17 December 2015
EMA/14337/2016
Procedure Management and Committees Support Division

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

Vectibix

panitumumab

Procedure no: EMEA/H/C/000741/P46/044

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

On 22nd of September 2015, the MAH submitted a study report for a completed paediatric study for panitumumab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Panitumumab is a fully human IgG2 monoclonal antibody directed against human EGFR that is indicated for the treatment of patients with wild-type RAS metastatic colorectal cancer in combination with oxaliplatin- or irinotecan-based chemotherapy, and as monotherapy after failure of standard chemotherapy.

Marketing authorisation was granted for panitumumab 20 mg/ml concentrate for solution for infusion on 03/12/2007.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 'Study 20050252 was a phase 1, open-label, single arm, dose-ranging study to evaluate the safety and pharmacokinetics of up to 3 different dose schedules of panitumumab in pediatric subjects with solid tumours'. This study has been conducted as part of a post marketing commitment in the US. The MAH stated that this is a stand-alone study.

Pursuant to Article 8 of Regulation (EC) No 1901/2006, EMA granted a class waiver (EMA Decision P/146/2009).

2.2. Information on the pharmaceutical formulation used in the study

Table 16-1.6.1 below provides details of the study medication used in study 20050252. Panitumumab was supplied at a concentration of 20 mg/mL in 10 cc vials.

Listing 16-1.6.1. Listing of Panitumumab Unique Manufacturing Lot Numbers (Safety Analysis Set)

Content	Manufacturing Lot Number
Panitumumab	1018407
	1018407, L007333
	1021285
	1021285, 1025059, 1037611, 1038237
	1025059
	1025059, 1037611
	1037611
	1038237
	L007333

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The data cutoff date for this analysis is 17JUN2015

CHMP's comment:

The marketed intravenous formulation was used in this study. This can be considered a suitable for this dose finding study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study 20050252 (Clinicaltrials.gov: NCT00658658), a phase 1 study to evaluate the safety and pharmacokinetics of panitumumab in children with solid tumours.

2.3.2. Clinical study

Study 20050252 – A phase 1 study to evaluate the safety and pharmacokinetics of panitumumab in children with solid tumours

Description

Study 20050252 was an open-label, multicentre (7 centres; all located in the US), single arm, dose-ranging study initiated in 2008 (first patient enrolled 14th of March 2008, last patient completed 25th of March 2015) investigating safety and pharmacokinetics of three different dose levels of panitumumab in children age 1 to <18 years with solid malignant tumours.

Methods

Objective(s)

*Primary objective according to the protocol was: '*To evaluate the safety and pharmacokinetics (PK) of up to 3 different dose schedules of panitumumab in pediatric subjects with solid tumors*'.*

*Secondary objective was: '*To evaluate the incidence of human anti-panitumumab antibody (HAPA) formation and to preliminarily determine if there is evidence of antitumor activity of panitumumab in this patient population*'.*

Study design

This was an open-label, single arm, dose ranging study.

Panitumumab was administered by IV infusion to 4 to 6 patients per cohort. Three planned cohorts (A to C) were investigated at 100% of the recommended adult dose schedules. Inclusion into the cohorts was stratified by age (1 to < 12 versus 12 to < 18 years) and enrolment into cohort A2 and B1 occurred in a staggered approach ones cohort A1 demonstrated sufficient safety (see table 8-1). Cohort D1 and D2 were optional cohorts that were to be studied in the event that Cohort A1 or A2 did not demonstrate sufficient safety.

Table 8-1. Study Design

Stratify by Age (years)			
12 to < 18	1 to < 12	Dose Level	Schedule
Cohort A1	Cohort A2	2.5 mg/kg	once weekly
Cohort B1	Cohort B2	6.0 mg/kg	once every 2 weeks
Cohort C1	Cohort C2	9.0 mg/kg	once every 3 weeks
Cohort D1[a]	Cohort D2	2.0 mg/kg	once weekly

[a] If dose-limiting toxicities are observed in > 2 subjects enrolled into cohorts A1 or A2, the respective de-escalation cohorts, D1 or D2, will be studied.

Study population /Sample size

Main inclusion criteria were:

- Children age 1 to < 18 years with a histologically or cytologically confirmed solid tumour that recurred after standard therapy or for which there was no standard therapy;
- Paraffin-embedded tumour tissue from primary tumour or metastasis for determination of EGFR expression and biomarker testing;
- Life expectancy of ⩾ 12 weeks;
- Performance status: Lansky play scale ⩾ 60% for children 1 to < 12 years of age and Karnofsky ⩾ 60% for children 12 to < 18 years of age;
- Adequate hematologic, renal, hepatic and pulmonary function.

Main exclusion criteria were:

- Diagnosis of leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, or other haematological malignancy.
- Any prior allogeneic transplant or prior autologous transplant less than 3 month prior to enrolment.
- Requirement to receive concurrent chemotherapy, immunotherapy, radiotherapy (except for pain control), or any other investigational drug while on study.

According to protocol 4 to 6 patients per cohort were planned until a maximum tolerated dose was reached.

Treatments

Panitumumab was the only investigational product administered in this study. It was given at planned doses ranging from 2.5 mg/kg intravenously every week to 9.0 mg/kg given once every 3 weeks.

Panitumumab was administered intravenously (IV) by an infusion pump over approximately 60 min min for doses ⩽ 1000 mg and over approximately 90 min for doses > 1000 mg.

Patients received panitumumab until disease progression, intolerance to study drug, withdrew of consent, or other reasons that warranted removal from the study.

Dose Escalation

The decision to advance to the next dose cohort was based on observing $\leqslant$ 33% of patients experiencing a dose limiting toxicity (DLT) in a given cohort during the DLT evaluation period.

Dose-Limiting Toxicity

Toxicities were evaluated using the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. Skin toxicity was evaluated using a modification of the CTCAE version 3.0 criteria.

Hypomagnesaemia, nausea, diarrhoea, vomiting, and skin or nail toxicities constituted DLT only if the following occurred:

- Grade 3 or 4 hypomagnesaemia that persisted for at least 5 days despite maximal magnesium replacement
- Grade 3 or 4 diarrhoea, nausea, or vomiting that persisted for at least 5 days despite maximal supportive therapy
- Grade 4 skin or nail toxicity

All other panitumumab-related grade 3 or 4 haematologic or non-haematologic toxicity (except fatigue and alopecia) was considered DLT.

If any toxicity that could be regarded as DLT occurred during the study period, the administration of panitumumab was discontinued for that patient.

DLT Evaluation Period

For Cohorts A1, A2, B1, B2, D1, and D2, the DLT evaluation period was 28 days from the initial administration of panitumumab. For Cohorts C1 and C2, the DLT evaluation period was 21 days from the initial administration of panitumumab.

No more than 2 patients at a time were enrolled and under evaluation for DLT at the highest open dose cohort.

If 3 or more patients of the initial 4 patients enrolled or of the expanded cohort of 6 patients in a given cohort experienced a DLT during the DLT evaluation period, then the maximum tolerated dose for that age group was defined as the previous cohort that was declared as safe.

CHMP's comment:

This is an open label, Phase I, dose escalation study enrolling paediatric patients with solid malignancies. A cautious staggered approach was followed with patients younger than 12 years of age recruited after safety had been established in the older cohort.

IMP handling, dose preparation, including dilution as well as method of administration followed the recommendations as outlined in Section 4.2 and 6.6 of the SmPC of panitumumab.

Outcomes/endpoints

Primary endpoint:

Safety and tolerability: Patient and cohort incidence of grade 3 and 4 adverse events including dose limiting toxicities (DLTs), serious adverse events, and events requiring the discontinuation of study drug.

Safety: Incidence of clinically significant laboratory changes, clinically significant changes in vital signs, and all adverse events.

PK parameters: Area under the concentration-time curve (AUC), minimum observed concentration (Cmin), maximum observed concentration (Cmax), half-life (t1/2), serum clearance (CL), and volume of distribution (V).

The following PK parameters during a dosing interval were estimated after the first and the third doses: Cmax after IV infusion; time at which Cmax occurred (tmax); Cmin; area under the serum concentration-time curve from time zero to the end of the dosing interval (AUCtau), estimated using the linear trapezoidal method; area under the drug concentration-time curve from time zero to infinity (AUCinf), estimated for the first dose as the sum of AUCtau and Cmin/λz values, where λz is the first-order terminal rate constant estimated via linear regression; t1/2 for the terminal phase (first dose) or dosing interval (third dose), calculated as t1/2 = ln(2)/λz; CL, estimated as dose divided by AUCinf for the first dose and as dose divided by AUCtau for the third dose.

Secondary endpoint:

Immunogenicity: Incidence of human anti-panitumumab antibody (HAPA) formation.

Three validated assays were used to detect the presence of antipanitumumab antibodies. Two screening immunoassays, an acid-dissociation enzyme-linked immunosorbent assay (ELISA) and a Biacore-based biosensor assay, were used to detect antibodies capable of binding to panitumumab. All samples confirmed to be positive by drug specificity in either screening immunoassay were further tested for neutralizing antibodies in a cell-based EGFR phosphorylation bioassay.

Efficacy: Tumour response.

Tumour response was assessed by the investigator (ie no central review) using a modification of the Response Evaluation Criteria in Solid Tumor (RECIST) criteria version 1.0.

Exploratory endpoints:

The exploratory objectives were to investigate potential biomarkers based on assessment of blood cells, tumour cells, the proposed mechanism of action of panitumumab, the effect of genetic variation in cancer genes, and drug target genes on patient response to panitumumab.

Statistical Methods

A formal hypothesis was not tested in this study. However, PK parameters and safety and tolerability were assessed. A formal sample size or power calculation was not performed. The sample sizes were based on the Guideline for Clinical Evaluation of Anticancer Drugs (PAB/NDD Notification No.9 dated February 4, 1991; Guideline for the Clinical Evaluation of Anticancer Drugs).

The sample size of 4 to 6 patients per cohort was considered sufficient to characterize the DLTs in paediatric subjects with relapsed solid tumours.

Results

Recruitment/ Number analysed

31 patients were enrolled in the study and received panitumumab; 17 patients in the age group 12 to < 18 years and 14 patients in the age group 1 to < 12 years. All patients discontinued panitumumab

with the most common reason having been disease progression (13 subjects [76.5%] age 12 to < 18 years, 9 subjects [64.3%] age 1 to < 12 years). The patient disposition is shown in Table 9-1.

Table 9-1. Subject Disposition (All Screened Subjects)

	Age 12-<18				Age 1-<12			
	Cohort A1 2.5mg/kg QW (N = 6)	Cohort B1 6.0mg/kg Q2W (N = 7)	Cohort C1 9.0mg/kg Q3W (N = 4)	Total (N = 17)	Cohort A2 2.5mg/kg QW (N = 6)	Cohort B2 6.0mg/kg Q2W (N = 8)	Total (N = 14)	Total (N = 52)
Subjects screened - n	6	7	4	17	6	8	14	52
Subjects enrolled - n	6	7	4	17	6	8	14	31
Subjects dosed[a] – n (%)	6 (100.0)	7 (100.0)	4 (100.0)	17 (100.0)	6 (100.0)	8 (100.0)	14 (100.0)	31 (100.0)
Number of subjects who discontinued panitumumab	6 (100.0)	7 (100.0)	4 (100.0)	17 (100.0)	6 (100.0)	8 (100.0)	14 (100.0)	31 (100.0)
Reason for ending panitumumab – n (%)								
Noncompliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (7.1)	1 (3.2)
Adverse event	2 (33.3)	0 (0.0)	0 (0.0)	2 (11.8)	2 (33.3)	1 (12.5)	3 (21.4)	5 (16.1)
Full consent withdrawn	0 (0.0)	2 (28.6)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)
Disease progression	4 (66.7)	5 (71.4)	4 (100.0)	13 (76.5)	3 (50.0)	6 (75.0)	9 (64.3)	22 (71.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)	1 (3.2)
Safety Analysis Set Inclusion	6 (100.0)	7 (100.0)	4 (100.0)	17 (100.0)	6 (100.0)	8 (100.0)	14 (100.0)	31 (100.0)
Safety Analysis Set Exclusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dose Limiting Toxicity Analysis Set Inclusion	4 (66.7)	5 (71.4)	4 (100.0)	13 (76.5)	4 (66.7)	5 (62.5)	9 (64.3)	22 (71.0)
Dose Limiting Toxicity Analysis Set Exclusion	2 (33.3)	2 (28.6)	0 (0.0)	4 (23.5)	2 (33.3)	3 (37.5)	5 (35.7)	9 (29.0)
Biomarker Analysis Set Inclusion	6 (100.0)	6 (85.7)	4 (100.0)	16 (94.1)	3 (50.0)	7 (87.5)	10 (71.4)	26 (83.9)
Biomarker Analysis Set Exclusion	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.9)	3 (50.0)	1 (12.5)	4 (28.6)	5 (16.1)

The data cutoff date for this analysis is 17JUN2015
[a] Percentages are based on subjects enrolled.

Baseline data

Baseline demographics for the Safety Analysis Set are summarised in Table 9-2.

Table 9-2. Baseline Demographics (Safety Analysis Set)

	Age 12-<18				Age 1-<12			
	Cohort A1 2.5mg/kg QW (N = 6)	Cohort B1 6.0mg/kg Q2W (N = 7)	Cohort C1 9.0mg/kg Q3W (N = 4)	Total (N = 17)	Cohort A2 2.5mg/kg QW (N = 6)	Cohort B2 6.0mg/kg Q2W (N = 8)	Total (N = 14)	Total (N = 31)
Sex - n (%)								
Male	3 (50.0)	6 (85.7)	1 (25.0)	10 (58.8)	3 (50.0)	4 (50.0)	7 (50.0)	17 (54.8)
Female	3 (50.0)	1 (14.3)	3 (75.0)	7 (41.2)	3 (50.0)	4 (50.0)	7 (50.0)	14 (45.2)
Race - n (%)								
Asian	0 (0.0)	2 (28.6)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)
Black (or African American)	1 (16.7)	1 (14.3)	0 (0.0)	2 (11.8)	1 (16.7)	0 (0.0)	1 (7.1)	3 (9.7)
Hispanic or Latino	0 (0.0)	0 (0.0)	1 (25.0)	1 (5.9)	0 (0.0)	1 (12.5)	1 (7.1)	2 (6.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)	1 (3.2)
White or Caucasian	5 (83.3)	4 (57.1)	3 (75.0)	12 (70.6)	4 (66.7)	7 (87.5)	11 (78.6)	23 (74.2)
Age (years)								
n	6	7	4	17	6	8	14	31
Mean	13.2	15.6	15.8	14.8	7.8	8.4	8.1	11.8
SD	0.8	1.5	1.9	1.8	3.1	2.8	2.9	4.1
Median	13.0	15.0	16.5	15.0	8.0	9.5	8.5	13.0
Q1, Q3	13.0, 14.0	15.0, 17.0	14.5, 17.0	13.0, 17.0	8.0, 10.0	6.5, 10.5	7.0, 10.0	9.0, 15.0
Min, Max	12, 14	13, 17	13, 17	12, 17	2, 11	3, 11	2, 11	2, 17

The data cutoff date for this analysis is 17JUN2015.

The study included 17 boys (54.8%) and 14 girls (45.2%); most were white (74.2%). The mean (SD) age was 14.8 (1.8) years for the age 12 to < 18 years group and 8.1 (2.9) years for the younger age group of 1 to < 12 years. The most common primary tumour types were osteosarcoma (9 patients [29.0%]) and ependymoma (3 patients [9.7%]). The mean (SD) time since primary diagnosis for all

patients was 34.5 (33.2) months. All patients received prior anti-tumour therapy. This included prior surgery (27 patients [87.1%]), chemotherapy (30 patients [96.8%]), and radiotherapy (30 patients [96.8%]).

All patients in the Biomarker Analysis Set (26 patients [100%]) had tumour samples that were positive for EGFR membrane staining.

CHMP's comment:

The enrolled patient characteristics represent the typical population of children participating in an early phase study in paediatric oncology.

All patients recruited were positive for EGFR membrane staining, thus this Phase I study selected an enriched patient population with tumour characteristics which aimed to maximise target inhibition and enhanced evaluation of early efficacy signals based on the compounds mechanism of action.

Efficacy results

A summary of the analysis of objective response and disease control are provided in Table 10-1 and Table 10-2, respectively.

Table 10-1. Summary of the Analysis of Objective Response
(Safety Analysis Set: Subjects with Presence of Baseline Measurable Disease)

	Age 12-<18				Age 1-<12			
	Cohort A1 2.5mg/kg QW (N = 4) n (%)	Cohort B1 6mg/kg Q2W (N = 3) n (%)	Cohort C1 9mg/kg Q3W (N = 4) n (%)	Total (N = 11) n (%)	Cohort A2 2.5mg/kg QW (N = 2) n (%)	Cohort B2 6mg/kg Q2W (N = 3) n (%)	Total (N = 5) n (%)	Total (N = 16) n (%)
Objective response over the study - n (%)								
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (PR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease (SD)	0 (0.0)	1 (33.3)	0 (0.0)	1 (9.1)	1 (50.0)	2 (66.7)	3 (60.0)	4 (25.0)
Disease progression	4 (100.0)	2 (66.7)	4 (100.0)	10 (90.9)	1 (50.0)	1 (33.3)	2 (40.0)	12 (75.0)
Unevaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not done	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects responding - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rate (95% CI)[a] - %	0.00 (0.00, 60.24)	0.00 (0.00, 70.76)	0.00 (0.00, 60.24)	0.00 (0.00, 28.49)	0.00 (0.00, 84.19)	0.00 (0.00, 70.76)	0.00 (0.00, 52.18)	0.00 (0.00, 20.59)

The data cutoff date for this analysis is 17JUN2015.
Disease assessments are based on investigator review of scans using modified-RECIST criteria.
A subject is considered a responder if their best response is either a complete or partial response. Subjects without a post-baseline assessment will be considered non-responders. A complete or partial response will be confirmed no less than 4-weeks after the criteria for response are first met.
[a]CIs are based on the exact binomial probability (Collett, 1991).

Table 10-2. Summary of the Analysis of Disease Control
(Safety Analysis Set: Subjects with Presence of Baseline Measurable Disease)

	Age 12-<18				Age 1-<12			
	Cohort A1 2.5mg/kg QW (N = 4) n (%)	Cohort B1 6mg/kg Q2W (N = 3) n (%)	Cohort C1 9mg/kg Q3W (N = 4) n (%)	Total (N = 11) n (%)	Cohort A2 2.5mg/kg QW (N = 2) n (%)	Cohort B2 6mg/kg Q2W (N = 3) n (%)	Total (N = 5) n (%)	Total (N = 16) n (%)
Disease control over the study - n (%)								
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (PR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease (SD)	0 (0.0)	1 (33.3)	0 (0.0)	1 (9.1)	1 (50.0)	2 (66.7)	3 (60.0)	4 (25.0)
Disease progression	4 (100.0)	2 (66.7)	4 (100.0)	10 (90.9)	1 (50.0)	1 (33.3)	2 (40.0)	12 (75.0)
Unevaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not done	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with disease control - n (%)	0 (0.0)	1 (33.3)	0 (0.0)	1 (9.1)	1 (50.0)	2 (66.7)	3 (60.0)	4 (25.0)
Rate (95% CI)[a] - %	0.00 (0.00, 60.24)	33.33 (0.84, 90.57)	0.00 (0.00, 60.24)	9.09 (0.23, 41.28)	50.00 (1.26, 98.74)	66.67 (9.43, 99.16)	60.00 (14.66, 94.73)	25.00 (7.27, 52.38)

The data cutoff date for this analysis is 17JUN2015.
Disease assessments are based on investigator review of scans using modified-RECIST criteria.
A subject is considered to have disease control if their best response is either a complete or partial response, or stable disease. Subjects without a post-baseline assessment will be considered to not have disease control. A complete or partial response will be confirmed no less than 4-weeks after the criteria for response are first met.
[a]CIs are based on the exact binomial probability (Collett, 1991).

No patient had an objective response. Stable disease was reported for 1 patient (9.1%) in the age group 12 to < 18 years and 3 for patients (60.0%) in the age 1 to < 12 years group. The remaining patients experienced disease progression. Thus, the rate of response was 0 and the rate of disease control was 9.1% (95% CI: 0.23, 41.28) in the age 12 to < 18 years group and 60.0% (95% CI: 14.66, 94.73) in the age 1 to < 12 years group.

CHMP's comment:

The reported objective response rate is what can be expected from a phase I trial in oncology.

The reported rate of disease control of 60% in the younger age group of heavily pre-treated patients is noted and may indicate some individual benefit from treatment with panitumumab.

PK results

The PK analysis set comprised a total of 341 panitumumab serum concentration records from 28 paediatric patients. Pharmacokinetic parameter estimates are summarised in Table 11-1.

Table 11-1. Descriptive Statistics of Panitumumab Pharmacokinetic Parameter Estimates After the First and Third IV Doses of Panitumumab at 2.5 mg/kg QW, 6 mg/kg Q2W, and 9 mg/kg Q3W in Pediatric Subjects With Solid Tumors

Parameter	Age (yr)	2.5 mg/kg QW N	Mean	SD	6 mg/kg Q2W N	Mean	SD	9 mg/kg Q3W N	Mean	SD
First Dose										
t_{max}[a]	12 to <18	6	0.058	(0.045-0.080)	7	0.063	(0.021-0.066)	3	0.063	(0.059-0.087)
(day)	1 to <12	4	0.063	(0.062-0.064)	7	0.065	(0.063-0.096)			
C_{max}	12 to <18	6	52.8	11.4	7	161	41.2	3	205	45.9
(µg/mL)	1 to <12	4	42.9	8.51	7	120	29.4			
C_{min}	12 to <18	4	6.62	6.83	7	24.7	18.6	2	35.3	NR
(µg/mL)	1 to <12	4	4.87	3.64	5	19.7	15.5			
AUC_{tau}	12 to <18	4	167	86.1	7	1040	357	2	1580	NR
(day•µg/mL)	1 to <12	4	127	37.9	5	708	247			
AUC_{inf}	12 to <18	3	144	61.1	5	941	64.8	1	1280	NR
(day•µg/mL)	1 to <12	4	145	51.9	3	748	120			
$t_{1/2}$	12 to <18	2	1.33	NR	5	4.49	1.09	1	4.27	NR
(day)	1 to <12	3	2.11	0.913	3	4.23	1.64			
CL	12 to <18	3	19.8	8.57	5	6.38	0.466	1	7.15	NR
(mL/day/kg)	1 to <12	4	18.7	6.35	3	8.06	1.40			
Third Dose										
t_{max}[a]	12 to <18	3	0.063	(0.042-0.076)	5	0.063	(0.044-0.064)	1	0.063	NR
(day)	1 to <12	3	0.069	(0.063-0.97)	2	0.054	(0.042-0.067)			
C_{max}	12 to <18	3	76.6	21.1	5	187	45.2	1	327	NR
(µg/mL)	1 to <12	3	60.8	15.7	2	126	NR			
C_{min}	12 to <18	3	24.2	22.9	5	48.1	25.1	0		
(µg/mL)	1 to <12	3	17.3	8.83	2	26.1	NR			
AUC_{tau}	12 to <18	3	306	178	5	1330	357	0		
(day•µg/mL)	1 to <12	3	255	70.7	2	754	NR			
$t_{1/2}$	12 to <18	2	2.94	NR	2	4.98	NR	0		
(day)	1 to <12	1	3.07	NR	1	4.91	NR			
CL	12 to <18	3	9.92	4.40	5	4.69	1.00	0		
(mL/day/kg)	1 to <12	3	10.1	2.44	2	8.05	NR			

[a]Median (range) is provided for t_{max}; SD values are not provided if N < 3.
AUC_{inf} = area under the concentration-time curve from time zero to infinity; AUC_{tau} = area under the concentration-time curve from time 0 to the end of the dosing interval; C_{max} = maximum observed concentration; C_{min} = minimum observed concentration; CL = clearance; IV = intravenous; NR = Not Reported; Q3W = every 3 weeks; QW = every week; $t_{1/2}$ = half-life for the terminal phase (first dose) or dosing interval (third dose); t_{max} = time of C_{max}.

Source: PKS/20050252 SAS_CDISC_V2/Base scenario (version 27)

After IV administration, panitumumab PK were nonlinear in paediatric subjects, similar to the observation in adult patients (Yang et al, 2010). After the first panitumumab dose, as the dose increased from 2.5 mg/kg to 6 mg/kg, the exposure to panitumumab (AUC) increased more than dose proportionally resulting in a more than 50% decrease in the mean time-average CL values for both age groups (see also Table 11-1). After repeated administration, the panitumumab PK profiles after the third dose were as expected based on the PK profiles after the first dose. A similar trend in the decrease of CL values was also observed, although the decrease in the CL value was smaller for the younger cohort. The PK parameter estimates for the 6 mg/kg cohort were similar to those reported for adult patients (Stephenson et al, 2009). Based on the mean AUCtau values, minimal accumulation after 3 doses of panitumumab at 2.5 mg/kg QW or 6 mg/kg Q2W was observed for both age groups, with the accumulation ratios ranging from 1.06 to 2.00.

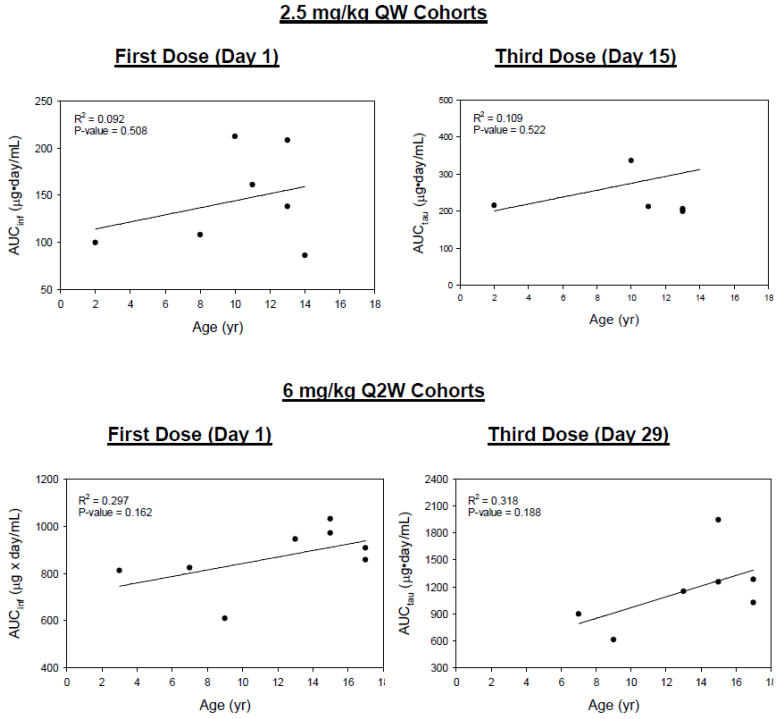
For the 2.5 mg/kg QW cohort, the mean PK profiles for patients aged 1 to < 12 years were similar to those age 12 to < 18 years after the first and the third doses.

For the 6 mg/kg Q2W cohort, although a trend of lower exposure to panitumumab in children aged 1 to < 12 years than in patients aged 12 to < 18 years was observed after the first and the third panitumumab doses, based on limited data, this relationship between AUCinf and age was not significantly different (see Figure 11-5, p-value = 0.173 for the first dose and 0.209 for the third dose).

Therefore age does not appear to have significant impact on the exposure to panitumumab in the paediatric population.

Because age does not appear to have an impact on the PK of panitumumab and the PK parameters estimated from noncompartmental analysis were sufficient to support this conclusion, compartmental analysis to estimate V was not performed.

Figure 11-5. Relationship Between Age and Either AUC_{inf} Estimates After the First Panitumumab Dose or AUC_{tau} Estimates After the Third Panitumumab Dose at 2.5 mg/kg and 6 mg/kg in Pediatric Subjects With Solid Tumors



Source: \\filesrv01\PCBard-Raw\QPData\AMG 954\Study 20050252\Final Analysis\Graphs\ Pmab Study 20050252 AUC vs Age.jnb

Anti-panitumumab Antibody Assays

Of 29 patients with anti-panitumumab antibody results, 3 patients had detectable anti-panitumumab antibodies (10.3%), with one patient (Subject 231003003) having had pre-existing immunoreactivity for panitumumab.

Two additional patients developed antipanitumumab binding antibodies after panitumumab administration (Subject 231001003 on day 43, and Subject 231005004 at the end of study visit).

No post-dose antibody specimens tested positive in the *in-vitro* neutralizing antibody assay.

Impact of Anti-panitumumab Antibodies on Panitumumab PK

For the 2 patients that tested positive only for binding antibodies after panitumumab treatment (Subjects 231001003 and 231005004), their PK profiles and PK parameter estimates were within the range observed for other subjects in their respective groups.

The PK profile for the patient who tested positive for pre-existing binding and neutralizing antibodies (Subject 231003003) was substantially lower than those for other patients in the same cohort. The AUCtau values were only 8% to 12% of the mean values obtained from patients tested negative for neutralizing antibodies (14.9 vs. 127 µg•day/mL after the first dose and 20.3 vs. 255 µg•day/mL after the third dose, respectively).

This patient was excluded from the mean concentration-time profiles and parameter descriptive statistics.

CHMP's comment:

Paediatric PK

In children as in adults panitumumab undergoes target mediated disposition (TMD) with non-linear PK once the target is saturated.

The MAHs states that age does not appear to have significant impact on the exposure. However the youngest child included in the study was 2 year of age. Such a conclusion would not be justified without further robust supporting data.

It remains unclear whether there is any clinically meaningful impact of bodyweight on the PK of panitumumab in paediatric patients.

The MAH did not present any data on the correlation between serum panitumumab concentrations and bodyweight in the paediatric population. An effect of bodyweight would be expected, as confirmed in adult patients. Children are dosed on a mg/kg basis, hence accounting for bodyweight assuming a linear PK relationship. The pk relationship would usually be expected to be less than linear in younger smaller children. Therefore smaller children might risk being under dosed.

Impact of Anti-panitumumab Antibodies on Panitumumab PK

Development of anti-panitumumab binding antibodies post dosing observed in this paediatric patient population did not appear to have an impact on the PK of panitumumab.

Safety results

All patients received ⩾ 1 dose of panitumumab and were included in the Safety Analysis Set. A summary of patient incidences of adverse events is provided in Table 12-2.

Table 12-2. Summary of Subject Incidence of Adverse Events (Safety Analysis Set)

	Age 12-<18				Age 1-<12			
	Cohort A1 2.5mg/kg QW (N = 6) n (%)	Cohort B1 6.0mg/kg Q2W (N = 7) n (%)	Cohort C1 9.0mg/kg Q3W (N = 4) n (%)	Total (N = 17) n (%)	Cohort A2 2.5mg/kg QW (N = 6) n (%)	Cohort B2 6.0mg/kg Q2W (N = 8) n (%)	Total (N = 14) n (%)	Total (N = 31) n (%)
Any adverse event	6 (100.0)	7 (100.0)	3 (75.0)	16 (94.1)	6 (100.0)	8 (100.0)	14 (100.0)	30 (96.8)
Serious adverse events	5 (83.3)	3 (42.9)	2 (50.0)	10 (58.8)	3 (50.0)	5 (62.5)	8 (57.1)	18 (58.1)
Treatment-related adverse event	5 (83.3)	5 (71.4)	3 (75.0)	13 (76.5)	5 (83.3)	6 (75.0)	11 (78.6)	24 (77.4)
Treatment-related serious adverse event	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	1 (16.7)	2 (25.0)	3 (21.4)	4 (12.9)
Withdrawals due to adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals due to treatment-related adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 1	5 (83.3)	7 (100.0)	3 (75.0)	15 (88.2)	6 (100.0)	6 (75.0)	12 (85.7)	27 (87.1)
Grade 2	5 (83.3)	6 (85.7)	3 (75.0)	14 (82.4)	4 (66.7)	7 (87.5)	11 (78.6)	25 (80.6)
Grade 3	4 (66.7)	5 (71.4)	2 (50.0)	11 (64.7)	4 (66.7)	6 (75.0)	10 (71.4)	21 (67.7)
Grade 4	4 (66.7)	0 (0.0)	0 (0.0)	4 (23.5)	1 (16.7)	2 (25.0)	3 (21.4)	7 (22.6)
Fatal	4 (66.7)	0 (0.0)	0 (0.0)	4 (23.5)	1 (16.7)	1 (12.5)	2 (14.3)	6 (19.4)

The data cutoff date for this analysis is 17JUN2015.
Coded using MedDRA version 18.0

Adverse Events

Adverse events were reported for 30 of the 31 patients (96.8%). Adverse events by preferred term that were reported for more than 5 subjects in all cohorts are provided in Table 12-3. The most common adverse events in total were dry skin (10 patients [32.3%]), fatigue (9 patients [29.0%]), and constipation (8 patients [25.8%]). The most common adverse events in the age 12 to <18 years group were fatigue, constipation, and dermatitis acneiform (7 patients each [41.2%]). The most common adverse events in the age 1 to <12 years group were vomiting (6 patients [42.9%]) and dry skin, dyspnea, and rash (4 patients each [28.6%]).

Table 12-3. Most Common Adverse Events by Preferred Term (Safety Analysis Set)

	Age 12-<18				Age 1-<12			
Preferred Term	Cohort A1 2.5mg/kg QW (N = 6) n (%)	Cohort B1 6.0mg/kg Q2W (N = 7) n (%)	Cohort C1 9.0mg/kg Q3W (N = 4) n (%)	Total (N = 17) n (%)	Cohort A2 2.5mg/kg QW (N = 6) n (%)	Cohort B2 6.0mg/kg Q2W (N = 8) n (%)	Total (N = 14) n (%)	Total (N = 31) n (%)
Number of subjects reporting adverse events	6 (100.0)	7 (100.0)	3 (75.0)	16 (94.1)	6 (100.0)	8 (100.0)	14 (100.0)	30 (96.8)
Dry skin	0 (0.0)	4 (57.1)	2 (50.0)	6 (35.3)	1 (16.7)	3 (37.5)	4 (28.6)	10 (32.3)
Fatigue	1 (16.7)	4 (57.1)	2 (50.0)	7 (41.2)	0 (0.0)	2 (25.0)	2 (14.3)	9 (29.0)
Constipation	3 (50.0)	3 (42.9)	1 (25.0)	7 (41.2)	1 (16.7)	0 (0.0)	1 (7.1)	8 (25.8)
Dermatitis acneiform	2 (33.3)	5 (71.4)	0 (0.0)	7 (41.2)	0 (0.0)	0 (0.0)	0 (0.0)	7 (22.6)
Dyspnoea	1 (16.7)	0 (0.0)	2 (50.0)	3 (17.6)	2 (33.3)	2 (25.0)	4 (28.6)	7 (22.6)
Rash	2 (33.3)	1 (14.3)	0 (0.0)	3 (17.6)	2 (33.3)	2 (25.0)	4 (28.6)	7 (22.6)
Vomiting	0 (0.0)	0 (0.0)	1 (25.0)	1 (5.9)	4 (66.7)	2 (25.0)	6 (42.9)	7 (22.6)
Abdominal pain	3 (50.0)	1 (14.3)	2 (50.0)	6 (35.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (19.4)
Erythema	2 (33.3)	2 (28.6)	0 (0.0)	4 (23.5)	2 (33.3)	0 (0.0)	2 (14.3)	6 (19.4)
Headache	2 (33.3)	1 (14.3)	1 (25.0)	4 (23.5)	0 (0.0)	2 (25.0)	2 (14.3)	6 (19.4)
Hypokalaemia	3 (50.0)	0 (0.0)	2 (50.0)	5 (29.4)	0 (0.0)	1 (12.5)	1 (7.1)	6 (19.4)
Hypomagnesaemia	1 (16.7)	1 (14.3)	2 (50.0)	4 (23.5)	0 (0.0)	2 (25.0)	2 (14.3)	6 (19.4)
Pruritus	2 (33.3)	2 (28.6)	1 (25.0)	5 (29.4)	0 (0.0)	1 (12.5)	1 (7.1)	6 (19.4)

The data cutoff date for this analysis is 17JUN2015.
Coded using MedDRA version 18.0.

Treatment-related Adverse Events

Treatment-related adverse events were reported for a total of 24 patients (77.4%); 13 patients (76.5%) in the age 12 to <18 years group and 11 patients (78.6%) in the age 1 to <12 years group (Table 12-4).

Treatment-related adverse events by preferred term that were reported for more than 3 patients in all cohorts are provided in Table 12-4. The most common treatment related adverse events in total were dermatitis acneiform (6 patients [19.4%]), dry skin (6 patients [19.4%]), hypomagnesemia (5 patients [16.1%]), and fatigue (5 patients [16.1%]).

The most common treatment-related adverse events in the age 12 to <18 years group were dermatitis acneiform (6 patients [35.3%]), dry skin (4 patients [23.5%]), hypomagnesemia (4 patients [23.5%]), and fatigue (4 subjects [23.5%]).

The most common treatment-related adverse events in the age 1 to <12 years group were dry skin, nausea, and vomiting (2 patients each [14.3%]).

Table 12-4. Most Common Treatment-related Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

	Age 12-<18				Age 1-<12			
System Organ Class Preferred Term	Cohort A1 2.5mg/kg QW (N = 6) n (%)	Cohort B1 6.0mg/kg Q2W (N = 7) n (%)	Cohort C1 9.0mg/kg Q3W (N = 4) n (%)	Total (N = 17) n (%)	Cohort A2 2.5mg/kg QW (N = 6) n (%)	Cohort B2 6.0mg/kg Q2W (N = 8) n (%)	Total (N = 14) n (%)	Total (N = 31) n (%)
Number of subjects reporting treatment-related adverse events	5 (83.3)	5 (71.4)	3 (75.0)	13 (76.5)	5 (83.3)	6 (75.0)	11 (78.6)	24 (77.4)
Skin and subcutaneous tissue disorders	4 (66.7)	4 (57.1)	3 (75.0)	11 (64.7)	2 (33.3)	5 (62.5)	7 (50.0)	18 (58.1)
Dermatitis acneiform	2 (33.3)	4 (57.1)	0 (0.0)	6 (35.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (19.4)
Dry skin	0 (0.0)	3 (42.9)	1 (25.0)	4 (23.5)	1 (16.7)	1 (12.5)	2 (14.3)	6 (19.4)
Erythema	2 (33.3)	1 (14.3)	0 (0.0)	3 (17.6)	1 (16.7)	0 (0.0)	1 (7.1)	4 (12.9)
Exfoliative rash	0 (0.0)	1 (14.3)	2 (50.0)	3 (17.6)	0 (0.0)	1 (12.5)	1 (7.1)	4 (12.9)
Metabolism and nutrition disorders	2 (33.3)	1 (14.3)	2 (50.0)	5 (29.4)	1 (16.7)	1 (12.5)	2 (14.3)	7 (22.6)
Hypomagnesaemia	1 (16.7)	1 (14.3)	2 (50.0)	4 (23.5)	0 (0.0)	1 (12.5)	1 (7.1)	5 (16.1)
General disorders and administration site conditions	0 (0.0)	4 (57.1)	0 (0.0)	4 (23.5)	1 (16.7)	1 (12.5)	2 (14.3)	6 (19.4)
Fatigue	0 (0.0)	4 (57.1)	0 (0.0)	4 (23.5)	0 (0.0)	1 (12.5)	1 (7.1)	5 (16.1)

The data cutoff date for this analysis is 17JUN2015.
Coded using MedDRA version 18.0.

Adverse Events of Interest

Hypocalcemia, hypomagnesemia, hypokalemia, infusion reaction, acute renal failure, severe cutaneous adverse reaction, embolic and thrombotic events, impaired wound healing, and cardiac arrhythmias were identified as adverse events of interest in this study.

Serious Adverse Events

Serious adverse events were reported for a total of 18 patients (58.1%) with 10 patients (58.8%) in the age 12 to <18 years group and 8 patients (57.1%) in the age group 1 to < 12 years of age. Serious adverse events by preferred term reported for more than 1 patient in all cohorts are provided in Table 12-8.

The most common serious adverse events in total were dyspnea, hypoxia, and pleural effusion (3 patients each [9.7%]). The most common serious adverse events in the age 12 to <18 years group were pleural effusion, pyrexia, and hemoglobin decreased (2 patients each [11.8%]). The most

common serious adverse events in the age 1 to < 12 years group were dyspnea, hypoxia, and vomiting (2 patients each 14.3%]).

Table 12-8. Subject Incidence of Most Common Serious Adverse Events by Preferred Term (Safety Analysis Set)

	Age 12-<18				Age 1-<12			
Preferred Term	Cohort A1 2.5mg/kg QW (N = 6) n (%)	Cohort B1 6.0mg/kg Q2W (N = 7) n (%)	Cohort C1 9.0mg/kg Q3W (N = 4) n (%)	Total (N = 17) n (%)	Cohort A2 2.5mg/kg QW (N = 6) n (%)	Cohort B2 6.0mg/kg Q2W (N = 8) n (%)	Total (N = 14) n (%)	Total (N = 31) n (%)
Number of subjects reporting serious adverse events	5 (83.3)	3 (42.9)	2 (50.0)	10 (58.8)	3 (50.0)	5 (62.5)	8 (57.1)	18 (58.1)
Dyspnoea	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	1 (16.7)	1 (12.5)	2 (14.3)	3 (9.7)
Hypoxia	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	2 (25.0)	2 (14.3)	3 (9.7)
Pleural effusion	0 (0.0)	1 (14.3)	1 (25.0)	2 (11.8)	0 (0.0)	1 (12.5)	1 (7.1)	3 (9.7)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (12.5)	2 (14.3)	2 (6.5)
Pain	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (12.5)	1 (7.1)	2 (6.5)
Pyrexia	1 (16.7)	0 (0.0)	1 (25.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)
Haemoglobin decreased	2 (33.3)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.5)

The data cutoff date for this analysis is 17JUN2015.
Coded using MedDRA version 18.0.

Treatment-related Serious Adverse Events

Treatment-related serious adverse events were reported for a total of 4 patients (12.9%) with 1 patient (5.9%) in the age 12 to <18 years group and 3 patients (21.4%) in the age group of 1 to <12 years (see Table 12-9).

Table 12-9. Treatment-related Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

	Age 12-<18				Age 1-<12			
System Organ Class Preferred Term	Cohort A1 2.5mg/kg QW (N = 6) n (%)	Cohort B1 6.0mg/kg Q2W (N = 7) n (%)	Cohort C1 9.0mg/kg Q3W (N = 4) n (%)	Total (N = 17) n (%)	Cohort A2 2.5mg/kg QW (N = 6) n (%)	Cohort B2 6.0mg/kg Q2W (N = 8) n (%)	Total (N = 14) n (%)	Total (N = 31) n (%)
Number of subjects reporting treatment-related serious adverse events	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	1 (16.7)	2 (25.0)	3 (21.4)	4 (12.9)
Nervous system disorders	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (12.5)	1 (7.1)	2 (6.5)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (7.1)	1 (3.2)
Seizure	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (12.5)	1 (7.1)	2 (6.5)
Apnoea	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Hypoxia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (7.1)	1 (3.2)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (7.1)	1 (3.2)
Respiratory acidosis	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)	1 (3.2)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)	1 (3.2)

The data cutoff date for this analysis is 17JUN2015.
Coded using MedDRA version 18.0.

CHMP's comment:

The observed toxicities are comparable to known adult safety data. Many of these can be considered on target effects, such as skin toxicities, a pharmacodynamic class effect known to be related to EGFR inhibition.

Deaths

Fatal events were reported for a total of 6 patients (19.4%); 4 patients (23.5%) in the age group 12 to <18 years and 2 patients (14.3%) in the age group 1 to <12 years. Five patients received a dose of 2.5 mg/kg QW and 1 patient received a dose of 6.0 mg/kg Q2W. The fatal event preferred terms included dyspnea (2 patients [6.5%]) and hypoxia, osteosarcoma, respiratory failure, and rhabdomyosarcoma (1 patients each [3.2%]).

The primary cause of death was disease progression for all 6 patients.

CHMP's comment:

All fatal events were considered to be due to disease progression and not related to panitumumab.

Dose Limiting Toxicity

In the age 12 to < 18 years age group, all 3 cohorts (A1, B1, and C1) were enrolled. In the age 1 to < 12 years age group, cohorts A2 and B2 were enrolled, but stopped before enrolment in cohort C2 due to DLTs.

5 patients (22.7%) reported DLTs during the DLT evaluation period with 1 patient (25.0%) in cohort A1, 1 patient (25.0%) in cohort A2, and 3 patients (60.0%) in cohort B2.

The patients incidence of DLTs by preferred term are provided in Table 12-6.

Table 12-6. Subject Incidence of Dose Limiting Toxicities (DLT) During DLT Evaluation Period by Preferred Term in Descending Order of Frequency (DLT Analysis Set)

	Age 12-<18				Age 1-<12			
Preferred Term	Cohort A1 2.5mg/kg QW (N = 4) n (%)	Cohort B1 6.0mg/kg Q2W (N = 5) n (%)	Cohort C1 9.0mg/kg Q3W (N = 4) n (%)	Total (N = 13) n (%)	Cohort A2 2.5mg/kg QW (N = 4) n (%)	Cohort B2 6.0mg/kg Q2W (N = 5) n (%)	Total (N = 9) n (%)	Total (N = 22) n (%)
Number of subjects reporting dose limiting toxicities	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (25.0)	3 (60.0)	4 (44.4)	5 (22.7)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (11.1)	1 (4.5)
Apnoea	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (4.5)
Hypoxia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (4.5)
Neutrophil count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (4.5)
Peripheral motor neuropathy	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (4.5)
Respiratory acidosis	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Seizure	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)

The data cutoff date for this analysis is 17JUN2015.
Coded using MedDRA version 18.0.

Program: /userdata/earlydev/AMG954/20050252/analysis/final/tables/t-ae-dlts-dltp-pref-saf.sas
Output: t14-06-023-ae-dlts-dltp-pref-saf-l.rtf (Date Generated: 14JUL15:09:12:29) Source: adam.adsl, adam.adae

CHMP's comment:

Dose limiting toxicities were only observed in the age group 1 to <12 years in cohort B2 (6.0 mg/kg Q2W). The older patient group (age 12 to < 18 years) tolerated all tested dosing schedules without reaching dose limiting toxicities. This is comparable to the adult dose finding results in whom no maximum tolerated dose was reached either.

2.3.3. Discussion on clinical aspects

The MAH discusses the clinical aspects of the submission of study 20050252 as follows:

- *The observed adverse events were similar to the known panitumumab safety profile for adults.*
- *Panitumumab exhibits nonlinear PK in pediatric subjects; as the dose increased from 2.5 mg/kg to 6 mg/kg, the exposure to panitumumab (AUC) increased more than dose proportionally. After repeated administration, the panitumumab PK profiles after the third dose were as expected based on the PK profiles after the first dose. In general, age does not appear to have a significant impact on the exposure to panitumumab in this pediatric population. The presence of pre-existing antipanitumumab binding and neutralizing antibodies was associated with reduced exposure in 1 subject.*
- *No objective response was observed in pediatric subjects with solid tumors enrolled in this study. The disease control rate (stable disease) was 9.1% in the age 12 to < 18 years group and 60.0% in the age 1 to < 12 years group.*
- *This application comprises of necessary documentation for submission of the completed study report for study 20050252 in accordance with Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation'). The study report is submitted as a post authorisation measure in line with revised guidance EMA/427505/2013 Rev.2 "Practical questions and answers to support the implementation of the variations guidelines in the centralized procedure".*

3. Rapporteur's overall conclusion and recommendation

The Rapporteur generally agrees with the MAHs overall discussion on the clinical aspects of study 20050252.

The submitted data do not impact on the existing benefit:risk profile of panitumumab. The applicant stated that no change of the product information is required as a consequence of the submitted data. Further paediatric development is not planned by the MAH.

The submitted dose finding study was initiated based on FDA requirements. The regulatory background discussion preceding this decision remains unclear.

EMA has waived paediatric development for panitumumab in 2008, which was before PDCO included the mechanism of action of a compound and its exclusivity in relation to the adult condition only in the general decision process of granting class waivers.

The current SmPC states that paediatric development for all subsets of the paediatric population for the condition of colorectal cancer has been waived (as per Section 5.1) and that there is no relevant use of panitumumab to be expected in the paediatric population in the indication treatment of colorectal cancer (as per Section 4.2) for which panitumumab is authorised in adults.

The provided data essentially described paediatric pharmacokinetics and established a recommended Phase 2 dose. This information might be of importance for potential further development in the future. The rapporteur considers it important to discuss the possibility to including the available paediatric data in Section 5.2 of the SmPC.

Panitumumab is licenced since 2007. However no obvious scientific discussions have been identified involving pantitumumab and its use to effectively target EGFR in paediatric solid tumours. This emphasises that panitumumab seems not to be a compound of therapeutic interest.

Although the data submitted showed a similar safety profile compared to known adult data, no dose recommendation can be made.

Given the above the Rapporteur concludes that inclusion of information from this paediatric study in the SmPC without being linked to an approved paediatric indication bears the risk of promoting off label use.

The Rapporteur is therefore of the opinion that no further regulatory action is required.

Comments were received from one Member State who agreed with the Rapporteur's conclusions. No further comments were received. The final outcome of this procedure is therefore that no regulatory action is required.

Recommendation:

☒ Fulfilled:

No regulatory action required.