=11
SEX [n (%)]			
n	6	5	11
Males	4 66.7%	2 40.0%	6 54.5%
Females	2 33.3%	3 60.0%	5 45.5%
AGE (years)			
n	6	5	11
Mean	24.3	28.8	26.4
Standard deviation	5.50	9.80	7.70
Median	26.0	28.0	27.0
Q1 , Q3	21.0 , 28.0	23.0 , 31.0	21.0 , 30.0
Min , Max	15.0 , 30.0	18.0 , 44.0	15.0 , 44.0
WEIGHT (kg)			
n	6	5	11
Mean	66.6	60.3	63.8
Standard deviation	9.30	10.30	9.80
Median	68.7	54.5	66.9
Q1 , Q3	66.9 , 69.8	53.7 , 66.7	53.7 , 69.8
Min , Max	49.0 , 76.7	51.3 , 75.3	49.0 , 76.7
RACE [n (%)]			
n	6	5	11
Caucasian/white	6 100%	5 100%	11 100%

- Efficacy results
  There were no statistically significant differences in response to treatment for any of the primary or secondary efficacy endpoints.

Table 2 Difference in change from baseline in Total Chloride Secretion between treatments
Analysis set: Per protocol for NPD measurements

	N=11
Placebo	
n	11
Mean	-0.09
Standard deviation	3.833
Standard error	1.156
95% CL of mean	-2.67 , 2.48
Median	0.00
95% CL of median	-4.00 , 3.00
Min , Max	-6.0 , 7.0
Miglustat	
n	11
Mean	0.55
Standard deviation	4.547
Standard error	1.371
95% CL of mean	-2.51 , 3.60
Median	-2.00
95% CL of median	-3.00 , 6.00
Min , Max	-4.0 , 8.0

Paired difference (miglustat - placebo)

n	11
Mean	0.64
Standard deviation	6.249
Standard error	1.884
95% CL of mean	-3.56 , 4.83
Median	-1.00
95% CL of median	-5.00 , 9.00
Min , Max	-6.0 , 10.0

UNADJUSTED TREATMENT EFFECT

p-value paired t-test 0.7426
p-value paired signed-rank 0.8135

SUPPLEMENTARY ANALYSIS: Least square means and least square means treatment effect

Mean miglustat	0.65
95% CL of mean	-2.11 , 3.41
Mean placebo	-0.12
95% CL of mean	-2.87 , 2.64
Mean treatment effect	0.77
95% CL of mean	-3.13 , 4.67
p-valuetreatment effect:	0.6845
p-value period effect:	0.4501
p-value carry-over effect:	0.6462

CL=confidence limits.
Least square means, least square mean treatment effects, p-values (parametric) and p-value period effect are calculated using a linear model with treatment, period and sequence as fixed effects and subject as random effect.
P-value reported for carry-over is the p-value for sequence.

Table 3 Pharmacodynamic parameters: summary statistics and change from baseline

Pharmacodynamic parameters: summary statistics and change from baseline
Analysis set: Combined per protocol for NPD, Sweat and FEV1 measurements

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	miglustat N=11	**placebo N=11**
TCS (mv)		
n	11	11
Baseline	-5.8 ± 3.80	-4.7 ± 3.40
Day 8	-5.3 ± 3.80	-4.8 ± 1.90
Change from baseline	0.5 ± 4.50	-0.1 ± 3.80
Basal NPD (mv)		
n	11	11
Baseline	-43.2 ± 7.20	-43.7 ± 7.10
Day 8	-41.0 ± 10.00	-45.2 ± 6.00
Change from baseline	2.2 ± 7.10	1.5 ± 6.50
Amiloride (mv)		
n	11	11
Baseline	21.3 ± 8.70	26.9 ± 7.30
Day 8	20.3 ± 9.10	24.9 ± 5.50
Change from baseline	-1.0 ± 10.50	-2.0 ± 8.30
Cl Diffusion (mv)		
n	11	11

Baseline	-4.5 ± 4.90	-4.7 ± 2.20
Day 8	-5.9 ± 3.60	-3.9 ± 2.00
Change from baseline	-1.5 ± 4.30	0.8 ± 3.20
ATP (mv)		
n	11	11
Baseline	-10.6 ± 10.00	-14.3 ± 12.00
Day 8	-8.3 ± 5.10	-16.5 ± 8.20
Change from baseline	2.4 ± 10.90	-2.3 ± 16.80
Clancy Index (mv)		
n	11	11
Baseline	15.5 ± 10.00	22.2 ± 7.00
Day 8	15.0 ± 10.20	20.1 ± 6.20
Change from baseline	-0.5 ± 13.30	-2.1 ± 8.40
Wilschanski Index (%)		
n	11	11
Baseline	33.26 ± 32.599	19.00 ± 10.876
Day 8	36.40 ± 26.067	20.61 ± 10.042
Change from baseline	3.14 ± 43.466	1.61 ± 14.026
Sweat sodium (µmol/L)		
n	10	11
Baseline	107.8 ± 15.10	107.6 ± 9.90
Day 8	105.3 ± 12.20	107.8 ± 15.40
Change from baseline	-2.5 ± 10.60	0.1 ± 9.60
Sweat chloride (µmol/L)		
n	10	11
Baseline	111.4 ± 12.40	110.6 ± 10.80
Day 8	109.5 ± 12.20	109.1 ± 12.50
Change from baseline	-1.9 ± 9.00	-1.5 ± 8.40

	miglustat N=11	**placebo N=11**
FEV1 (% of predicted)		
n	11	11
Baseline	79.5 ± 19.30	79.0 ± 20.50
Day 8	78.1 ± 20.70	76.7 ± 20.90
Change from baseline	-1.4 ± 4.60	-2.3 ± 4.00

Note: Values are mean ± standard deviation. Values are included for a patient only if both a baseline and day 8 measurement exist for a particular parameter.

Assessor's comment: Post hoc analysis of the data by a team of experts identified several problems as follows: No NPD evaluation was performed at screening to exclude patients with residual TCS, there was no established procedure for repositioning of the electrode in the nostril, both nostrils were used for measurements, there was an inconsistent flow rate of perfusate, a failure to readjust the junction current with zero chloride solution, NPD was measured at different times during the day and baseline NPD responses of the two treatment periods were inconsistent for several patients. This was unexpected as no carry-over effect was anticipated, given the 14-day washout period. Furthermore there was a use of concomitant medications (local steroid, antibiotics, macrolide and salbutamol) by some patients. These methodological issues might have contributed to the inconclusive results.

- Safety results
  All patients experienced at least one AE when treated with miglustat. 6 patients experienced at least one AE during treatment with placebo. There were no deaths, SAEs or AEs leading to discontinuation of study treatment. Thirty two of 36 events were mild in intensity and 4 AEs were of moderate intensity. The most frequently reported AE was diarrhoea, followed by abdominal discomfort, headache, abdominal pain and pharyngolaryngeal pain. Twenty five of the 28 AEs reported during miglustat treatment were considered by the investigator to be related to the study treatment. All incidences of diarrhoea, abdominal pain, abdominal discomfort and headache during miglustat treatment were assessed as treatment related.

Table 4 Summary of all treatment-emergent adverse events by frequency
Analysis set: Safety

System Organ Class / Preferred Term	miglustat N=11 n %	placebo N=11 n %
ALL SYSTEM ORGAN CLASSES		
Total subjects with at least one AE	11 100%	6 54.5%
Total number of AEs	28	8
DIARRHOEA	10 90.9%	2 18.2%
ABDOMINAL PAIN	2 18.2%	2 18.2%
DECREASED APPETITE	-	1 9.1%
EPISTAXIS	-	1 9.1%
INITIAL INSOMNIA	-	1 9.1%
RHINORRHOEA	-	1 9.1%
ABDOMINAL DISCOMFORT	3 27.3%	-
HEADACHE	3 27.3%	-
PHARYNGOLARYNGEAL PAIN	2 18.2%	-
APHTHOUS STOMATITIS	1 9.1%	-
CHILLS	1 9.1%	-
DIZZINESS	1 9.1%	-
GASTROINTESTINAL DISORDER	1 9.1%	-
HYPERTENSION	1 9.1%	-
INSOMNIA	1 9.1%	-
PSEUDOMONAS INFECTION	1 9.1%	-
STOMACH DISCOMFORT	1 9.1%	-

AE = adverse event

Assessor's comment: During treatment with miglustat one patient experienced a slight decrease in haemoglobin, one patient experienced worsening of hypertension and two treatment-emergent ECG abnormalities were observed (of which none was deemed clinically relevant by the applicant). The clinical relevance of these findings cannot be assessed due to the small sample size.

3. Discussion on clinical aspects

This trial was conducted outside the current indications for miglustat. The trial failed to meet the pre-defined efficacy endpoints, thus providing no evidence for the efficacy of miglustat in the CF F508del mutation patient population. The sample size was very small (11 patients) and only one patient was below 18 years of age. Furthermore, the study may have been statistically underpowered and there may also have been methodological aspects contributing to the inconclusive findings. Thus, we agree that there is not much information to be derived from this study due to the methodological problems and the small sample size. Furthermore, the study does not contribute any relevant data for the paediatric population (only one patient). The safety data was reported in full, and was for the most part consistent with that already established. A few, potentially "new" adverse events occurred during the course of the study, the clinical significance of these findings, however, cannot be assessed due to the small sample size.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

This very small study did not provide any evidence for the efficacy of Miglustat in the CF F508del mutation population. Furthermore, due to the small sample size (11 patients, of which only one patient was under the age of 18) it is not possible to draw any conclusions about possible new adverse events, nor does the study provide any information about miglustat in the paediatric population. The safety profile of miglustat seems to be consistent with that already established.

➢ Recommendation

☒ Fulfilled –

No further action required

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable