Annex 1 – detailed information on conditional marketing authorisations

Annex to the EMA report on 10 years of experience with conditional marketing authorisations

Description of data in tables and table columns:

Basic information

Therapeutic area	Therapeutic are corresponding to the indication of the product
Date of authorisation	Date of adoption of EC decision
Duration of procedure	Time from procedure start till adoption of CHMP opinion, including clock-stops, in days
SA/PA	Whether scientific advice/ protocol assistance was provided before MAA
SA/PA adherence	Whether the application adhere to the SA/PA received with respect to primary study endpoint(s), comparator and statistical methods
Indent for scope	Indent(s) in Article 2 of Commission Regulation (EC) No 507/2006 applicable for the product
CMA first considered	Stage of procedure when CMA was requested/ proposed for the first time
Unmet medical need	Category of unmet medical need(s) being addressed, as per CHMP AR
Safety database	Safety database (number of subjected who received product) in the MAA

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Phase III	Whether (interim) results from a phase III study were included in MAA as part of main/pivotal evidence

Granting of standard MA

Date of granting standard MA	Date of granting standard MA instead of CMA
Procedure of granting standard MA	Short reference number of procedure leading to granting of a standard MA
Changes to indication	Indication showing any changes made while the authorisation was conditional (changes based on data generated as part of SOs marked in bold, all insertions underlined, all deletions strikethrough)

Main/pivotal evidence at time of granting CMA (main/pivotal evidence as identified in CHMP AR)

Study ID	Identifier of the study
Phase	Phase of the study
Interventional	Whether study was interventional
Multiple arm	Whether study was multiple arm
Randomised	Whether study was randomised
Blinding	Whether study was blinded
Co-adm. therapy	Treatments co-administered with the CMA product
Comparator	Comparator(s) used in the study
Posology for CMA product	Posology for the CMA product (excluding dose modifications)
Study population	Description of patient population included in the study
Study size total	Total number of subjects included in the study, in brackets for primary analysis (if different)
Study Size CMA	Number of subjects receiving CMA product in the study
Duration	Duration post randomisation/treatment initiation for CMA product (actual median or pre-defined time point for primary analysis)
Primary endpoint	Primary endpoint
Effect size	Effect size (for multiple arm studies result shown for CMA product vs. control group)

SOs imposed

Original description of SO scope	Description of SO scope as imposed originally
Due date	Due date for completion of SO as imposed originally
Type of SO	Category of the SO type

Status	Status of the activity at the time of imposition

SO amendments and fulfilment

Latest/final description of SO scope	Description of the SO scope at the time of completion (if applicable) or at the cut-off date of the report
Latest/ final due date	SO dues date at the time of completion (if applicable) or at the cut-off date of the report
Subm. date	Actual date of submission of SO results
Accuracy of subm.	Number of days for difference between due date and actual submission date (positive number indicates early submission, negative number indicated delay)
SO status	Status of the SO at cut-off date
Change in scope	Whether the scope of SO has/had been changed
Change in due date	Whether the due date for completion of SO has/had been changed
Change description	Description of changes to SO
Due date ext.	Total extension granted for the completion of SO, days
Ext. reasons	Reasons for accepting the change(s) in due date
Scope reasons	Reasons for accepting the change(s) in scope

Details of data provided to fulfil SOs

Details of outstanding data

Please see descriptions under ‘Main/pivotal evidence at time of granting CMA’

Adcetris (brentuximab vedotin)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	25/10/2012	393	Yes	Yes	Art. 2(1) and 2(3)	During the procedure	No approved satisfactory treatment	357	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
SG035-0003	II	N	N	N	supportive measures consistent with optimal patient care	-	1.8 mg/kg IV q3 wk, 16 cycles	Patients with relapsed or refractory CD30+ HL post-ASCT	102	102	Median treatment duration 27 weeks + follow-up (data not reported)	Overall response rate	75%	CR rate of 33% (34/102) by IRF analysis; estimated median duration of response per IRF 6.7 months [95% CI (3.6, 14.8)], estimated median PFS per IRF 5.6 months [95% CI (5.0, 9.0 months)]

SG035-0004	II	N	N	N	supportive measures consistent with optimal patient care	-	1.8 mg/kg IV q3 wk, 16 cycles	Patients with relapsed or refractory Systemic Anaplastic Large Cell Lymphoma (sALCL)	58	58	Median treatment duration 23.5 weeks + follow-up (data not reported)	Overall response rate	86%	median duration of response per IRF 13.2 months [95% CI (5.7,-)], estimated median PFS per IRF 14.3 months [95% CI (6.9,-)]
N/A	-	-	-	-	not specified	-	1.8 mg/kg IV q3 wk (41 patients)	Patients with relapsed or refractory HL without prior ASCT	59	59	not reported	N/A for pooled analysis	N/A (ORR 46%, CR 21%)	Pooled analysis for patients from phase I/II studies, a Japanese-only study (TBBC010088) and Named Patient Programmes

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
Further Overall Survival follow up of the patients included in study SG035-0003 should be provided, including sub-analysis of patients' ≥ 100 kg. The data should be presented in the context of historical controls. SG035-003 annual reports until 2015 or when the overall survival data is sufficiently mature (at least 50% OS events observed), whichever occurs earlier.	31/12/2015	Clinical study	Ongoing (some results in MAA)
Further Overall Survival follow up of the patients included in study SG035-0004 should be provided, including sub-analysis of patients' ≥ 100 kg. The data should be presented in the context of historical controls. SG035-003 annual reports until 2015 or when the overall survival data is sufficiently mature (at least 50% OS events observed), whichever occurs earlier.	31/12/2016	Clinical study	Ongoing (some results in MAA)
A Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101). Report on interim analysis: 30/04/2016, Final study report: 31/12/2018	31/12/2018	Clinical study	New study

To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP agreed protocol (Study C25006). Protocol submission by: Q4 2012, Final Study Report by: Q1 2016	31/03/2016	Clinical study	New study
To perform a single-arm studying r/r HL population not eligible for ASCT investigating response rate, PFS, OS, proportion of patients proceeding to transplant and safety (n=approx 60 pts) based on a CHMP agreed protocol. Protocol submission by: Q1 2013, Final study report by: Q2 2016	30/06/2016	Clinical study	New study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	change in scope	change in due date	Scope change description	due date ext.	Ext. reasons	Scope reasons
Further Overall Survival follow up of the patients included in study SG035-0003 should be provided, including sub-analysis of patients' ≥ 100 kg. The data should be presented in the context of historical controls. SG035-003 annual reports until 2016 or when the overall survival data is sufficiently mature (at least 50% OS events observed), whichever occurs earlier.	31/12/15	31/10/2013	791	Completed	N	N	-	0	-	-
Further Overall Survival follow up of the patients included in study SG035-004 should be provided,	31/12/16	-	-	Due	N	N	-	0	-	-

including sub-analysis of patients ≥ 100 kg. The data should be presented in the context of historical controls.										
A Non-interventional Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101).	31/12/18	-	-	Due	Minor	N	SO description updated to specify that the study in question should be non-interventional in procedure II/2	0	-	-
To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP agreed protocol (Study C25006).	31/03/2021	-	-	Due	N	Y	Due date extended in IB/34/G	1826	Slow recruitment. Extension granted due to 'rarity of the disease and the further limiting effects on patient availability due to the characteristics of the patient population to be studied in the context of an already registered indication'	-
To perform a single-arm studying r/r HL population not eligible for ASCT investigating response rate, PFS, OS, proportion of patients proceeding to transplant and safety (n=approx 60 pts) based on a CHMP agreed protocol.	30/06/2017	-	-	Due	N	Y	Due date extended in IB/34/G	365	Delays in study conduct, in particular obtaining approvals for the study	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Scope (e.g. E vs. S)?	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	SG035-0003	II	N	N	N	E & S	supportive measures consistent with optimal patient care	-	1.8 mg/kg IV q3 wk	Patients with relapsed or refractory CD30+ HL post-ASCT	102	102	median duration of OS follow-up 32.7 months (range, 1.8-48.3 months)	Overall survival (SO scope)	median duration of OS 40.5 months (95% CI, 28.7 months, -)	median PFS per investigator was 9.3 months (95% confidence interval, 7.1-12.2 months; range 1.2-44.5+ months),

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Scope (e.g. E vs. S)?	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Notes
Clinical study	SG035-0004	II	Y	N	N	N	E & S	supportive measures consistent with optimal patient care	-	1.8 mg/kg IV q3 wk, 16 cycles	Patients with relapsed or refractory Systemic Anaplastic Large Cell Lymphoma (sALCL)	58	58	till 50% OS events observed	Overall survival (SO scope)	
Clinical study	MA25101	IV	N	N	N	N	S	as per clinical practice	-	As per SmPC / clinical practice	Patients with relapsed or refractory CD30+ HL or relapsed or refractory sALCL and treated with brentuximab vedotin	500	500	up to 5 years	Various safety endpoints related to occurrence of serious adverse events and specified adverse events of special interest and potential risk factors for peripheral neuropathy	multi-centre prospective, observational cohort study

Clinical study	C25006	IV	Y	N	N	N	E & S	none	-	1.8 mg/kg IV q3 wk, up to 16 cycles	Patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen	45	45	up to 5 years or 50% of OS events	Overall objective response rate (ORR) per independent review facility (IRF)	
Clinical study	C25007	IV	Y	N	N	N	E & S	not required	-	1.8 mg/kg IV q3 wk, 16 cycles	CD30+ r/r cHL who have not received a prior ASCT and are considered to be not suitable for SCT or multi-agent chemotherapy	60	60	up to 5 years	ORR by IRF assessment	

Arepanrix (Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted))

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	23/03/2010	187	NO	NA	Art. 2(2)	Initial MAA	For use in emergency situations	5731[1]	Yes

Granting of standard MA

MA withdrawn for commercial reasons

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Q-Pan-001	I/II	Y	Y	Partial	-	Product manufactured at a different site and various amount of adjuvant	2 doses (at D0 and D21) 3.8µg H5N1 split/ AS03, half dose AS03 or no AS03	18 - 64 y.o. healthy adults	662	662	6 months	Immunogenicity	various parameters (see EPAR)	

[1] total number of subjects receiving vaccine (i.e. excluding placebo arms) in studies identified as main in the CHMP AR. Please see European Public Assessment report for further information on safety information available at the time of authorisation.

Q-Pan-010	I/II	Y	Y	Partial	-	Unadjuvanted vaccine	1 booster dose of H5N1 3.8 µg/ full AS03 (vs. no adjuvant) at month 15	18-64 y y.o. healthy adults primed in Q-Pan-001	650	650	10 days after booster dose (treatment duration 1 year)	Immunogenicity	various parameters (see EPAR)	Booster phase of study Q-Pan-001
Q-Pan-002	III	Y	Y	Partial	-	different batches of the product and placebo	2 doses (at D0 and D21) 3.8µg H5N1 / AS03	healthy adults	4343	3263	6 m - 1 y	Immunogenicity	various parameters (see EPAR)	
Q-Pan-009	II	Y	Y	N	-	different time points for administration of the two doses	Two doses of H5N1 3.8 µg / full AS03 at various times	18-64 y.o. Canadian healthy adults	312	312	14 days after 2nd dose (treatment duration 6 months)	Immunogenicity	various parameters (see EPAR)	
Q-Pan-011	II	N	N	N	-	-	2 doses of H5N1 3.8 µg/ full AS03	20-64 y.o. Japanese healthy adults	100	100	6 months	Immunogenicity	various parameters (see EPAR)	

SOs imposed

Original description of SO scope	Due date	Type of SO	Status	Notes
The Applicant/MAH commits not to release lots prepared using the extended formulation/fill process until the relevant validation data have been submitted and approved (RR#7Q5)	31/01/2010	Quality	-	
The Applicant/MAH commits to set a maximum decrease of 20% of HA content for the Drug Substance and to review when data for H1N1 become available. (Arise from Q1 RR#13)	26/02/2010	Quality	-	
The Applicant/MAH commits to provide abridged report for the following study performed in children Study Q-Pan H1N1-003 (6 months-8 yrs, Dose finding,) - abridged report for post dose 1 Wave 1 immuno data, solicited and unsolicited symptoms, SAEs)	05/03/2010	Clinical study (interim)	ongoing	
[..] The Applicant/MAH commits to provide abridged report for the following study performed in children Study Q-Pan H1N1-003 (6 months-8 yrs, Dose finding,) - abridged report for post dose 2 Waves 1 and 2 (immuno data, solicited and unsolicited symptoms, SAEs)	04/06/2010	Clinical study	ongoing	
The Applicant/MAH commits to provide abridged report for the following study performed in adults: Study Q-Pan H1N1-001 abridged report for post dose 1 and post dose 2 (>/ 18 yrs, Dose finding, adjuvanted vaccine vs plain)	30/04/2010	Clinical study	ongoing	
The Applicant/MAH commits to provide abridged report for the following study performed in adults Study Q-Pan H1N1-019 (18-60 yrs, TIV effect and co-administration) - abridged report for post dose 3 (immuno & solicited and unsolicited symptoms, SAEs)	04/06/2010	Clinical study	ongoing	
The Applicant/MAH commits to provide abridged report for the following study performed in children. Study Q-Pan H1N1-031 (9-17 yrs, Safety/ Immunogenicity) - abridged report for post dose 1 & post dose 2 (immuno & solicited and unsolicited symptoms, SAEs)	04/06/2010	Clinical study	ongoing	

The Applicant/MAH commits to provide abridged report for the following study performed in children Study Q-Pan H1N1-032 (2-5 months, Safety/ Immunogenicity) - abridged report for post dose 1 & post dose 2 (immuno & solicited and unsolicited symptoms, SAEs)	08/07/2010	Clinical study	ongoing	
The Applicant/MAH will support one prospective cohort safety study with Arepanrix, in at least 9,000 patients, in accordance with the protocols submitted with the Risk Management Plan. Interim and final results will be submitted one week after being available.	28/02/2010	Clinical study	New study	Prospective cohort study
The Applicant/MAH will support one retrospective cohort safety study with Arepanrix, in at least 9,000 patients, in accordance with the protocols submitted with the Risk Management Plan. Interim and final results will be submitted one week after being available.	30/04/2010	Clinical study	New study	Retrospective cohort study
The Applicant/MAH commits to provide the results of a study in a pregnancy registry conducted with Arepanrix.	PSUR	Clinical study	New study	
The Applicant/MAH commits to support an effectiveness study with Arepanrix ongoing and submit the results one week after being available.	30/04/2010	Clinical study	ongoing	
The Applicant/MAH commits to support a Post-authorisation study in immunocompromised subjects (adults with HIV) being conducted by PCIRN (Public Health Agency of Canada - Canadian Institutes of Health Research Influenza Research Network) and provide the final result	PSUR	Clinical study	ongoing	
The Applicant/MAH commits to establish the mechanisms to promptly investigate issues affecting the benefit-risk balance of the vaccine. The MAH should provide an inventory of all valuable database ready to be use to promptly investigate issues affecting the benefit-risk balance of the vaccine. Details regarding databases (e.g., data sources, characteristics of the data, potential analysis) need to be reported.	one month after granting MA	Other measure	-	

SO amendments and fulfilment

N/A (MA withdrawn)

Details of data provided to fulfil SOs

N/A (MA withdrawn before removal of any SO)

Details of outstanding data

N/A (MA withdrawn)

Arzerra (ofatumumab)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	19/04/2010	330	NO	NA	Art. 2(1) and 2(3)	During the procedure	No approved satisfactory treatment	648	No

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
24/04/2015	II/35	in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy; treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
Hx-CD20-406	II	N	N	N	none	N/A	300mg × 1 2000mg × 7 (weekly) 2000mg × 4 (every 4 weeks)	Subjects with CLL refractory to fludarabine and alemtuzumab, or refractory to fludarabine and inappropriate for alemtuzumab due to bulky lymphadenopathy	154	154	Primary analysis at week 24	Objective response from screening to week 24	52%

Hx-CD20-402	I/II	Y	N	N	none	N/A	Group A: 100mg×1, 500mg×3 (weekly) Group B: 300mg×1, 1000mg×3 (weekly) Group C: 500mg×1, 2000mg×3 (weekly)	Relapsed/refractory CLL	33	33	Primary analysis at week 19, FU up to 12 months	Overall response rate (objective response) from screening to week 19	50 % (high dose group, n=27)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
1. To conduct an open label, multicenter study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory chronic lymphocytic leukaemia (CLL). The final protocol will be submitted for CHMP agreement within 3 months of conditional marketing authorisation date. The study report is to be submitted by December 2014, but the timing will be confirmed at the time of submission of the final protocol, when feasibility will be complete.	31/12/2014	Clinical study	New study
2. To conduct a phase IV observational study to provide further data on the clinical efficacy and safety of ofatumumab. The final protocol will be submitted for CHMP agreement within 3 months of conditional marketing authorisation date. The time needed to recruit the target number of subjects (100) will depend on the date of availability on the market of Arzerra across EU, degree of use and on the willingness of patients and physicians to participate in the study. The study report is to be submitted by June 2013, but the timing may be changed at the time of submission of the final protocol.	30/06/2013	Clinical study	New study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	change in scope	change in due date	Scope change description	due date ext.	Ext. reasons	Scope reasons
To submit an open label, multicenter study investigating the safety and efficacy of ofatumumab therapy versus physicians' choice in patients with bulky fludarabine refractory chronic lymphocytic leukaemia (CLL)	31/12/2014	20/11/2014	41	Completed	N	N	-	0	-	-
To submit a phase IV observational study to provide further data on the clinical efficacy and safety of ofatumumab. The time needed to recruit the target number of subjects (100) will depend on the date of availability on the market of Arzerra across the EU, degree of use and on the willingness of patients and physicians to participate in the study.	30/06/2013	28/05/2013	33	Completed	N	N	-	0	-	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	Hx-CD20-406	II	N	N	N	E & S	none	N/A	300mg × 1 2000mg × 7 (weekly) 2000mg × 4 (every 4 weeks)	Subjects with CLL refractory to fludarabine and alemtuzumab, or refractory to fludarabine and inappropriate for alemtuzumab due to bulky lymphadenopathy	154	154	Primary analysis at week 24	Objective response from screening to week 24	52%	

Clinical study	Hx-CD20-402	I/II	Y	N	N	E & S	none	N/A	Group A: 100mg×1, 500mg×3 (weekly) Group B: 300mg×1, 1000mg×3 (weekly) Group C: 500mg×1, 2000mg×3 (weekly)	Relapsed/refractory CLL	33	33	Primary analysis at week 19, FU up to 12 months	Overall response rate (objective response) from screening to week 19	50 % (high dose group, n=27)	
Clinical study	-	III	Y	Y	Not specified	E & S	not specified	Physician's choice	not specified	patients with bulky fludarabine refractory chronic lymphocytic leukaemia (CLL)	not specified	not specified	not specified	not specified	-	

Clinical study	OMB 114242	III	Y	Y	N	E & S	none / pre-medication	Any other treatment approved for CLL	300mg × 1 2000mg × 7 (weekly) 2000mg × 4 (every 4 weeks)	Subjects with fludarabine-refractory CLL, received at least 2 prior therapies for CLL, and with bulky lymphadenopathy	122	79	median treatment duration 161 days for CMA product, median duration of safety observation 362 (CMA product) vs. 149 (control) days	Median progression free survival	5.4 months (vs. 3.6 months)	
Clinical study	-	IV	N	N	N	E & S	not specified	N/A	as per SmPC	as per indication	100	100	not specified	Not specified	-	
Clinical study	WEU SRTP 4799	IV	N	N	N	E & S	not restricted	N/A	as per clinical practice	CLL patients who had previously received Ofatumumab (excluding phase II and III CTs)	103	103	median 9 cycles	N/A (a descriptive retrospective medical record review)	N/A	Median OS 11.2 months, median PFS 5.0 months

Details of outstanding data

N/A

Blincyto (blinatumomab)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	23/11/2015	330	Yes	NA	Art. 2(1) and 2(3)	Initial MAA	Improved treatment effect and/or safety vs. available therapies	475	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
MT103-211	II	N	N	N	none	-	9 - 28 µg/day	subjects with relapsed/refractory B-precursor ALL	189	189	3 months	complete remission (CR) or a complete remission with partial hematological recovery (CRh*) rate within 2 cycles	42.9% (81/189)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
Post-authorisation efficacy study (PAES):Study 00103311 (TOWER): A Study of BITE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL)	31/03/2017	Clinical study	ongoing

SO amendments and fulfilment

Latest/final description of SO scope	Latest/ final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
Post-authorisation efficacy study (PAES):Study 00103311 (TOWER): A Study of BITE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL)	31/03/2017	-	-	Due	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	00103311	III	Y	Y	Y	N	E & S	none	standard of care chemotherapy	9 - 28 µg/day	adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia	405	271	as needed to reach sufficient no. of OS events	Overall survival

Bosulif (bosutinib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	27/03/2013	519	Yes	yes	Art. 2(1) and 2(3)	During the procedure	No approved satisfactory treatment	1572	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
3160A4-200-WW (part 2, 'unmet medical need' subgroup)	I/II	N	N	N	none	-	500-mg daily	CP, AP, and BP CML patients who may not be candidates for treatment with at least 1 of the currently approved TKI due to intolerance, mutations, or comorbidities	52	52	24 to 215+ weeks	rate of attaining major cytogenetic response (MCyR)	9/36, 3/5, 2/11

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	30/09/2018	Clinical study	New study

SO amendments and fulfilment

Latest/final description of SO scope	Latest/final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	30/09/2018	-	-	Due	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	-	IV	Y	N	N	N	E & S	none	'	500 mg daily	patients with Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate	150	150	at least 1 year	probability of Major Cytogenetic Response (MCyR) (chronic phase) and Confirmed Overall Hematological Response (OHR) (accelerated and blast phase) by one year

Caprelsa (vandetanib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	17/02/2012	421	Yes	No	Art. 2(1)	During the procedure	No approved satisfactory treatment	4000	Yes

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
D4200C00058	III	Y	Y	Y	none	placebo	300mg once daily	Subjects with unrespectable locally advanced or metastatic hereditary or sporadic medullary thyroid cancer	331	231	103 weeks	median PFS	30.5 vs. 19.3 months (HR=0.46, 95% CI, 0.31 to 0.69)	a Weibull model was used to estimate the median PFS

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
An open label trial based on a CHMP approved protocol, comparing RET negative and RET positive patients with sporadic medullary thyroid cancer treated with vandetanib. The study will include approximately 60 % of patients who receive vandetanib within the EU. Inclusion criteria: to meet criteria based on SmPC indication. In addition, RET mutation negative patients who do not receive vandetanib due to RET status or contraindication will be allowed to enrol and followed. Exclusion Criteria: limited to contraindications outlined in section 4.3 of the SmPC Data to be collected on study: • History and physical examination • RET mutation status • Patients not required to have tissue biopsy to determine RET status for enrolment RET mutation status: Patients will not be required to have a fresh tissue biopsy to determine RET status before enrolment. However investigator should be strongly requested to obtain a recent sample for determination of the RET status as often as possible, even in patients previously tested at an earlier stage of their disease. Determination of RET status should be made preferably just prior to the initiation of treatment. Tissue type used for assay, date of tissue biopsy, assay type and definition used for RET mutation positive and negative will be collected. RET mutation negative patients who do not receive vandetanib due to RET status or contraindication will be allowed to enrol and followed. RET mutation status should be assessed according to pre-defined mutational analysis, where type of test and exons to be analyzed are protocol pre-specified. • Safety Assessments at each visit including QT prolongation information. • Objective tumour responses / duration of response / progression • Assessed in accordance with study physicians normal medical practice. Within a centre, patients will be assessed for efficacy in a consistent manner, irrespective of their RET status at pre-defined time points • Method used for assessment (e.g. CT, MRI) Disease status at each efficacy visit: objective response, stable disease or progressive disease. • The final analysis will be performed when at least 40 patients identified with RET mutation and 40 patients identified without evidence of RET mutation have been enrolled into the study and received vandetanib for 14 months. The total	31/12/2015	Clinical study	New study

duration of the study is expected to be 38 months. Analyses: • The study will run for 2 years and at pre-specified times, the data will be collected and analyzed (e.g., 12 months and 24 months) • Objective response rate, progression status and DCR in the overall population, RET mutation negative and RET mutation positive patients • Safety analyses in the overall population, RET mutation negative and RET mutation positive patients			

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due d.	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of ch.	Due date ext.	Ext. reasons	Scope reasons
An open label trial based on a CHMP approved protocol, comparing RET negative and RET positive patients with sporadic medullary thyroid cancer treated with vandetanib. The study will include approximately 60 % of patients who receive vandetanib within the EU. Inclusion criteria: to meet criteria based on SmPC indication. In addition, RET mutation negative patients who do not receive vandetanib due to RET status or contraindication will be allowed to enrol and followed. Exclusion Criteria: limited to contraindications outlined in section 4.3 of the SmPC Data to be collected on study: · History and physical examination · RET mutation status · Patients not required to have tissue biopsy to determine RET status for enrolment RET mutation status: Patients will not be required to have a fresh tissue biopsy to determine RET status before enrolment. However, investigator should be strongly requested to obtain a recent sample for determination of the RET status as often as possible, even in patients previously tested at an earlier stage of their disease. Determination of RET status should be made preferably just prior to the initiation of treatment. Tissue type used for assay, date of tissue biopsy, assay type and definition used for RET mutation positive and negative will be collected. RET mutation negative patients who do not receive vandetanib due to RET status or contraindication will be allowed to enrol and followed. RET mutation status should be assessed according to pre-defined mutational analysis, where type of test and exons to be analyzed are protocol pre-specified. · Safety Assessments at each visit including QT prolongation information. · Objective tumour responses / duration of response / progression · Assessed in accordance with study physicians normal medical practice. Within a centre, patients will be assessed for efficacy in a consistent manner, irrespective of their RET status at pre-defined time points · Method used for assessment (e.g. CT, MRI) Disease status at each efficacy visit: objective response, stable disease or progressive disease. · The final analysis will be performed when at least 40 patients identified with RET mutation and 40 patients identified without evidence of RET mutation have been enrolled into the study and received vandetanib for 14 months. The total duration of the study is expected to be 38 months. Analyses: · The study will run for 2 years and at pre-specified times, the data will be collected and analysed (e.g. 12 months and 24 months) · Objective response rate, progression status and DCR in the overall population, RET mutation negative and RET mutation positive patients · Safety analyses in the overall population, RET mutation negative and RET mutation positive patients	30/09/2020	-	-	Due	N	Y	No change in scope. Due date extended in procedure IB/19	1735	Slow recruit-ment due to diffi-culties in meeting the inclu-sion criteria	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	-	IV	N	N	N	N	E & S	not specified	-	as per SmPC	RET negative and RET positive patients with sporadic medullary thyroid cancer	80 (40 per RET status)	80	14 months	Objective response rate, progression status and DCR (to be selected)

Cayston (aztreonam)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	21/09/2009	456	Yes	No	Art. 2(3)	Initial MAA	Improved treatment effect and/or safety vs. available therapies	373	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
05/09/2011	R/15	Suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis aged 18 years and older. The primary support for this indication is based on two single 28-day course placebo-controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited. Consideration should be given to official guidance on the appropriate use of antibacterial agents. (no change)

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
CP-AI-005	III	Y	Y	Y	products for obstructive airway diseases, prior administration a short-acting bronchodilator	placebo (same co-administered therapy)	75 mg BID or TID	CF patients with stable pulmonary disease and a recent positive sputum culture for PA	211	135	28 days treatment + 56 days observation	Median time to need for IV or inhaled anti-PA antibiotics other than trial drug with documented symptom(s) predictive of pulmonary exacerbation	92 days (vs. 71 days)	Mean (adjusted) change in FEV1 predicted at Day 28: 4.08% (vs. -2.52%)
CP-AI-007	III	Y	Y	Y	products for obstructive airway diseases, prior administration a short-acting bronchodilator	placebo (same co-administered therapy)	75 mg TID	CF patients with stable pulmonary disease and a recent positive sputum culture for PA	164	80	28 days treatment + 14 days observation	change from baseline to D28 in clinical symptoms as assessed by the respiratory domain of the CFQ R	7.08 (vs. -2.63)	Mean (adjusted) change in FEV1 predicted at Day 28: 3.58% (vs. -1.68%)

CP-AI-006	III	N	N	N	at investigator's discretion	-	75 mg BID or TID	Patients aged ≥ 6 years with CF, who had completed either study CP-AI-005 or CP-AI-007 or who withdrew from either of the studies	207	207	250 days in study (117 days of treatment with Cayston)	safety	N/A	Measures of pulmonary function (FEV1), CFQ-R respiratory symptoms scores, and log10 P. aeruginosa CFUs showed a trend to improvement while the patients were on treatment compared with off treatment

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
The applicant commits to submit the results of study GS-US-205-0110 and other available long term data by July 2010.	31/07/2010	Additional analysis	New analysis
(ongoing study, age 6 years and older) Study GS-US-205-0110: Open-label, randomized Phase 3 study to evaluate the efficacy and safety of AZLI versus Tobramycin Nebulizer Solutions (TNS) in an intermittent aerosolized regimen in patients with CF. The final clinical study report will be available by Jul 2010.	31/07/2010	Clinical study	Ongoing
(ongoing study, age 6 years and older) Study GS-205-0117: Phase 3, double-blind, multi-centre, multinational randomized, placebo controlled trial evaluating AZLI in patients with cystic fibrosis, mild lung disease, and PA. The final clinical study report will be available by Dec 09.	31/12/2009	Clinical study	Ongoing
A review of all paediatric data from controlled studies will be provided by Sep 2010.	30/09/2010	Additional analysis	New analysis

The applicant commits to a paediatric development of the product consisting of well controlled trials to support short-term and long-term repeated use in this patient group. Protocols will be drafted by Mar 2010 (after availability of results from GS-US-205-0110), with the studies anticipated to be completed within 3 years following finalisation of the protocol.	01/03/2010	Other measure	New measures

SO amendments and fulfilment

Latest/final description of SO scope	Latest/final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
. The applicant commits to submit the results of study GS US 205 0110 in September 2010 [Note: study 110 subject also of another specific obligation; here results presented for study 006, submitted in context of this SO in procedure R/6]	30/09/2010	29/09/2010	1	Completed	minor	Y	Following submission of final results of study CP-AI-006, the SO re-worded (from study + other available long term data to study results only) and due date extended in R/6	61	Increase in sample size and additional analysis at request from FDA	-
(ongoing study, age 6 years and older) Study GS-US-205-0110: Open-label, randomized Phase 3 study to evaluate the efficacy and safety of AZLI versus Tobramycin Nebulizer Solutions (TNS) in an intermittent aerosolized regimen in patients with CF. The final clinical study report will be available by September 2010.	30/09/2010	29/09/2010	1	Completed	N	Y	Due date extended in R/6 (two SOs affected)	61	Increase in sample size and additional analysis at request from FDA	-

(ongoing study, age 6 years and older) Study GS-205-0117: Phase 3, double-blind, multi-centre, multinational randomized, placebo controlled trial evaluating AZLI in patients with cystic fibrosis, mild lung disease, and PA. The final clinical study report will be available by Dec 09.	31/12/2009	22/12/2009	9	Completed	N	N	-	0	-	-
A review of all paediatric data from controlled studies will be provided by Sep 2010.	30/09/2010	29/09/2010	1	Complete	N	N	-	0	-	-
The applicant commits to a paediatric development of the product consisting of well controlled trials to support short-term and long-term repeated use in this patient group. Protocols will be drafted by Mar 2010 (after availability of results from GS-US-205-0110), with the studies anticipated to be completed within 3 years following finalisation of the protocol.	01/03/2010	08/03/2010	-7	Completed	N	N	-	0	-	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	CP-AI-006	III	N	N	N	E & S	none	-	75 mg BID or TID	CF patients with stable pulmonary disease and a recent positive sputum culture for PA (extension study for patients from Studies CP-AI-005 and CP-AI-007)	274	274	up to nine 28-day cycles over 18 months	Safety	N/A	
Clinical study	GS-US-205-0110	III	Y	Y	N	E & S	none	TOBI (tobramycin)	3 cycles of 75 mg TID for 28 days	CF patients aged ≥ 6 years with CF, FEV1 < 75% predicted at screening, and PA	268	136	28 days	Relative change from baseline in FEV1 percent predicted at Day 28 (other co-	8.35 vs 0.55	

										present in expectorated sputum or throat swab culture within the 3 months, without intolerance to previous aerolized antibiotics				primary endpoint requested by FDA - actual change from baseline in FEV1 % predicted across 3 courses)		
Clinical study	GS – US-205-0117	III	Y	Y	Y	E & S	none	placebo	75 mg TID for 28 days	Patients aged ≥ 6 years with CF, chronic pulmonary PA, and mild lung disease (FEV1 > 75% predicted)	160 (157)	76	28 days	change in the respiratory symptoms domain of the CFQ-R at Day 28 from baseline	3.22 vs. 1.41 (treatment effect 1.80, p = 0.443)	Only marginal improvement in the various FEV1 findings and a modest decrease in sputum PA density. The possibility for improvement is limited in this relatively healthy population and second this population cannot be considered representa

																tive for the population CF patients.
Additional analysis	-	-	-	-	-	E & S	-	-	-	Paediatric patients with CF	-	-	-	N/A	-	
Other measure	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

Details of outstanding data

N/A

Cometriq (cabozantinib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	21/03/2014	393	NO	NA	Art. 2(1) and 2(3)	During the procedure	Improved treatment effect and/or safety vs. available therapies	295	Yes

Granting of standard MA N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
XL184-301	III	Y	Y	Y	none	placebo	138 mg qd	Patients with unresectable locally advanced or metastatic MTC, experiencing disease progression within 14 months from previous radiological assessment	330	219	13.9 months (range 3.6 months to 32.5 months)	PFS (IRC determined, according to modified RECIST criteria)	48.6 vs. 17.4 weeks (HR 0.28, 95% CI 0.19-0.40, p<0.0001)	Population enrolled in the study reflects the target population of the indication, but patients with locally advanced MTC represented < 5% of patients. ORR 27.9% vs. 0%. Disease stabilisation rate 55.3% vs. 13.5%.

SOs imposed

Original description of SO scope	Due date	Type of SO	Status	Notes
A dose-comparison study (XL-184-401) (140 mg vs 60 mg) in 112 patients with hereditary or sporadic medullary thyroid cancer. Patients with both sporadic and hereditary forms of MTC will be eligible for the study. Fresh tumour samples for tumour genetic analysis from the most recent metastatic site in patients enrolled in the dose-comparison study should be collected. Samples will undergo thorough evaluation for RET and RAS mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality by a PCR-based amplification test, and by Sanger sequencing for RET M918T. A replacement sample will be requested if an original sample fails during the PCR quality or the Sanger sequencing tests. Next generation sequencing of RET exons 10, 11, and 13-16 will be performed, which covers the vast majority of known RET mutations. In addition, samples will be evaluated for mutations in RAS gene hotspots (HRAS, KRAS, and NRAS genes). PK assessments will be required for all subjects (both dose groups). Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolites in this population.	31/03/2019	Clinical study	New study	Non-inferiority study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
A dose-comparison study (XL-184-401) (140 mg vs 60 mg) in 112 patients with hereditary or sporadic medullary thyroid cancer. Patients with both sporadic and hereditary forms of MTC will be eligible for the study. Fresh tumour samples for tumour genetic analysis from the most recent metastatic site in patients enrolled in the dose-comparison study should be collected. Samples will undergo thorough evaluation for RET and RAS mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality by a PCR-based amplification test, and by Sanger sequencing for RET M918T. A replacement sample will be requested if an original sample fails during the PCR quality or the Sanger sequencing tests. Next generation sequencing of RET exons 10, 11, and 13-16 will be performed, which covers the vast majority of known RET mutations. In addition, samples will be evaluated for mutations in RAS gene hotspots (HRAS, KRAS, and NRAS genes). PK assessments will be required for all subjects (both dose groups). Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolites in this population.	31/03/2019	-	-	Due	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	XL-184-401	?[2]	Y	Y	Y	Y	E, S, PK	not specified	different posology for CMA product	140 mg vs. 60 mg	Subjects with progressive, metastatic hereditary or sporadic medullary thyroid cancer	188	188	ultil disease progression (estimated treatment duration median 11 months)	PFS per independent radiology review

[2] Study phase not declared in the study protocol, the study could be considered as phase IV

Darzalex (daratumumab)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	20 May 2016	183	Yes	Yes	Art. 2(1) and 2(3)	Initial MAA	Improved treatment effect and/or safety vs. available therapies	331	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
MMY2002	II	Y	Y	N	none	different doses of CMA product	8 or 16 mg/kg	MM patients who have received at least 3 prior lines of therapy (incl. PI and IMiD) or double refractory to PI and IMiD	124 (106)	124	14.7 months for the 16 mg/kg group	ORR	29% (16 mg/kg group)
GEN501 (part 2)	I/II	Y	Y	N	none	different doses of CMA product	8 or 16 mg/kg	MM patients relapsed from or refractory to at least 2 different cytoreductive therapies and without further treatment options	104 (42)	104	15.2 months for the 16 mg/kg group	ORR	36% (16 mg/kg group)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	30/09/2017	Clinical study	ongoing
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	31/12/2016	Clinical study	ongoing

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	30/09/2017	-	-	Due	N	N	-	0	-	-
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	31/12/2016	-	-	Due	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	MMY3003	III	Y	Y	Y	N	E & S	lenalidomide, low dose dexamethasone	lenalidomide and low-dose dexamethasone	16 mg/kg	subjects with relapsed or refractory multiple myeloma	569	286	Until disease progression or unacceptable toxicity	PFS
Clinical study	MMY3004	III	Y	Y	Y	N	E & S	bortezomib and low-dose dexamethasone	bortezomib and low dose dexamethasone	16 mg/kg	subjects with relapsed or refractory multiple myeloma	498	251	Until disease progression or unacceptable toxicity	PFS

Deltyba (delamanid)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	28/04/2014	715	NO	NA	Art. 2(1) and 2(3)	During the procedure	Patient population with limited/no treatment options	887	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
242-07-204	II	Y	Y	Y	OBR	placebo + OBR	100 mg or 200 mg twice daily	subjects with pulmonary tuberculosis caused by organisms that were at least resistant to rifampicin and isoniazid	481 (402)	277	8 w	sputum culture conversion (SCC)	45%, 42% and 30% in those treated with 100 mg bid, 200 mg bid and placebo, respectively	for patients with XDR-TB SCC was 4/24 (17%), 5/18 (28%) and 2/27 (7%) in 100 mg bid, 200 mg bid and placebo groups, respectively. In follow-up delamanid for ≥6 months (any combination of doses) yielded a sustained culture conversion in 91% of patients with MDR-TB (130/143), and in 78% (31/40) in those with XDR-TB.

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
To complete a confirmatory trial examining delamanid added to optimal background regimen in licensed indication: Phase 3 trial comparing delamanid 100 mg BID for 2 months + 200 mg QD for 4 months plus OBR for 18-24 months versus OBR for 18-24 months with placebo for the first 6 months.	30/06/2017	Clinical study	ongoing
To resolve the uncertainties around exposure and antimicobacterial activity, by conducting a further study exploring the relationship between different doses with respect to 2 months SCC and longer term outcome : to perform a controlled study of the efficacy, safety and pharmacokinetics of delamanid 100 mg twice daily for 2 months followed by delamanid 200 mg in a single daily dose for 4 months or delamanid 400 mg single daily dose for 6 months in adult patients with pulmonary multidrug-resistant tuberculosis, based on a CHMP-agreed protocol.	31/12/2018	Clinical study	New study

SO amendments and fulfilment

Latest/final description of SO scope	Latest/ final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
To complete a confirmatory trial examining delamanid added to optimal background regimen in licensed indication: Phase 3 trial comparing delamanid 100 mg BID for 2 months + 200 mg QD for 4 months plus OBR for 18-24 months versus OBR for 18-24 months with placebo for the first 6 months.	30/06/2017	-	-	Due	N	N	-	0	-	-
To resolve the uncertainties around exposure and antimicobacterial activity, by conducting a further study exploring the relationship between different doses with	31/12/2018	-	-	Due	N	N	-	0	-	-

respect to 2 months SCC and longer term outcome : to perform a controlled study of the efficacy, safety and pharmacokinetics of delamanid 100 mg twice daily for 2 months followed by delamanid 200 mg in a single daily dose for 4 months or delamanid 400 mg single daily dose for 6 months in adult patients with pulmonary multidrug-resistant tuberculosis, based on a CHMP-agreed protocol.														

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	242-09-213	III	Y	Y	Y	Y	E & S	OBR	placebo + OBR	100 mg BID for two months, followed by delamanid 200 mg QD for four months	with sputum culture-positive, pulmonary MDR TB or with sputum smears positive for acid fast bacilli (AFB) and a positive rapid test demonstrating resistance to both rifampicin and isoniazid	390	260	6 months + OBR continuation period and follow-up	(1) proportion of patients achieving SCC at 2 months (8 weeks) using MGIT, and (2) distribution of the time to SCC using the MGIT system during the 6-month Intensive Treatment Period

Clinical study	242-13-xxx	IV	Y	Y	Y	Y	E & S	OBR	different posology of CMA product	100 mg twice daily for 2 months followed by 200 mg in a single daily dose for 4 months vs. 400 mg single daily dose for 6 months	adult patients with culture-positive pulmonary MDRTB confirmed MDR-TB at baseline	208	208	6 months	Time-to-Conversion over six months

Diacomit (stiripentol)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Neurology	04/01/2007	518	NO	NA	Art. 2(3)	During the procedure	Improved treatment effect and/or safety vs. available therapies	1172	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
08/01/2014	R/14	in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
BC-299 (STICLO-FR)	III	Y	Y	Y	valproic acid and clobazam	placebo	50/mg/kg/day	3-18 years old, with diagnosed SMEI, and at least 4 tonic-clonic seizures per month	42	22	3 months	responders (> 50% seizure reduction after 2 months)	71.4% (vs 5)	increase in the concentration of co-medication in active group
BC-385 (STICLO-IT)	III	Y	Y	Y	valproic acid and clobazam	placebo	50/mg/kg/day	3-18 years old, with diagnosed SMEI, and at least 4 tonic-clonic seizures per month	23	12	3 months	responders (> 50% seizure reduction after 2 months)	66.7% (vs. 9.1)	increase in the concentration of co-medication in active group

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
1. A randomised controlled clinical trial with stiripentol in the add-on therapy using maximally safe doses of clobazam+valproate by 2009 (STP 165).	31/12/2009	Clinical study	New study
2. A bioavailability study in 24 subjects to determine the relative bioavailability of thcaystonine stiripentol sachet versus stiripentol capsule by 2007 (STP 166)	31/12/2007	Clinical study	New study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
1. To provide further observational data to support the intrinsic anticonvulsant activity of stiripentol, and to further support its safety and efficacy in the treatment of Dravet's syndrome.	30/06/2012	10/01/2013	-194	Completed	Major	Y	In R/11 the SO to provide results from randomised placebo controlled study was amended to "robust observational study data to support the efficacy and safety of stiripentol to control clonic seizure or tonic-clonic seizure in Dravet's Syndrome"	912	SO replaced with another study	Difficulties in conduct of the study (consortium disbanded, slow approval process) + new PK data indicate that original study would unlikely address the research question
A bioavailability study in 24 subjects to determine the relative bioavailability of the stiripentol sachet versus stiripentol capsule	31/12/2007	21/12/2007	10	Completed	N	N	-	0	-	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	BC-609 (ME2080)	III	N	N	N	E & S	valproic acid and clobazam	-	50 mg/kg/day	1 to 30 y old patients with Dravet's syndrome not adequately controlled with clobazam and valproate	30	30	60 wks	percentage of responders (>50% decrease in frequency of seizures per 30 days in evlauation period vs. baseline)	65%	primary endpoint result in patients <18 y old (n=20)
Clinical study	STP166	I	Y	Y	N	PK	-	different formulations of same product (sachet vs.	1000 mg (single dose)	Healthy male volunteers	24	24	single dose corss-over PK study	bioequivalence	1.10 (1.04-1.16) for AUCt, 1.23 (1.10-1.37) for Cmax	not bioequivanet, which is being addressed in the PI

Details of outstanding data N/A

Erivedge (vismodegib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	12/07/2013	491	Yes	NA	Art. 2(1)	During the procedure	No approved satisfactory treatment	677	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
SHH4476g	II	N	N	N	none	-	150 mg daily	Patients with advanced BCC	104 (96)	104	10 months	IRF determined objective response rate (ORR)	30.3% (95% CI 15.6-48.2%) for mBCC, 42.9% (95% CI 30.5-56.0%) for laBCC

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
The applicant should provide [..] a final SHH4476g (pivotal study) [..].	30/06/2014	Clinical study	Ongoing (some results in MAA)
[..] The applicant should provide a safety update of the pooled safety population	30/06/2014	Additional analysis	N/A
[..] The applicant should provide an interims analysis of study MO25616 of 500 patients with a potential one year follow up.	30/06/2014	Clinical study (interim)	Ongoing
The applicant should provide further data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of MO25616.	30/06/2015	Clinical study	Ongoing

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
The applicant should provide [..] a final SHH4476g (pivotal study) [..].	30/06/2014	26/06/2014	4	Completed	N	N	-	0	-	-
[..] The applicant should provide a safety update of the pooled safety population	30/06/2014	26/06/2014	4	Completed	N	N	-	0	-	-
[..] The applicant should provide an interims analysis of study MO25616 of 500 patients with a potential one year follow up.	30/06/2014	26/06/2014	4	Completed	N	N	-	0	-	-
The applicant should provide further data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of MO25616.	31/03/2016	-	-	Under assessment	N	Y	Due date changed in R/16	275	To ensure that all patients could be followed for at least 6 months	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	SHH4476g	II	N	N	N	E & S	none	-	150 mg daily	Patients with advanced BCC	104 (96)	104	39.1 months (at time of updated primary endpoint result - 16.6 months)	IRF determined objective response rate (ORR)	33.3% (95% CI 19.2-51.8%) for mBCC, 47.6% (95% CI 35.5-60.6%) for laBCC	Median OS 33.4 months for mBCC, NE for laBCC
Additional analysis	-	-	-	-	-	S	-	-	-	-	138	138	16.4 months	Safety	consistent with the known safety profile	

Clinical study (interim)	MO25616	II	N	N	N	E & S	none	-	150 mg daily	patients with locally advanced or metastatic BCC	501	501	12.0 months for mBCC and 8.3 months for laBCC	Safety	consistent with the known safety profile	

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	MO25616	II	Y	N	N	N	E & S	none	-	150 mg daily	patients with locally advanced or metastatic BCC	1215	1215	3.5 years	Safety

Fampyra (fampiridine)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Neurology	20/07/2011	483	NO	NA	Art. 2(1)	During re-examination	No approved satisfactory treatment	1952	Yes

Granting of standard MA

N/A

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
MS-F203	III	Y	Y	Y	none	placebo	10 mg b.i.d.	multiple sclerosis patients able to perform all required study procedures	301	229	14 weeks	proportion of 'consistent' responders	34.8% (vs. 8.3%, p<0.001)
MS-F204	III	Y	Y	Y	none	placebo	10 mg b.i.d.	multiple sclerosis patients able to perform all required study procedures	239	120	9 weeks	proportion of 'consistent' responders	42.9% (vs. 9.3%, p<0.001)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
To conduct a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment. A study report is to be submitted.	01/06/2016	Clinical study	New study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
To provide results of a double-blinded, placebo-controlled, long-term efficacy and safety study to investigate a broader primary endpoint clinically meaningful in terms of walking ability and to further evaluate the early identification of responders in order to guide further treatment based on a CHMP agreed protocol. An update of the progress in completing the obligation should be provided every 6 months.	31/12/2016	-	-	Due	minor	Y	Explicit requirement for CHMP agreement of the protocol included in procedure R/6 and 6-monthly progress reports included in procedure R/11 and due dates amended in R/6, R/11 and R/14 (eventually resulting in an extension).	213	In view of the two-step approach proposed (first conducting an exploratory study) + due to additionla consultation with CHMP on study design	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Notes
Clinical study	218MS305	III	Y	Y	Y	Y	E & S	none	placebo	10 mg b.i.d.	primary-progressive, secondary-progressive, progressive-relapsing, or relapsing-remitting MS of at least 3 months' duration, and with an EDSS score of 4 to 7, inclusive	590	295	24 weeks	Proportion of subjects who achieve a mean improvement on the MSWS-12 of ≥8 points from baseline over a 24-week treatment period	R/14 link

Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Ophthalmology[3]	17/02/2015	631	Yes	yes	Art. 2(1) and 2(3)	Initial MAA	No approved satisfactory treatment	135	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
HLSTM01	?	N	N	N	as required for transplant	-	transplant procedure	patients with limbal stem cell deficiency due to ocular burns	106	106	12 months	rate of success of transplantations, based on stable corneal epithelium without significant recurrence of neovascularisation	72.10%	Retrospective uncontrolled, case series-based observational study.

[3] Correction: typographical error corrected in word “Ophthalmology”

SOs imposed

Original description of SO scope	Due date	Type of SO	Status	Notes
Multinational, multicentre, prospective, open-label, uncontrolled interventional study (HLSTM03) to assess the efficacy and safety of autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns	31/12/2020	Clinical study	New study	Prospective study.

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
Multinational, multicentre, prospective, open-label, uncontrolled interventional study (HLSTM03) to assess the efficacy and safety of autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns	31/12/2020	-	-	Due	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Notes
Clinical study	HLSTM03	?	Y	N	N	N	E & S	as required for transplant	-	transplant procedure	patients with stable LSCD (at least 24 months after injury) secondary to unilateral or bilateral ocular burns (with at least 1-2 mm2 of undamaged limbus) with superficial neo-vascularization invading at least two corneal quadrants, severe impairment in visual acuity (score of 1/10th or less at the Snellen chart), and history of at least one failed surgical intervention	70	70	12 - 25 months + extension	percentage of clinically successful transplantations	Prospective study.

Humenza (Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted))

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	08/06/2010	240	NO	NA	Art. 2(2)	Initial MAA	For use in emergency situations	1020[4]	No

Granting of standard MA

N/A

[4] Please see European Public Assessment report for further information on safety information available at the time of authorisation.

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
GPF07	II	Y	Y	N	none	different A/H1N1 formulations with or without adjuvant	3.8 µg HA + AF03 or 7.5 µg HA + AF03 or 15 µg HA	healthy adults aged 18 to 60 years and elderly subjects aged >60 years	450	450	42 days	immunogenicity	various parameters (see EPAR)
GPF08	II	Y	Y	N	none	different A/H1N1 formulations with or without adjuvant	3.8 µg HA + AF03 or 7.5 µg HA + AF03 or 15 µg HA	healthy paediatric subjects aged 3 to 17 years	303	303	42 days	immunogenicity	various parameters (see EPAR)
GPF09	II	Y	Y	N	none	different A/H1N1 formulations with or without adjuvant, given as half or full doses	1.9 µg HA + ½ AF03 or 3.8 µg HA + ½ AF03 or 3.8 µg HA + AF03 or 7.5 µg HA	healthy paediatric subjects aged 6 to 35 months	401	401	21 days	immunogenicity	various parameters (see EPAR)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status	Notes
Independently of the cohort safety study (9 000 subjects), the MAH commits to implement a post-licensure prospective clinical safety study (N=3 000 subjects from 6 months of age). The RMP will be updated accordingly to reflect this study within 15 calendar days of the receipt of the opinion.	Initiation of the study by July 2010	Clinical study	New study	
The MAH commits to update the observational study protocol to screen for auto-antibodies those patients presenting visual or ocular events during the study follow-up	15/06/2010	Other measure	-	
The MAH commits to submit the data from pregnancy registry as described in the RMP.	PSUR	Clinical study	New study	
The MAH will submit the results of a prospective cohort safety study in at least 9,000 patients in different age groups, including immunocompromised subjects, in accordance with the protocol submitted with the Risk Management Plan.	as per protocol	Clinical study	New study	
The MAH commits to present a plan for the definition of the sources to collect safety data on immunocompromised patient within the prospective cohort safety study.	15/06/2010	Other measure	-	
The MAH will submit the results of the GBS surveillance study.	as per protocol	Clinical study	New study	Case control study of Guillain-Barre syndrome (GBS) cases as compared to controls without the disease, compared for their exposure to H1N1 vaccination.

SO amendments and fulfilment

N/A (MA withdrawn)

Details of data provided to fulfil SOs

N/A (MA withdrawn before removal of any SO)

Details of outstanding data

N/A (MA withdrawn)

Intelence (etravirine)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	28/08/2008	316	Yes	yes	Art. 2(1)	Initial MAA	Patient population with limited/no treatment options	2278	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
20/11/2013	II/31	in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients and in antiretroviral treatment-experienced paediatric patients from 6 years of age. The indication in adults is based on **week 48** analyses from 2 Phase III trials in highly pre-treated patients where INTELENCE was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir. The indication in paediatric patients is based on 48-week analyses of a single-arm, Phase II trial in antiretroviral treatment-experienced paediatric patients.

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
C206 (DUET-1)	III	Y	Y	Y	darunavir/r + optimised background regimen	placebo (+optimised background regimen)	200 mg BID	HIV-1 infected with limited to no treatment options (with at least 1 NNRTI mutation and with at least 3 primary PI mutations, HIV-1 RNA > 5000 copies/ml)	612	304	24 weeks	viral response (< 50 copies / mL)	55.9% vs. 38.6%
C216 (DUET-2)	III	Y	Y	Y	darunavir/r + optimised background regimen	Placebo (+optimised background regimen)	200 mg BID	HIV-1 infected with limited to no treatment options (with at least 1 NNRTI mutation and with at least 3 primary PI mutations, HIV-1 RNA > 5000 copies/ml)	591	295	24 weeks	viral response (< 50 copies / mL)	62.0% vs. 43.6%

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
The applicant will provide the final report of the pooled 48 weeks data from the two pivotal trials C206 and C216 (DUET-1 and DUET-2) to substantiate the durability of the virologic suppression achieved with etravirine and to further assess the safety profile of the compound. A proposal for an update of the SmPC and Package Leaflet based on the available data will be provided in parallel.	31/12/2008	Clinical studies (pooled)	Ongoing (some results in MAA)
The applicant commits to conduct a confirmatory study with the objective to provide reassurance on the extrapolation of the study results from the two pivotal studies (DUET-1 and DUET-2) to the combined use of etravirine with boosted PIs other than darunavir/ritonavir. To meet this objective an adequately powered clinical study should be designed to allow for a valid statistical comparison between combination therapy including etravirine + boosted PIs other than darunavir/ritonavir and standard triple therapy. The design should employ NNRTI resistance as part of the inclusion criteria, as well as individual stopping rules for non response and failure to treatment. A DSMB should be set-up. The applicant will provide the draft protocol of the study to the CHMP for agreement before study start. The applicant will provide regular updates on study progress within the PSURs. The final study report will be submitted for assessment whether the objective of the study has been met. The SmPC and Package Leaflet will be updated with the study results.	30/06/2012	Clinical study	New study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
The applicant will provide the final report of the pooled 48 weeks data from the two pivotal trials C206 and C216 (DUET-1 and DUET-2) to substantiate the durability of the virologic suppression achieved with etravirine and to further assess the safety profile of the compound. A proposal for an update of the SmPC and Package Leaflet based on the available data will be provided in parallel.	31/12/2008	21/12/2008	10	Completed	N	N	-	0	-	-
TMC125IFD0000003 is a retrospective observational study which will be conducted to describe the antiretroviral activity of and resistance to etravirine in combination with background regimens containing boosted PI other than darunavir/ritonavir, using clinical cohort data of HIV 1 infected patients. Following agreement with the CHMP on the protocol, the final results for the study should be provided to the CHMP no later than 2Q 2013.	30/06/2013	26/06/2013	4	Completed	Major	Y	In procedure R/15 confirmatory study on the combined use of etravirine with boosted PIs other than darunavir/ritonavir was replaced with a retrospective observational study (recommended in CHMP SA)	365	SO replaced with another study	Due to slow recruitment in the original study

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
Clinical studies (pooled)	C206, C216	III	Y	Y	Y	E	current ART regimen continued	placebo (+ current ART regimen)	200 mg BID	HIV-1 infected patients with at least 1 NNRTI mutation and with at least 3 primary PI mutations	1203	599	48 weeks	viral response (< 50 copies / mL)	60.6% vs. 39.7%
Clinical study	TMC125IFD0000003	IV	Y	N	N	E	background regimen containing DRV/rtv vs. a boosted PI other than DRV/rtv	different co-administered therapies	as per clinical practice	HIV-1 infected patients who started treatment with ETR for the first time with a background regimen containing a boosted PI	1115	1115	not reported	various (main objective virological activity and resistance)	Virologic response (HIV-1 RNA <50 copies/mL) at week 48 75.4% vs. 72.9%

Details of outstanding data N/A

Isentress (raltegravir)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	20/12/2007	176	Yes	Yes	Art. 2(1)	During the procedure	Patient population with limited/no treatment options	1214	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
14/07/2009	SW/13	in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy. Indication is based on safety and efficacy data from two double-blind, placebo-controlled trials of **48 weeks duration** in treatment-experienced patients.

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
018	III	Y	Y	Y	OBT	OBT + placebo	400 mg BID	Treatment experienced with plasma HIV RNA ≥1000 copies/ml and documented resistance to 3 ART classes, at least 16 years of age	350	232	16 weeks	Viral reponse (< 400 copies/ml)	76.7 % (vs. 40.7%)	24 week results also provided (N=350, primary endpoint result 75.4% vs. 39.0%)
019	III	Y	Y	Y	OBT	OBT + placebo	400 mg BID	Treatment experienced with plasma HIV RNA ≥1000 copies/ml and documented resistance to 3 ART classes, at least 16 years of age	349	230	16 weeks	Viral reponse (< 400 copies/ml)	77.0% (vs. 42.9%)	24 week results also provided (N=349, primary endpoint result 74.8% vs. 41.2%)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status	Notes
To further support the benefit:risk assessment, the Applicant commits to provide CHMP with the 48-week safety and efficacy data from the ongoing Phase III Protocol 018 (A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0518 in Combination With an Optimized Background Therapy (OBT), Versus Optimized Background Therapy Alone, in HIV-Infected Patients With Documented Resistance to at Least 1 Drug in Each of the 3 Classes of Licensed Oral Antiretroviral Therapies) for review. [..]	31/03/2008	Clinical study	Ongoing (some results in MAA)	Minor delay is submission (from 31/01/2008 to 11/04/20008) agreed separately in writing, but without the update of Annex II.
[..] To further support the benefit:risk assessment, the Applicant commits to provide CHMP with the 48-week safety and efficacy data from [..] the ongoing Phase III Protocol 019 (A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0518 in Combination With an Optimized Background Therapy (OBT), Versus Optimized Background Therapy Alone, in HIV-Infected Patients With Documented Resistance to at Least 1 Drug in Each of the 3 Classes of Licensed Oral Antiretroviral Therapies) for review.	31/03/2008	Clinical study	Ongoing (some results in MAA)	Minor delay is submission (from 31/01/2008 to 11/04/20008) agreed separately in writing, but without the update of Annex II.
The Applicant commits to provide the CHMP with detailed specific plans for monitoring of resistance with frequent reporting intervals.	31/12/2007	Other measure	New activity	
The Applicant commits to provide the CHMP with the full protocol for an observational post-authorisation safety study as specified in the RMP for assessment prior to study initiation.	31/03/2008	Other measure	New activity	Study size for subjects receiving CMA product approximate (1000 person-years / 5 years expected exposure). Resulsts not part of the SO.

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
To further support the benefit risk assessment, the MAH has provided the CHMP with the 48-week safety and efficacy data from the ongoing Phase III Protocol 018 (A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0518 in Combination With an Optimized Background Therapy (OBT), Versus Optimized Background Therapy Alone, in HIV Infected Patients With Documented Resistance to at Least 1 Drug in Each of the 3 Classes of Licensed Oral Antiretroviral Therapies) for review.	31/03/2008	02/04/2008	-2	Completed	N	N	-	0	-	-

To further support the benefit risk assessment, the MAH has provided the CHMP with the 48-week safety and efficacy data from the ongoing Phase III Protocol 019 (A Multicenter, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0518 in Combination With an Optimized Background Therapy (OBT), Versus Optimized Background Therapy Alone, in HIV-Infected Patients With Documented Resistance to at Least 1 Drug in Each of the 3 Classes of Licensed Oral Antiretroviral Therapies) for review	31/03/2008	02/04/2008	-2	Completed	N	N	-	0	-	-
The MAH commits to provide the CHMP with detailed specific plans for monitoring of resistance with frequent reporting intervals.	31/10/2008	22/10/2008	9	Completed	N	Y	Due date extended in procedure R/08	305	Initial proposal from MAH not accepted by the CHMP - need to update the plan for proposed actions	-
The Applicant commits to provide the CHMP with the full protocol for an observational post-authorisation safety study as specified in the RMP for assessment prior to study initiation.	31/03/2008	31/03/2008	0	Completed	N	N	-	0	-	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	018	III	Y	Y	Y	E & S	OBT	OBT + placebo	400 mg BID	Treatment experienced with plasma HIV RNA ≥1000 copies/ml and documented resistance to 3 ART classes, at least 16 y.o.	350	232	48 wks	Viral reponse (< 400 copies/ml)	73.3 % vs. 36.4 %	
Clinical study	019	III	Y	Y	Y	E & S	OBT	OBT + placebo	400 mg BID	Treatment experienced with plasma HIV RNA ≥1000 copies/ml and documented resistance to 3 ART classes, at least 16 y.o.	349	230	48 wks	Viral reponse (< 400 copies/ml)	70.4 % vs. 37.8 %	
Other measure	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Detailed plans for monitoring of resistance

Other measure	EuroSIDA/ protocol 058	IV	Y	N	N	S	routine clinical practice	historical cohort of HIV-infected patients who started a new anti-retroviral medication	routine clinical use	routine clinical use	1,000 person-years (expected)	1,000 person-years (expected)	5 years expected	incidence rates and characteristics of medical outcomes in patients treated with raltegravir	results not part of SO	Results not part of the SO.

Details of outstanding data N/A

Pandemic influenza vaccine H5N1 MedImmune (pandemic influenza vaccine (h5n1) (live attenuated, nasal))

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	20 May 2016	373	NO	NA	Art. 2(2)	Initial MAA	For use in emergency situations	55523	No

Granting of standard MA

N/A

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
CIR 217	I	Y	N	N	none	comparision between two dose levels	H5N1 A/Vietnam/1203/2004 ca vaccine at 10¬6.7 TCID50 (low dose) and 10¬7.5 TCID50 (high dose) 4 to 8 weeks apart	healthy adults 18 to 49 years of age	42	42	Follow-up visit at 28-35 days	Immunogenicity	various parameters (see EPAR)
CIR 239	I	N	N	N	none	-	twice 10¬7.5 TCID50 H5N1 A/Hong Kong/213/2003 vaccine	healthy adults 18 to 49 years of age, H5N1-seronegative (H5 HAI ≤ 1:8)	17	17	follow-up visit at 28 days	Immunogenicity	various parameters (see EPAR)
CIR 277	I	Y	Y	N	none	comparisoin between patient groups with different previous vaccination status	45 Microgram Dose of inactivated, non-adjuvanted H5N1 Vaccine	healthy adults 22 to 54 years of age, H5N1 and H7N3 LAIV Recipients and LAIV Naive Individuals	69	69	56 days	Immunogenicity	various parameters (see EPAR)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
Non-interventional post-authorisation safety study (PASS) in order to further investigate the tolerability of Pandemic influenza vaccine H5N1 MedImmune and estimate the incidence of adverse reactions of special interest in children and adolescents. The MAH should conduct an observational prospective cohort safety study in a large sample of children and adolescents from 12 months to less than 18 years of age during the next declared pandemic. The MAH should submit the final results of this study.	After declaration of a pandemic and implementation of the vaccine	Clinical study	New study
In order to further corroborate the efficacy of Pandemic influenza vaccine H5N1 MedImmune, the MAH should conduct an observational effectiveness study in community dwelling children and adolescents from 12 months to less than 18 years of age against laboratory confirmed influenza during the next declared pandemic. The MAH should submit the final results of this study.	After declaration of a pandemic and implementation of the vaccine	Clinical study	New study
In order to further investigate the safety and reactogenicity of Pandemic influenza vaccine H5N1 MedImmune, the MAH should conduct an open-label single arm interventional study to evaluate the safety and immunogenicity of P/LAIV in children and adolescents from 12 months to less than 18 years of age during the next declared pandemic. The MAH should submit the final results of this study.	After declaration of a pandemic and implementation of the vaccine	Clinical study	New study
In order to define the shelf life of Pandemic influenza vaccine H5N1 MedImmune on a strain-specific basis, the MAH should generate strain-specific stability data for the actual pandemic strain. The MAH should submit the final results of this study.	At next pandemic variation	Quality	-

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
Non-interventional post-authorisation safety study (PASS) in order to further investigate the tolerability of Pandemic influenza vaccine H5N1 MedImmune and estimate the incidence of adverse reactions of special interest in children and adolescents. The MAH should conduct an observational prospective cohort safety study in a large sample of children and adolescents from 12 months to less than 18 years of age during the next declared pandemic. The MAH should submit the final results of this study.	After declaration of a pandemic and implementation of the vaccine	-	-	Due	N	N	-	0	-	-
In order to further corroborate the efficacy of Pandemic influenza vaccine H5N1 MedImmune, the MAH should conduct an observational effectiveness study in community dwelling children and adolescents from 12 months to less than 18 years of age against laboratory confirmed influenza during the next declared pandemic. The MAH should submit the final results of this study.	After declaration of a pandemic and implementation of the vaccine	-	-	Due	N	N	-	0	-	-
In order to further investigate the safety and reactogenicity of Pandemic influenza vaccine H5N1 MedImmune, the MAH should conduct an open-label single arm interventional study to evaluate the safety and immunogenicity of P/LAIV in children and adolescents from 12 months to less than 18 years of age during the next declared pandemic. The MAH should submit the final results of this study.	After declaration of a pandemic and implementation of the vaccine	-	-	Due	N	N	-	0	-	-

In order to define the shelf life of Pandemic influenza vaccine H5N1 MedImmune on a strain-specific basis, the MAH should generate strain-specific stability data for the actual pandemic strain. The MAH should submit the final results of this study.	At next pandemic variation	-	-	Due	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	-	IV	N	N	N	N	S	none	none	as per clinical practice	children and adolescents from 12 months to less than 18 years of age	4000	4000	up to 6 months	tolerability + incidence of adverse reactions of special interest
Clinical study	-	IV	N	N	N	N	E	none	none	as per clinical practice	community dwelling children and adolescents from 12 months to less than 18 years of age	not specified	not specified	not specified	effectiveness (laboratory confirmed influenza)
Clinical study	-	?	Y	N	N	N	Immunogenicity and	none	none	not specified	children and adolescents from 12 months to less than 18 years of age	not specified	not specified	not specified	safety and immunogenicity
Quality	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Pixuvri (pixantrone dimaleate)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	10/05/2012	456	Yes	No	Art. 2(1)	During the procedure	No approved satisfactory treatment	348	Yes

Granting of standard MA

N/A

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
PIX301	III	Y	Y	Partial	none	Other Chemotherapeutic Agents (investigator's choice of vinorelbine, oxaliplatin, ifosfamide, etoposide, or mitoxantrone; gemcitabine and rituximab (CD 20+ patients only))	85 mg/m2 on days 1, 8, and 15 of 28-day cycles	Patients with Relapsed/Refractory Aggressive (de novo or transformed) Non-Hodgkin's Lymphoma (3rd line), with measurable disease, prior treatment with ≥ 2 chemotherapy regimen and sensitivity to the last anthracycline/ anthracenedione regimen	140	70	3.8 months (duration of therapy)	Complete response (CR) and complete response unconfirmed (Cru) rate as assessed by the Independent Assessment Panel (IAP)	20 % vs. 5.7%; difference 14.3% (95% CI 3.5% - 25.1%)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
To conduct a randomised controlled Phase 3 study (PIX306) of pixantrone-rituximab vs gemcitabine-rituximab in patients with aggressive B-cell NHL, who failed front line CHOP-R who are not eligible for autologous stem cell transplant (ASCT) (2nd line) or failed ASCT (3rd or 4th line). A clinical study report should be submitted.	30/06/2015	Clinical study	New study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons	Notes
To conduct a randomised controlled Phase 3 study (PIX306) of pixantrone-rituximab vs gemcitabine-rituximab in patients with aggressive B-cell NHL, who failed front line CHOP-R who are not eligible for autologous stem cell transplant (ASCT) (2nd line) or failed ASCT (3rd or 4th line). A clinical study report should be submitted.	30/11/2016	-	-	Due	N	Y	No change in scope. Due date extended in procedure R/20	519	Delays in opening new sites and enrolment	-	Primary endpoint changed after authorisation without affecting the scope of SO in Annex II (PFS instead of OS, but OS maintained as secondary endpoint). After report data cut-off the due date extended further till 31/12/2018.

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	PIX306	III	Y	Y	Y	Partial	E & S	rituximab	gemcitabine-rituximab	85 mg/m2 on days 1, 8, and 15 of 28-day cycles	patients with aggressive B-cell NHL, who failed front line CHOP-R who are not eligible for autologous stem cell transplant (ASCT) (2nd line) or failed ASCT (3rd or 4th line)	350	175	Up to six 28-day cycles + follow-up	Progression free survival

Prezista (darunavir)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	12/02/2007	316	Yes	No	Art. 2(1)	Initial MAA	Patient population with limited/no treatment options	1783	No

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
16/12/2008	R/22	Co-administered with 100 mg ritonavir in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in **treatment-experienced** adult patients**, including those that have been highly pre-treated** ~~**who failed more than one regimen containing a protease inhibitor**~~. Careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
C202 (POWER 1)	IIb	Y	Y	Partial	low dose ritonavir + background therapy	different strengths of CMA product + optimised backgroud regimen arm	DRV/r: 400/100 mg q.d., 800/100 mg q.d., 400/100 mg b.i.d. or 600/100 mg b.i.d.	3-class-experienced HIV-1 infected patients with HIV-1 RNA > 1000 copies/ml on PI containing regimen, excluding patients co-infected with viral hepatitis	201	159	24 wks	virologic response at w24 (at least 1.0 log10 decrease in viral load vs. baseline)	45 - 61.5 % (vs. 14.3)	Effect size for 600/100 mg b.i.d. group in updated analysis with 66/61 subjects 63.6% (vs. 13.1), and at week 72 with N=65 was 49%
C213 (POWER 2)	IIb	Y	Y	Partial	low dose ritonavir + background therapy	different strengths of CMA product + optimised backgroud regimen arm	DRV/r: 400/100 mg q.d., 800/100 mg q.d., 400/100 mg b.i.d. or	3-class-experienced HIV-1 infected patients with HIV-1 RNA > 1000 copies/ml on PI containing	301	241	24 wks	virologic response at w24 (at least 1.0 log10 decrease in viral load vs.	70 - 76.7 % (vs. 25.0)	Effect size for 600/100 mg b.i.d. group in updated analysis with

							600/100 mg b.i.d.	regimen				baseline)		65/63 subjects 76.9% (vs. 28.6), and at week 72 with N=65 was 69%
C215/C208 (POWER 3)	IIb	N	N	N	low dose ritonavir + background therapy	N/A	DRV/rtv 600/100 mg b.i.d.	Treatment experienced HIV-1 infected subjects who might derive benefit from DRV therapy, as judged by the investigator	324	324	48 weeks	virologic response at w48 (at least 1.0 log10 decrease in viral load vs. baseline)	60.80%	Result for de novo patient group

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
1. The final study report from the interaction study TMC114-C163 (A Phase I, open-label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between rifabutin and TMC114, coadministered with low-dose ritonavir, at steady-state) should be submitted.	31/10/2007	Clinical study	Ongoing
2. The final study report from the interaction study TMC114-C123 (A Phase I, open label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between didanosine and TMC114, coadministered with low-dose ritonavir, at steady-state) should be submitted.	30/04/2007	Clinical study	Ongoing
3. The 48 week (primary analysis) final study report from study TMC114-C214 (A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of TMC114/RTV versus LPV/RTV in treatment-experienced HIV-1 infected subjects) should be provided and should contain an analysis assessing the effect of coadministered nevirapine and efavirenz on darunavir; in addition estimation of intra-subject variability.	31/07/2007	Clinical study (interim)	Ongoing
[..] The week 96 final study report from study TMC114-C214 should be provided.	30/09/2008	Clinical study	Ongoing
4. The week 96 final study report from study TMC114-C202 (A Phase II randomized, controlled, partially blinded trial to investigate dose response of TMC114/RTV in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV) should be submitted.	31/07/2007	Clinical study (interim)	Ongoing (some results in MAA)
[..] The week 144 final study report from study TMC114-C202 should be submitted.	30/09/2008	Clinical study	Ongoing (some results in MAA)
5. The week 96 final study report from study TMC114-C213 (A Phase II randomized, controlled, partially blinded trial to investigate dose-response of TMC114/RTV in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV) should be submitted.	30/04/2007	Clinical study (interim)	Ongoing (some results in MAA)

[..] The week 144 final study report from study TMC114-C213 should be submitted.	31/03/2008	Clinical study	Ongoing (some results in MAA)
6. The week 96 final study report from study TMC114-C215 (An open label trial of TMC114/RTV in HIV-1 infected, treatment experienced subjects) should be submitted.	31/12/2007	Clinical study (interim)	Ongoing (some results in MAA)
[..] The week 144 final study report TMC114-C215 should be submitted.	30/09/2008	Clinical study	Ongoing (some results in MAA)
7. The cut-off Q2 2007 study report from study TMC114-C208 (An open label trial of TMC114/RTV in HIV-1 infected subjects who were randomized in the trials TMC114-C201, TMC114-C207 or in sponsor selected Phase I trials) should be submitted.	31/12/2007	Clinical study	Ongoing (some results in MAA)
8. The cut-off Q2 2007 study report from study TMC114-C209 (Open-label safety study of TMC114 in combination with low dose RTV and other ARVs in highly experienced HIV-1 infected patients with limited or no treatment options) should be submitted.	31/12/2007	Clinical study	Ongoing
9. The data from the darunavir treatment arm that do not receive the candidate NNRTI (TMC125) for the two following studies should be provided: - week 24 (primary analysis) final study report from study TMC125-C206 (A Phase III randomized, double-blinded, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC125 as part of an ART including TMC114/RTV and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options) - week 24 (primary analysis) final study report from study TMC125-C216 (A Phase III randomized, double-blinded, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC125 as part of an ART including TMC114/RTV and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options) should be submitted.	31/10/2007	Clinical studies (pooled)	Ongoing

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
[Former SOB: The final study report from the interaction study TMC114 C163 (A Phase I, open-label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between rifabutin and DRV, co-administered with low-dose ritonavir, at steady state)]	-	N/A	N/A	Downgraded	downgraded	N/A	In R/8 downgraded to a FUM in the light of otherwise accumulated evidence of efficacy and safety on Prezista	N/A	-	In the light of otherwise accumulated evidence of efficacy and safety
2 The final study report from the interaction study TMC114 C123 (A Phase I, open label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between didanosine and TMC114, coadministered with low-dose ritonavir, at steady-state) should be submitted.	30/04/2007	10/05/2007	-10	Completed	N	N	-	0	-	-

The data of the 48 week (primary analysis) final study report from study TMC114-C214 (A randomized, controlled, open-label trial to compare the efficacy, safety and tolerability of TMC114/RTV versus LPV/RTV in treatment experienced HIV-1 infected subjects) should be presented within a Type II variation to extend the indication to the patient population studied, as appropriate	28/02/2008	26/02/2008	2	Completed	minor	Y	In R/8: removal of explicit reference to assessment of effects of nevirapine and efavirenz and of intra-subject variability, addition of reference to possible extension of indication (in view of the relevance of this information to the indication), also due date extended	212	due to need for a follow-up variation after submission of study report	-
[Former SOB: The week 96 final study report from study TMC114-C214 should be provided.]	-	N/A	N/A	Downgraded	downgraded	N/A	Downgraded to FUM in R/8 since "the 96 weeks data are no longer considered relevant as a SOB within the context of this MA (highly	N/A	-	The 96 weeks data are no longer considered relevant as a SOB within the context of this MA

							experienced patients). Data remain of relevance for expansion of present indication."			(highly experienced patients). Data remain of relevance for expansion of present indication.
4 The week 96 final study report from study TMC114 C202 (A Phase II randomized, controlled, partially blinded trial to investigate dose response of TMC114/RTV in 3 class-experienced HIV 1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV) should be submitted.	31/07/2007	01/08/2007	-1	Completed	N	N	-	0	-	-
The week 144 final study report from study TMC114-C202 (A Phase II randomized, controlled, partially blinded trial to investigate dose response of TMC114/RTV in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of	30/09/2008	01/08/2008	60	Completed	N	N	-	0	-	-

TMC114/RTV) should be submitted										
5 The week 96 final study report from study TMC114 C213 (A Phase II randomized, controlled, partially blinded trial to investigate dose-response of TMC114/RTV in 3-class-experienced HIV 1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV) should be submitted.	30/04/2007	27/04/2007	3	Completed	N	N	-	0	-	-
The week 144 final study report from study TMC114-C213 (A Phase II randomized, controlled, partially blinded trial to investigate dose-response of TMC114/RTV in 3-class-experienced HIV-1 infected subjects, followed by an open-label period on the recommended dose of TMC114/RTV) should be submitted	31/03/2008	01/04/2008	-1	Completed	N	N	-	0	-	-
6 The week 96 final study report from study TMC114 C215 (An open label trial of	31/12/2007	01/08/2007	152	Completed	N	N	-	0	-	-

TMC114/RTV in HIV 1 infected, treatment experienced subjects) should be submitted.										
The week 144 final study report from study TMC114-C215 (An open label trial of TMC114/RTV in HIV-1 infected, treatment experienced subjects) should be submitted	30/09/2008	01/08/2008	60	Completed	N	N	-	0	-	-
[Former SOB: The cut-off Q2 2007 study report from study TMC114 C208 (An open label trial of TMC114/RTV in HIV-1 infected subjects who were randomized in the trials TMC114 C201, TMC114 C207 or in sponsor selected Phase I trials) should be submitted.]	-	N/A	N/A	Downgraded	downgraded	N/A	In R/8 downgraded to a FUM since "the results of this study are not expected to modify the outcome of the other Phase IIb studies included in this renewal application"	N/A	-	Results of this study are not expected to modify the outcome of the other Phase IIb studies
The cut-off Q2 2007 study report from study TMC114-C209 (Open-label safety study of DRV in combination with low dose ritonavir and other ARVs in highly experienced HIV-1 infected patients with	31/12/2007	05/12/2007	26	Completed	N	N	-	0	-	-

limited or no treatment options) should be submitted.										
Based on the darunavir treatment arms [that do not receive the candidate NNRTI (TMC125)] of studies TMC125-C206 and -C216, the MAH should submit an integrated safety analysis of the 24 week data, and propose, if appropriate, the necessary changes to section 4.8 of the PREZISTA SPC.	31/01/2008	16/01/2008	15	Completed	minor	Y	In R/8 reworded, requesting instead of two final study reports to provide integrated safety analysis for these 2 studies in a sub-group of study population, due date also amended	92	to conduct targeted pooled safety analysis in addition to the submission of study reports	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	TMC114-C163	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Clinical study	TMC114-C123	I	Y	Y	N	PK	Low dose ritonavir, didanosine	PK interaction study	DRV/r 600/100 mg BID	healthy volunteers	17	17	14 days	PK	No clinical significant differences were observed in the pharmacokinetics of darunavir and ritonavir after co-administration with didanosine	
Clinical study	TMC114-C214	III	Y	Y	N	E & S	ritonavir + optimised background regimen	lopinavir/ritonavir + optimised background regimen	DRV/r 600/100 mg BID	treatment-experienced HIV-1 infected subjects	595	298	48 weeks	Virological response at 48 weeks	78.2 % (vs. 68.6%)	

Clinical study	TMC114-C214	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical study (interim)	TMC114-C202	IIb	Y	Y	N	E & S	ritonavir, optimised background regimen	optimsed background regimen	DRV/r 600/100 mg BID	3-class experienced HIV-1 infected subjects	319	258	96 weeks	Virologic response at week 96	43.4% (vs. 6.6%)	
Clinical study	TMC114-C202	IIb	Y	Y	N	E & S	ritonavir, optimised background regimen	optimsed background regimen	DRV/r 600/100 mg BID	3-class experienced HIV-1 infected subjects	319	258	144 weeks	Virologic response at week 144	37.6% (vs. 6.6%)	
Clinical study (interim)	TMC114-C213	IIb	Y	Y	N	E & S	ritonavir, optimised background regimen	optimised background regimen	DRV/r 600/100 mg BID	3-class experienced, HIV-1 infected subjects	318	255	96 weeks	Virologic response at week 96	61.60%	Report pertains to open-label part of the study
Clinical study	TMC114-C213	IIb	Y	Y	N	E & S	ritonavir, optimised background regimen	optimised background regimen	DRV/r 600/100 mg BID	3-class experienced, HIV-1 infected subjects	318	255	144 weeks	Virologic response at week 144	58%	Report pertains to open-label part of the

																study
Clinical study (interim)	TMC114-C215	IIb	N	N	N	E & S	ritonavir, other ARVs	-	DRV/r 600/100 mg BID	HIV-1 infected subjects who failed previous trial treatment	452 (422)	452	96 weeks	safety	N/A for safety (virologic response at w 96 in de novo group 52.2%)	
Clinical study	TMC114-C215	IIb	N	N	N	E & S	ritonavir, other ARVs	-	DRV/r 600/100 mg BID	HIV-1 infected subjects who failed previous trial treatment	452 (432)	452	144 weeks	safety	N/A for safety (virologic response at w 114 in de novo group 39.1%)	
Clinical study	TMC114-C208	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Clinical study	TMC114-C209	III	N	N	N	E & S	ritonavir, other ARVs	-	DRV/r 600/100 mg BID	Highly ARV experienced HIV-1 infected subjects who have failed and exhausted treatment	262	262	45.6 weeks	safety	N/A for safety	

										options based on commercially available ARVs						
Clinical studies (pooled)	TMC114-C206 and TMC114-C216	III	Y	Y	Y	S	ritonavir, optimised background regimen	N/A for required analysis	DRV/r 600/100 mg BID	Treatment experienced (i.e., ≥ 1 NNRTI) resistance associated and ≥ 3 PI mutations, plasma viral load > 5000 copies/mL) HIV-1 infected subjects (subjects with limited to no treatment options)	604	604	31 weeks	safety	N/A for safety	

Details of outstanding data N/A

Sirturo (bedaquiline)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Infectious diseases	05/03/2014	456	Yes	yes	Art. 2(1) and 2(3)	Initial MAA	Patient population with limited/no treatment options	645	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
C208	II	Y	Y	Y	background regimen including an injectable, a fluoroquinolone, and other anti-TB drugs	placebo + background regimen including an injectable, a fluoroquinolone, and other anti-TB drugs	400 mg once daily (q.d.) for 2 weeks, 200 mg 3 times/week (t.i.w.) for following 22 weeks	patients with MDR or pre-XDR TB	160 (132)	79	24 weeks (+ follow up for other endpoints)	Time to culture conversion	83 vs. 125 days	culture conversion rates at week 24 79% vs. 58%

SOs imposed

Original description of SO scope	Due date	Type of SO	Status	Notes
The MAH will evaluate additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory phase III study) following an agreed protocol. Annual updates on study progress in the frame of annual renewal submissions, Interim IDMC analysis when half of the patients reach W68: 1Q 2018, W68 primary analysis - Clinical Study Report 3Q 2020, W92 analysis - Clinical Study Report 1Q 2021, W132 final analysis - Clinical Study Report November 2021	30/11/2021	Clinical study	Ongoing	Submission of interim analyses not shown here as separate obligations

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
The MAH will evaluate additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory phase III study) following an agreed protocol. Annual updates on study progress in the frame of annual renewal submissions, Interim IDMC analysis when half of the patients reach W76: 2Q 2018, W76 primary analysis - Clinical Study Report 4Q 2020, W132 analysis - Clinical Study Report November 2021	30/11/2021	-	-	Due	minor	N	Primary analysis changed from W68 to W76 and timlienes for interim reports amended in procedure II/2	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	STREAM stage 2	III	Y	Y	Y	N	E & S	BR for MDR-TB	BR for MDR-TB	400 mg once daily (q.d.) for 2 weeks, 200 mg 3 times/week (t.i.w.) for following weeks	Patients with multi-drug resistance tuberculosis (MDR-TB)	1155	660	Primary analysis at week 68, follow-up to week 132	proportion of subjects with favorable treatment outcome (confirmed culture conversion)

Sutent (sunitinib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	19/07/2006	211	NO	NA	Art. 2(3)	During the procedure	Improved treatment effect and/or safety vs. available therapies	588	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
11/01/2007	II/01	treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance treatment of advanced and/or metastatic renal cell carcinoma (MRCC) ~~**after failure of interferon alfa or interleukin-2 therapy**~~

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
A6181004	III	Y	Y	Y	-	placebo	50 mg QD for 4 weeks in 6 week cycles	patients with malignant GIST who had tumours that were resistant to imatinib, or who were intolerant of imatinib	312	207	84 d	Time to progression	27.3 wks (vs. 6.4) HR 0.329; 95% CI: 0.233-0.466
A6181006	II	N	N	N	-	N/A	50 mg daily for 4 weeks in 6-week cycles	MRCC not amenable to therapy with curative intent + failure during or intolerance to previous cytokine therapy	106	106	23.6 w	objective response rate	25.50%
RTKC-0511-014	II	N	N	N	-	N/A	50 mg daily for 4 weeks in 6-week cycles	MRCC not amenable to therapy with curative intent + failure during or intolerance to previous cytokine therapy	63	63	34 w	objective response rate	25.40%

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
The Marketing Authorisation Holder commits to provide results of an ongoing study in cytokine-naïve patients with metastatic renal cell carcinoma.	30/09/2006	Clinical study	Ongoing

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
The Marketing Authorisation Holder commits to provide results of an ongoing study in cytokine-naïve patients with metastatic renal cell carcinoma.	30/09/2006	07/08/2006	54	Completed	N	N	N/A	0	-	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
Clinical study	A6181034	III	Y	Y	N	E & S	-	interferon-alfa	50 mg daily for 4 weeks in 6-week cycles	cytokine-naïve patients with metastatic renal cell carcinoma	750	375	337 d (+28 d FU)	progression-free survival based on blinded core imaging laboratory assessment	47.3 wks (vs. 22.0) HR 0.415 (95% CI: 0.320-0.539)

Details of outstanding data N/A

Tagrisso (osimertinib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	02/02/2016	175	NO	NA	Art. 2(1)	Initial MAA	Improved treatment effect and/or safety vs. available therapies	1221	No

Granting of standard MA

N/A

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
AURA extension	II	N	N	N	none	-	80 mg daily	Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC	201 (199)	201	at least 6 months follow up from first dose	Confirmed objective response rate (ORR)	61.3 % (95% CI 54.2-68.1%)
AURA 2	II	N	N	N	none	-	80 mg daily	Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC	210 (199)	210	at least 6 months follow up from first dose	Confirmed objective response rate (ORR)	70.9 % (95% CI 64.0-77.1%)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
In order to further confirm the efficacy and safety of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, the applicant should submit the clinical study report of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy.	30/06/2017	Clinical study	ongoing

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
In order to further confirm the efficacy and safety of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, the applicant should submit the clinical study report of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy.	30/06/2017	-	-	Due	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	AURA3	III	Y	Y	Y	N	E & S	none	platinum-based doublet chemotherapy	80 mg daily	patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC	410	273	until disease progression or longer	PFS using investigator assessments

Translarna (ataluren)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Neurology	31/07/2014	547	Yes	No	Art. 2(1) and 2(3)	Initial MAA	No approved satisfactory treatment	588	No

Granting of standard MA

N/A

Main/pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
PTC124-GD-007-DMD	II	Y	Y	Y	none	placebo	10-10-20 mg/kg or 20-20-40 mg/kg daily (in 3 doses)	Subjects with Nonsense-Mutation-Mediated Duchenne and Becker Muscular Dystrophy with ability to walk ≥75 meters unassisted	174	117	48 weeks	Change in 6-minute walk distance from baseline to Week 48	Mean (SD): high dose -41.8 (89.2), low dose -12.9 (72.0), placebo -42.6 (90.1)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
To complete a multicentre, randomised, double-blind, placebo-controlled confirmatory study to examine efficacy and safety of ataluren 10, 10, 20 mg/kg in patients with non-sense mutation Duchenne muscular dystrophy (Study PTC124-GD-020-DMD)	31/12/2015	Clinical study	ongoing

SO amendments and fulfilment

Latest/final description of SO scope	Latest/final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
To complete a multicentre, randomised, double-blind, placebo-controlled confirmatory study to examine efficacy and safety of ataluren 10, 10, 20 mg/kg in patients with non-sense mutation Duchenne muscular dystrophy (Study PTC124-GD-020-DMD)	31/12/2015	08/01/2016	-8	Under assessment[5]	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

[5] After the cut-off date for this report the SO was removed from Annex II to the MA and a new SO was imposed

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	PTC124-GD-020-DMD[6]	III	Y	Y	Y	Y	E & S	none	placebo	10, 10, 20 mg/kg daily (in 3 doses)	Patients with non-sense mutation Duchenne muscular dystrophy	220	110	48 weeks	Change in 6MWD

[6] Study results under assessment at the data cut-off time for this report. See also 'SO amendments and fulfilment' above

Tyverb (lapatinib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	10/06/2008	547	Yes	No	Art. 2(1)	During the procedure	Improved treatment effect and/or safety vs. available therapies	1149	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
17/02/2015	II/37	treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2): • in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting, • in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy, • in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor. No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor in this patient population

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
EGF100151	III	Y	Y	N	capecitabine (2000 mg/m2/day on days 1-14 every 21 days)	capecitabine alone (2500 mg/m2/day on days 1-14 every 21 days)	1250 mg once daily	ErbB2 over-expressing, locally advanced or metastatic breast cancer patients, who were progressing after prior treatment that included anthracyclines, taxanes and trastuzumab	399	198	21.6 w (lapatinib treatment)	Median time to progression (disease progression or death due to breast cancer prior to progression)	27.1 w (vs. 18.6 w)	TTP by an independent review committee based on radiological (CT or MRI) results. No statistically significant effect has been observed on overall survival

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
To perform and submit an updated analysis of survival data for study EGF100151. A data cut-off date of August 2008 will be applied, with the results of the analysis to be submitted by Dec 2008.	31/12/2008	Clinical study	Ongoing (some results in MAA)
To conduct a Phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate, trastuzumab-containing control arm. The study protocol will be finalised and submitted to the EMEA by July 2008. The final study report for the trial will by submitted by May 2013.	31/05/2013	Clinical study	New study

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
To perform and submit an updated analysis of survival data for study EGF100151. A data cut-off date of August 2008 will be applied, with the results of the analysis to be submitted by Dec 2008.	31/12/2008	10/12/2008	21	Completed	N	N	-	0	-	-
To provide comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO)	31/12/2014	03/10/2014	89	Completed	Major	Y	Revised in R/28: from dedicated randomised clinical study to evaluate the incidence of brain metastases (terminated due to lower than expected incidence of CNS metastases) to combination of data from 3 studies on incidence CNS metastases	579	SO replaced with another activity	Original study terminated due to lower than expected rate of CNS metastases

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	EGF100151	III	Y	Y	N	E & S	capecitabine (2000 mg/m2/day on days 1-14 every 21 days)	capecitabine alone (2500 mg/m2/day on days 1-14	1250 mg once daily	women with ErbB2 overexpressing advanced or metastatic breast cancer who had received prior treatment with anthracyclines, taxanes and trastuzumab	408	207	not reported	hazard ratio for overall survival	0.87 (95% CI 0.71 - 1.08, p=0.210)	

Clinical studies (pooled)	EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO)	III	Y	Y	Partial	E	combination taxane-based chemotherapy / full supportive care / full supportive care	trastuzumab / placebo / trastuzumab	1250 mg / 1500 mg / 1000 - 1500 mg once daily	women with documented evidence of HER2 positive MBC who had received no prior chemotherapy or HER2 targeted therapy in the metastatic setting / Women with early-stage HER2-positive breast cancer who had not been previously treated with trastuzumab / patients with early stage non-metastatic HER2-positive breast cancer	652 / 3147 / 6281	6081	36.6 w / not reported (5 years median observation period for patients alive at the end of study) / not reported (median treatment exposure 33.9 - 51.9)	incidence rate of CNS metastasis at first progression / incidence of CNS as site of first recurrence / incidence of CNS metastases as the first site of breast cancer recurrence	13% vs. 16% / <1% vs. 1% / 3% vs. 3%	Primary endpoint for the specific requested analysis (not primary endpoint of the studies)

Details of outstanding data

N/A

Vectibix (panitumumab)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	03/12/2007	484	NO	NA	Art. 2(1)	During re-examination	Ability to selects patients that will respond	1304	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
15/01/2015	R/64	treatment of adult patients with wild-type ~~K~~RAS **~~EGFR expressing~~** metastatic colorectal cancer: **· in first-line in combination with FOLFOX.** **· in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).** · as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
20020408	III	Y	Y	N	best supportive care	best supportive care only	6 mg/kg every two weeks	Patients with EGFR expressing metastatic colorectal carcinoma that has progressed on or after treatment with a fluoropyrimidine, irinotecan, and oxaliplatin	463	231	20 weeks	progression-free survival (time from randomisation to the date of the first observed progression or death)	median 8.0 weeks (vs. 7.3)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
To ensure the availability of KRAS test kit.	30/11/2007	Other measure	New activity
To provide a Statistical Analysis Plan describing the analysis of wild-type KRAS subpopulation for 20050181 and 20050203 studies. This SAP would need CHMP approval prior to implementation.	31/03/2008	Other measure	New analysis plan planned
To submit the clinical study reports of 20030167 study including the safety-efficacy analysis in relation with KRAS. [..]	31/03/2008	Clinical study	Ongoing
[..] To submit the clinical study reports of 20030250 study including the safety-efficacy analysis in relation with KRAS.	31/03/2008	Clinical study	Ongoing
To submit the clinical study report of PACCE study (even if interim) including the safety-efficacy analysis in relation with KRAS.	31/03/2008	Clinical study (interim)	Ongoing
To submit the clinical study summary report of 20050181 study to confirm the hypothesis on wild-type KRAS as a biomarker for selecting patients to be treated.	31/12/2008	Clinical study (interim)	Ongoing
To provide data on Quality of Life of 20050181 study.	31/12/2008	Additional analysis	Ongoing
To submit the clinical study report of STEPP study including the safety-efficacy analysis in relation with KRAS.	31/03/2009	Clinical study	Ongoing
To submit the clinical study summary reports of SPIRITT study including the safety-efficacy analysis in relation with KRAS. [..]	30/06/2009	Clinical study	Ongoing
[..] To submit the clinical study summary reports of PRECEPT study including the safety-efficacy analysis in relation with KRAS.	30/06/2009	Clinical study	Ongoing
To submit the clinical study report summary of 20050203 study including the safety-efficacy analysis in relation with KRAS.	31/12/2009	Clinical study (interim)	Ongoing

To provide additional data on Quality of Life of 20050203 study.	31/12/2009	Additional analysis (interim)	Ongoing
To submit the final clinical study summary report of 20050203 study including the safety-efficacy analysis in relation with KRAS.	31/03/2010	Clinical study	Ongoing
To provide additional data on Quality of Life of 20050203 study	31/03/2010	Additional analysis	Ongoing
To submit the final clinical study report of 20050181 study including the safety-efficacy analysis in relation with KRAS.	31/03/2010	Clinical study	Ongoing
To submit the final clinical study report of PACCE study including the safety-efficacy analysis in relation with KRAS.	30/06/2011	Clinical study	Ongoing
Imposed in procedure R/9: To complete a confirmatory trial examining panitumumab monotherapy in licensed indication. In particular to - Provide a study protocol outline for this study by February 2009 - Based on Rapporteur feedback on the outline to provide a final protocol to CHMP in April 2009 to allow agreement of the final protocol with CHMP - Commit to start the study as soon as is possible - Agree a timeline for provision of data from the study once the design has been agreed	not exact (then 31/12/2012 for 20080763 study)	Clinical study	New study
Imposed in procedure R/18: To resolve the uncertainties about KRAS testing by end May 2012 by: - Collecting information about the range of diagnostic tests conducted in clinical practice and their performance - Collecting data on and evaluating the compliance of physicians with the recommend use of Vectibix in confirmed cases of wild-type tumours	31/05/2012	Other measure	-

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
To ensure the availability of KRAS test kit.	30/11/2007	03/12/2007	-3	Complete	N	N	N/A	0	-	-
To provide a Statistical Analysis Plan describing the analysis of wild-type KRAS subpopulation for 20050181 and 20050203 studies. This SAP would need CHMP approval prior to implementation.	31/03/2008	06/12/2007	116	Completed	N	N	N/A	0	-	-
To submit the clinical study reports of 20030167 study including the safety-efficacy analysis in relation with KRAS. [..]	31/03/2008	14/04/2008	-14	Completed	N	N	N/A	0	-	-
[..] To submit the clinical study reports of 20030250 study including the safety-efficacy analysis in relation with KRAS.	31/03/2008	14/04/2008	-14	Completed	N	N	N/A	0	-	-
To submit the clinical study report of PACCE study (even if interim) including the safety-efficacy analysis in relation with KRAS.	31/03/2008	01/07/2008	-92	Completed	N	N	N/A	0	-	-

To submit the clinical study summary report of 20050181 study to confirm the hypothesis on wild-type KRAS as a biomarker for selecting patients to be treated.	31/12/2008	19/10/2009	-292	Completed	N	N	N/A	0	-	-
To provide data on Quality of Life of 20050181 study	30/06/2010	16/04/2010	75	Completed	N	Y	Due date extended in R/12	546	not specified	-
To submit the clinical study report of STEPP study including the safety-efficacy analysis in relation with KRAS.	31/03/2009	16/04/2009	-16	Completed	N	N	-	0	-	-
To submit the clinical study summary report of the SPIRITT study including the safety efficacy analysis in relation with KRAS	30/09/2012	28/09/2012	2	Completed	N	Y	Due date extended in R/12 and R/34	1188	Due to slow enrolment and due to delays in the occurrence of the relevant events necessary for the event-driven primary endpoint (PFS)	-

[..] To submit the clinical study summary reports of PRECEPT study including the safety-efficacy analysis in relation with KRAS.	30/06/2009	12/08/2009	-43	Completed	N	N	N/A	0	-	-
To submit the clinical study report summary of 20050203 study including the safety-efficacy analysis in relation with KRAS.	31/12/2009	19/10/2009	73	Completed	N	N	N/A	0	-	-
To provide additional data on Quality of Life of 20050203 study.	31/12/2009	19/10/2009	73	Complete	N	N	N/A	0	-	-
To submit the final clinical study summary report of 20050203 study including the safety efficacy analysis in relation with KRAS	30/06/2010	16/04/2010	75	Completed	N	Y	Due date extended in R/12	91	not specified	-
To provide additional data on Quality of Life of 20050203 study	30/06/2010	16/04/2010	75	Completed	N	Y	Due date extended in R/12	91	not specified	-
To submit the final clinical study report of 20050181 study including the safety-efficacy analysis in relation with KRAS.	30/06/2010	16/04/2010	75	Completed	N	Y	Due date extended in R/12	91	not specified	-

To submit the final clinical study report of PACCE study including the safety-efficacy analysis in relation with KRAS	-	N/A	N/A	Downgraded	downgraded	N/A	Trial discontinued early (outcome communicated in SOB 004) and CHMP agreed (in SOB 014 and R/12) to remove the SOB to provide final study report (study discontinued)	N/A	-	No additional conclusions would be drawn from this study.

To complete a confirmatory trial examining panitumumab monotherapy in licensed indication. In particular to provide the clinical study report of the primary data analysis from the 20080763 study	30/09/2013	10/10/2013	-10	Completed	new SO	Y	New SO imposed in procedure R/9, dues date extended in R/43	273	the overall survival appears to be longer than expected	Data submitted post-authorisation increased the level of uncertainty as to whether the results from the combination trials will be able to support the monotherapy indication, therefore additional SO was imposed

To resolve the uncertainties about RAS testing by: - collecting information about the range of diagnostic tests conducted in clinical practice and their performance - collecting data on and evaluating the compliance of physicians with the recommended use of Vectibix in confirmed cases of wild-type tumours	31/12/2014	04/09/2014	118	Completed	new SO	Y	New SO imposed in procedure R/18 and due date extended in R/34	944	due to a delay in the launch of the studies	New SO to address concerns about reliability of the current methods of KRAS testing and compliance of the prescribers with the recommended use of CMA product

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	20030167	II	N	N	N	E & S	none	-	6 mg/kg Q2W	mCRC; failed therapy with fluoropyrimidine, irinotecan, and oxaliplatin, ≥ 10% cell membrane EGFR staining	182 (142)	182	16 weeks	objective response rate	3.5% (95% CI 1.2-8.0)	Efficacy analysis in Adjudicated Prior Failure Set
Clinical study	20030250	II	N	N	N	E & S	none	-	6 mg/kg Q2W	mCRC; failed therapy with fluoropyrimidine, irinotecan, and oxaliplatin; < 10% cell membrane	203 (158)	203	16 weeks	objective response rate	3.8 % (95% CI 1.4-8.1)	Efficacy analysis in Adjudicated Prior Failure Set

										EGFR staining						
Clinical study	20040249	III	Y	Y	N	E & S	oxaliplatin-based or irinotecan-based chemotherapy	bevacizumab and oxaliplatin-based or irinotecan-based chemotherapy	6 mg/kg Q2W	Subjects with mCRC (first line)	865 (519)	440	Median dosing duration 22.9 weeks for wild-type KRAS + follow-up	PFS	KRAS wild-type: 9.8 vs 11.5 months for oxaliplatin groups and 10.0 vs 12.5 for irinotecan groups	SO for submission of final report later abandoned, this remaining last submission of results of this study as SO.
Clinical study (interim)	20050181	III	Y	Y	N	E & S	FOLFIRI	FOLFIRI	6.0 mg/kg Q2W	previously treated mCRC (second line)	1186 (597)	591	56.1 weeks	OS	14.5 (95% CI 13.0-16.0) vs. 12.5 (95% CI 11.2-14.2) months	

Additional analysis	20050181	III	Y	Y	N	E & S	FOLFIRI	FOLFIRI	6.0 mg/kg Q2W	previously treated mCRC (second line)	1186	591	58 weeks (for wild-type group)	QoL (SO scope)	quality of life was not significantly affected by treatment with panitumumab and numerically, the results were in favour of FOLFIRI alone	See separate SO for efficacy results
Clinical study	20050184	II	Y	Y	N	E & S	FOLFIRI or irinotecan	6.0 mg/kg + FOLFIRI Q2W vs. 9.0 mg/kg + irinotecan Q3W	6.0 mg/kg + FOLFIRI Q2W vs. 9.0 mg/kg + irinotecan Q3W	mCRC with failed 1st line treatment due to disease progression or toxicity	95	95	6 weeks	Safety (incidence of ≥ G2 skin toxicities of interest)	Lower in pre-emptive treatment arm vs reactive treatment arm	

Clinical study	20060141	II	Y	Y	N	E & S	chemotherapy (FOLFIRI)	bevacizumab + chemotherapy (FOLFIRI)	6 mg/kg Q2W	mCRC with wild-type KRAS; failed 1st-line oxaliplatin + bevacizumab	264 (182)	133	75 weeks	PFS	7.7 (95% CI 5.7-11.8) vs. 9.2 (95% CI 7.8-10.6) months for wild type KRAS (n=182)	
Clinical study	20060277	II	N	N	N	E & S	chemotherapy (FOLFIRI)	-	6 mg/kg Q2W	subjects with metastatic colorectal cancer (mCRC) after failing first-line treatment containing fluoropyrimidine and oxaliplatin-based chemotherapy with bevacizumab	115 (107)	115	25 weeks	ORR	23% for wild-type KRAS, 16% for mutant KRAS	The median overall survival time was 19 weeks longer in subjects wild-type KRAS tumours compared with subjects with mutant KRAS tumours

																(50 versus 31 weeks, respectively)
Clinical study (interim)	20050203	III	Y	Y	N	E & S	chemotherapy (FOLFOX)	chemotherapy (FOLFOX) only	6.0 mg/kg Q2W	Previously untreated mCRC with either wildtype or mutant KRAS tumors	1183 (656)	593	Mean 55.3 weeks in wild-type KRAS test arm	PFS	9.6 (95% CI 9.2-11.1) vs. 8.0 (95% CI 7.5-9.3) months in Wild type KRAS patients (n=325+331)	
Additional analysis (interim)	20050203	III	Y	Y	N	E & S	chemotherapy (FOLFOX)	chemotherapy (FOLFOX) only	6.0 mg/kg Q2W	Previously untreated mCRC with either wildtype or mutant KRAS tumors	1183 (656)	593	Mean 55.3 weeks in wild-type KRAS test arm	QoL	not reported in AR	

Clinical study	20050203	III	Y	Y	N	E & S	chemotherapy (FOLFOX)	chemotherapy (FOLFOX) only	6.0 mg/kg Q2W	Previously untreated mCRC with either wildtype or mutant KRAS tumors	1183 (656)	593	Median follow-up for wild-type KRAS 57 wks	PFS	10.0 (95% CI 9.3-11.4) vs. 8.6 (95% CI 7.5-9.5) months in Wild type KRAS patients (n=325+331)	
Additional analysis	20050203	III	Y	Y	N	E & S	chemotherapy (FOLFOX)	chemotherapy (FOLFOX) only	6.0 mg/kg Q2W	Previously untreated mCRC with either wildtype or mutant KRAS tumors	1183 (656)	593	Median follow-up for wild-type KRAS 57 wks	QoL	QoL data did not show any benefit of adding CMA product	
Clinical study	20050181	III	Y	Y	N	E & S	FOLFIRI	chemotherapy (FOLFIRI) only	6.0 mg/kg Q2W	previously treated mCRC (second line)	1186 (597)	591	58 weeks (for wild-type group)	OS	14.5 (95% CI 13.0-16.1) vs. 12.5 (95% CI 11.2-14.2)	

															months	
Clinical study	20080763	III	Y	Y	N	E & S	none	cetuximab	6 mg/kg every 14 days	subjects with previously treated, wild-type KRAS, metastatic colorectal cancer	1010 (999)	500	41 weeks	Overall Survival	10.4 months vs. 10.0 months	

Details of outstanding data

N/A

Votrient (pazopanib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	14/06/2010	393	Yes	yes	Art. 2(1)	During the procedure	Improved treatment effect and/or safety vs. available therapies	1645	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
14/06/2013	R/17	In adults for the first line treatment of advanced Renal Cell Carcinoma and for patients who have received prior cytokine therapy for advanced disease. Treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Efficacy and safety has only been established in certain STS histological tumour subtypes

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
VEG105192	III	Y	Y	Y	none	placebo	800 mg once daily	patients with advanced RCC who had received no prior systemic treatment or only received prior cytokine treatment for advanced disease	435	290	median exposure 7.4 months for CMA product	median PFS	9.2 vs 4.2 months	hazard ratio HR=0.46, 95% CI 0.34-0.62; p<0.0000001

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
Submit the study report for VEG108844 (a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic renal cell carcinoma).	28/02/2012	Clinical study	Ongoing
Submit a pooled analysis of data from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844). The studies should be appropriately powered to demonstrate non-inferiority with a margin of 1.22. A discussion on the applicability of the efficacy data from VEG113078 to the European population should be provided by June 2012.	30/06/2012	Additional analysis	New analysis planned

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons
Submit the study report for VEG108844 (a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic renal cell carcinoma). This study report will contain a pooled analysis of data from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844). A discussion on the applica-bility of the efficacy data from VEG113078 to the European population will be provided	30/06/2013	05/12/2012	207	Comp leted	minor	Y	Due date amended in R/12 and wording amended to require pooled data including also Study VEG113078 (pooled data already subject to a separate SO)	488	Due to a substantial amendment in the final analysis of the studies to increase the sample size
Submit an updated pooled analysis of the PFS data as assessed by the Investigator from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844). The studies should be appropriately powered to demonstrate non-inferiority with a margin of 1.22 with 794 PFS events per Investigator.	30/09/2013	05/12/2012	299	Comp leted	minor	Y	In R/12: Endpoint for pooled analysis and power calculation specified in the description of the specific obligation (due to higher than expected discontinuation rate and more than expected missing assessments) and due date amended	457	To reach required 794 progression events, based on MAH's projection.

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Pooled clinical studies	VEG108844 and VEG113078	III	Y	Y	N	E & S	full suppor-tive care	sunitinib + full supportive care	800 mg once daily	subjects with advanced RCC who had not received prior systemic therapy for advanced or metastatic RCC	1110	557	median exposure 8.0 months for CMA product	median progression free survival	8.4 vs. 9.5 months	pazopanib was non-inferior to sunitinib with regard to PFS and OS using the CHMP defined HR limit for non-inferiority (1.22)
Additional analysis	VEG108844 and VEG113078 (with 794 PFS events)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Results submitted in R/17 together with the other SO (which following amendments also required pooled analysis from these studies)

Details of outstanding data

N/A

Votubia (everolimus)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	02/09/2011	309	Yes	Yes	Art. 2(1) and 2(3)	Initial MAA	No approved satisfactory treatment	143[7]	Yes

Granting of standard MA

Date of granting standard MA	Procedure of granting standard MA	Changes to indication by time of granting standard MA
16/11/2015	II/34	Treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume. Treatment of patients ~~**aged 3 years and older**~~ with subependymal giant cell astrocytoma associated with tuberous sclerosis complex who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated

[7] including data from a phase III renal transplant study

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size
C2485	II	N	N	N	none	N/A	titrated to achieve target concentrations of 5-15 ng/mL	confirmed diagnosis of TSC and radiological evidence of serial SEGA growth	28	28	6 months	Change from baseline in primary SEGA volume as per Independent Central Radiological Review	Median reduction 0.80 cm^3
M2301	III	Y	Y	Y	none	placebo	titrated to achieve target concentrations of 5-15 ng/mL	patients diagnosed with TSC associated SEGAs and have radiological evidence of one of the following three conditions prior to randomization: 1) serial growth, or 2) presence of a new SEGA lesion, or 3) new or worsening hydrocephalus.	117	78	median 41.93 weeks vs. 36.14 weeks	SEGA response rate (proportion of patients with a best overall SEGA response as per Independent Central Radiological Review)	34.6% (95% CI: 24.2% - 46.2%) vs. 0% (95% CI: 0% - 9.0%)

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
The applicant should commit to providing long-term follow-up on duration of response and time to progression for study C2485 [..]	31/03/2015	Clinical study	Ongoing (some results in MAA)
The applicant should commit to providing long-term follow-up on duration of response and time to progression for study [..] M2301.	31/03/2015	Clinical study	Ongoing (some results in MAA)
The MAH shall complete the ongoing pivotal clinical study M2301 and provide the interim and final safety and efficacy results within the stated timeframe. Within the interim analysis, the MAH shall: * analyse the adverse event incidence as a function of plasma drug concentration with and without inducer stratified by age, * readdress the starting dose strategy, utilising what is understood about the relationship between Cmin and dose in this patient population, as well as the experience gained on the need for dosage adjustment during study C2485, * provide a new simulation that predicts the mean and confidence interval around Cmin as a result of the recommended posology in appropriate subgroups of patients, keeping in mind that the population pharmacokinetic analysis of everolimus in children may lead the applicant to different age stratification than in the current analysis (i.e., a cut-off of 10 years may not be optimal).	30/09/2012	Clinical study (interim)	Ongoing (some results in MAA)

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
Long term follow up on duration of response and time to progression for studies C2485 [..]	31/03/2015	22/07/2014	252	Compl	N	N	-	0	-	-
Long term follow up on duration of response and time to progression for studies [..] M2301.	31/03/2015	27/03/2015	4	Compl	N	N	-	0	-	-
The MAH shall complete the ongoing pivotal clinical study M2301 and provide the interim and final safety and efficacy results within the stated timeframe. Within the interim analysis, the MAH shall: • analyse the adverse event incidence as a function of plasma drug concentration with and without inducer stratified by age, • readdress the starting dose strategy, utilising what is understood about the relationship between Cmin and dose in this patient population, as well as the experience gained on the need for dosage adjustment during study C2485, • provide a new simulation that predicts the mean and confidence interval around Cmin as a result of the recommended posology in appropriate subgroups of patients, keeping in mind that the population pharmacokinetic analysis of everolimus in children may lead the applicant to different age stratification than in the current analysis (i.e., a cut-off of 10 years may not be optimal).	30/09/2012	02/03/2012	212	Completed	N	N	-	0	-	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	C2485	II	N	N	N	E & S	none	N/A	titrated to achieve target concentrations of 5-15 ng/mL	confirmed diagnosis of TSC and radiological evidence of serial SEGA growth	28	28	median duration of exposure 67.8 months	duration of response and time to progression[8]	CHMP report: results of the final analysis confirm the evidence regarding the efficacy of everolimus over 60 months in patients with SEGA	
Clinical study	M2301	III	Y	Y	Y	E & S	none	placebo	titrated to achieve target concentrations of 5-	patients diagnosed with TSC associated SEGAs and	117	111	Median exposure to CMA produc	duration of response and time to	estimated progression-free rate at 3 years 88.8%	CHMP report: The data suggest that

[8] Information requested as part of the SO. The primary endpoint of the study remained the Change from baseline in primary SEGA volume.

									15 ng/mL	have radiological evidence of one of the following three conditions prior to randomization: 1) serial growth, or 2) presence of a new SEGA lesion, or 3) new or worsening hydrocephalus.			t 204.9 weeks	progression[9]	(95% CI: 80.6%-93.6%)	everolimus is a long term treatment since (further) improvements occur also after longer time of treatments
Clinical study (interim)	M2301	III	Y	Y	Y	E & S	none	placebo	titrated to achieve target concentrations of 5-15 ng/mL	patients diagnosed with TSC associated SEGAs and have radiological evidence of one of the following three	117	78	Same exposure as in MAA data	N/A for this submission (Reported in MAA)	-	CHMP conclusion: no new efficacy or safety data has become available which changed the

[9] Information requested as part of the SO. The primary endpoint of the study remained the SEGA response rate.

										conditions prior to randomization: 1) serial growth, or 2) presence of a new SEGA lesion, or 3) new or worsening hydrocephalus.						benefit/risk assessment for Votubia for its currently authorised indication

Details of outstanding data

N/A

Xalkori (crizotinib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	23/10/2012	337	Yes	Yes	Art. 2(1)	Initial MAA	Improved evidence on efficacy	588	Yes

Granting of standard MA

N/A

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
A8081001 (pre-treated ALK-positive NSCLC patients only)	I/II	N	N	N	none	N/A for ALK-positive NSCLC Cohort	250 mg BID in continuous 28-day cycles	previously treated ALK-positive advanced NSCLC	149 (121)	149	42.3 weeks	PK/PD, safety	-	ORR 60%; median DRs 48.1 weeks; PFS 9.2 months
A8081005	II	N	N	N	none	-	250 mg BID in continuous 21-day cycles	previously treated ALK-positive advanced NSCLC population	439 (255)	439	24.6 weeks	ORR	53%	Median DRs 42.9 weeks; PFS 8.5 months
1007	III	Y	Y	N	none	second-line standard of care chemotherapy, pemetrexed or docetaxel	daily crizotinib at a starting dose of 250 mg BID in 3-week cycles	ALK-positive, advanced NSCLC patients who received only one prior chemotherapy regimen that was platinum-based	347	173	10.5 cycles (31.5 weeks)	PFS	7.7 months (95% CI: 6.0, 8.8) vs. 3.0 months (95% CI: 2.6, 4.3)	

SOs imposed

Original description of SO scope	Due date	Type of SO	Status	Notes
The MAH should submit the CSR of study A8081007, expected in Q1 2013. The CSR should also include a detailed analysis of outcome on post-progression treatments in Study 1007 as well as efficacy and baseline data according to race (Caucasian/Asian) by treatment groups.	31/03/2013	Clinical study	Ongoing (some results in MAA)	Stuy size indicated as actually recruited at time of MAA (initialy expected sample size only 318, with 50% receiving CMA product).
The MAH should submit updated safety (SAEs and deaths) and efficacy (PFS, OS) data for both studies 1001 and [..]. The MAH should compare and explain potential differences in OS for crizotinib in the 3 studies (1001, 1005 and 1007).	31/03/2013	Clinical study	New study	
The MAH should submit updated safety (SAEs and deaths) and efficacy (PFS, OS) data for both studies [..] and 1005. The MAH should compare and explain potential differences in OS for crizotinib in the 3 studies (1001, 1005 and 1007).	31/03/2013	Clinical study	New study	
The MAH should submit the safety review of main (severe) hepatic disorders from all available main studies of crizotinib (including 1001, 1005 and 1007).	31/03/2013	Additional analysis	New study	

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
The MAH is requested to update OS status of study A8081007 and provide the final data within 9 months after the required 238 OS events have been reached. The CSR should also include a detailed safety analysis.	30/06/2016	16/06/2016	-	Under assessment	Minor	Y	The cut-off for the study report required to fulfill the SO changed from a set date to a number of OS events required for final OS analysis (change in procedure II/4)	1187	In order to obtain mature OS data	-
The MAH should submit updated safety (SAEs and deaths) and efficacy (PFS, OS) data for both studies 1001 and [..]. The MAH should compare and explain potential differences in OS for crizotinib in the 3 studies (1001, 1005 and 1007).	31/03/2013	08/03/2013	23	Completed	N	N	-	0	-	-
The MAH should submit updated safety (SAEs and deaths) and efficacy (PFS, OS) data for both studies [..] and 1005. The MAH should compare and explain potential differences in OS for crizotinib in the 3 studies (1001, 1005 and 1007).	31/03/2013	08/03/2013	23	Completed	N	N	-	0	-	-

The MAH should submit the safety review of main (severe) hepatic disorders from all available main studies of crizotinib (including 1001, 1005 and 1007).	31/03/2013	08/03/2013	23	Completed	N	N	-	0	-	-

Details of data provided to fulfil SOs

Type of data	Study ID	Phase	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
Clinical study	1001	I/II	N	N	N	E & S	none	N/A for ALK-positive NSCLC Cohort	250 mg BID in continuous 28-day cycles	previously treated ALK-positive advanced NSCLC	153 (131)	153	53.4 treatment + 25.4 follow-up weeks	PFS, OS (for the requested analysis)	PFS 9.7 months, OS 29.6 months	CHMP conclusion: updated data confirms the efficacy and safety profile established at the time of initial marketing authorisation
Clinical study	1005	II	N	N	N	E & S	none	-	250 mg BID in continuous 21-day cycles	previously treated ALK-positive advanced NSCLC population	934 (807)	934	23.7 treatment + 8.6 follow-up weeks	PFS, OS (for the requested analysis)	PFS 8.1 months, OS not reached	CHMP conclusion: updated data confirms the efficacy and safety profile established at the time of initial marketing authorisation

Additional analysis	several	-	-	-	-	S	-	-	-	-	-	-	-	-	-	CHMP conclusion: The mechanism by which the elevation in liver enzymes occurs is not identified since the MAH cannot determine whether the hepatotoxicity mechanism is dose and/or time dependent. Risk factors predisposing to liver injury are difficult to identify: concomitant treatment, pre-existing liver disease, medical history, viral infection or reactivation did not reveal any patterns but in most cases relevant information is missing. Hepatotoxicity is an important identified risk and the SmPC has been updated to reflect new information submitted by the MAH.

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	1007	III	Y	Y	Y	N	E & S	none	second-line standard of care chemotherapy, pemetrexed or docetaxel	daily crizotinib at a starting dose of 250 mg BID in 3-week cycles	ALK-positive, advanced NSCLC patients who received only one prior chemotherapy regimen that was platinum-based	347	173	until 238 OS events	PFS

Zykadia (ceritinib)

Basic information

Therapeutic area	Date of authorisation	Duration of procedure	SA/PA	SA/PA Adherence	Indent for scope	CMA first considered	Unmet medical need	Safety database	Phase III
Oncology	06/05/2015	357	NO	NA	Art. 2(1)	During the procedure	No approved satisfactory treatment	587	No

Granting of standard MA

N/A

Main / pivotal evidence at time of granting CMA

Study ID	Phase	Multiple arm	Randomised	Blinding	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint	Effect size	Notes
X2101 (Efficacy analysis set)	I	Y	N	N	none	-	50 - 750 mg once daily continuously	adult patients with tumors characterized by genetic abnormalities in ALK	246 [10]	246 [11]	at least 18 weeks	N/A for this analysis set	-	Overall response rate 56.4% (patients treated with ALK inhibitor), 72.3% (naïve to ALK inhibitors); duration of response 8.25 and 17.0 months, respectively.
A2201	II	N	N	N	none	-	750 mg once-daily	patients with ALK-positive NSCLC who have progressed on crizotinib	140	140	11.3 months	Overall response rate by investigator assessment	37.10%	Median duration of response 9.2 months
A2203	II	N	N	N	none	-	750 mg once-daily	Crizotinib naïve adult patients with ALK-activated NSCLC	124	124	8.31 months	Overall response rate by investigator assessment	63.70%	Median duration of response 9.3 months

[10] Efficacy analysis set
[11] Efficacy analysis set

SOs imposed

Original description of SO scope	Due date	Type of SO	Status
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase III efficacy study A2303 comparing ceritinib to chemotherapy.	30/09/2018	Clinical study	Ongoing (some results in MAA)
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase II single-arm efficacy study A2201.	30/06/2016	Clinical study	Ongoing (some results in MAA)

SO amendments and fulfilment

Latest / final description of SO scope	Latest / final due date	Subm. Date	Accuracy of subm.	SO status	Change of scope	Change of due date	Description of changes	Due date ext.	Ext. reasons	Scope reasons
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase III efficacy study A2303 comparing ceritinib to chemotherapy.	30/09/2018	-	-	Due	N	N	-	0	-	-
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase II single-arm efficacy study A2201.	30/06/2016	28/06/2016	-	Under assessment	N	N	-	0	-	-

Details of data provided to fulfil SOs

N/A

Details of outstanding data

Type of SO	Study ID	Phase	Interventional	Multiple arm	Randomised	Blinding	Objectives	Co-adm. therapy	Comparator	Posology for CMA product	Study population	Study size total	Study size CMA	Duration	Primary endpoint
Clinical study	A2303	III	Y	Y	Y	N	E & S	none	standard, second-line chemo-therapy, pemetrexed or docetaxel	750 mg once-daily	adult patients with ALK-positive advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib	Approx.236	Approx. 118	until disease progression	PFS as assessed by Blinded Independent Review Committee
Clinical study	A2201	II	Y	N	N	N	E & S	none	-	750 mg once-daily	patients with ALK-positive NSCLC who have progressed on crizotinib	140	140	when at least 75% of OS events reached	Overall response rate by investigator assessment