Reference: *EORTC 26082 – 22081* Radiation therapy and concurrent plus adjuvant Temsirolimus (CCI-779) versus chemo-irradiation with Temozolomide in newly diagnosed glioblastoma without methylation of the MGMT gene promoter – a randomized multicenter, open-label, Phase II study
EudraCT Number : 2008-003003-31
VHP-No : VHP200903

REPORT ON THE VOLUNTARY HARMONIZATION PROCEDURE – PILOT PHASE -

The main goal of the European non-profit Organization for Research and Treatment of Cancer (EORTC) is to improve the standards of cancer treatment in Europe, through the evaluation of innovative drugs and new regimens, and to establish more effective therapeutic strategies, using drugs already commercially available, or surgery and radiotherapy.

The EORTC is the European Sponsor of this academic clinical trial and takes full responsibility for the conduct of this Clinical Trial in Europe.

The national European Competent Authorities to which the final Clinical Trial Application has been submitted are AUSTRIA, BELGIUM, FRANCE, GERMANY, ITALY, SPAIN, THE NETHERLANDS, and THE UNITED KINGDOM

1-Voluntary Harmonization Procedure

All the timelines are summarized in table 1, below. Both EORTC and the CTFG were able to keep up with the strict deadlines during all the steps of the procedure.

Request for VHP					
Electronic submission of Request to VHP-C			Answer to VHP request- Go or no GO submission VHP dossier		
Deadline	Done	Acknldgmt	Expected	Received	
05/04/2009	03/04/2009	03/04/2009	21/04/2009	24/04/2009	

VHP draft CTA assessment step I					
Request CTA			Answer to CTA		
Deadline	Done	**DAY1**	Day --> Expected date		Received
09/05/2009	04/05/2009	05/05/2009	29	03/06/2009	29/05/2009

VHP draft CTA assessment step II					
Answer to GNAs			Final Assessment- Go or no Go		
Deadline D40	Deadline D40 -Weekend	Done	Day --> Expected date		Received
14/06/2009	12/06/2009	09/06/2009	50	24/06/2009	17/06/2009

Table 1

We have four comments.

1- It is very useful for a Sponsor to receive simultaneously all the comments on the scientific aspects of the protocol and also an opinion on the admissibility of the study in one or in several involved countries. However, one can regret that some of the Competent Authorities do/may not comment on the PIS/ICs during the VHP because PIS/ICs are not part of the submission dossier which they require during the national phase.

2- Upon the receipt of the VHP positive assessment, the submissions in the national phases have to be done within 20 days. One of the major problems of the current legislation is the quantity of forms that are required to be filled out and sent in different formats depending on the participating countries. Hence, the preparation for the submission of the dossiers has increased the pressure and the workload of our unit within a short timeframe. So it could be useful to extend the timeline from 20 days to 30 days.

3- Upon the receipt of the VHP positive assessment, some grounds for non-acceptance might have to be taken into consideration at the discretion of the Sponsor before going to the national phases, e.g. the protocol or the PIS/ICs might have to be amended. Unfortunately, it could be very difficult to do it within 20 days from the receipt of the VHP positive assessment and still have time to do the national submissions on time. This point should be considered by CTFG when the guidelines will be amended. Also, a clarification might be given on the following sentence [page 6, paragraph 5.3] "*Generally, no changes between the final CTA and the draft CTA approved during the VHP will be accepted"*. A list of changes which could be allowed needs to be provided in the updated guidelines.

4- In some countries (e.g. Greece, Spain), the competent authorities are obliged by the national laws to receive the Ethics Committees' approval before giving their own approval. It is not clear if in this case, the submission to these competent authorities have to be done within timeframe of 20 days (hence with an

incomplete dossier) or if it can be postponed, and then done within 20 days from the receipt of a positive opinion from the Ethics Committees.

2-National Phases

Both EORTC and the Competent Authorities were able to keep up with the strict deadlines (table 2). The approvals were given within 10 days from the acknowledgement of the receipt of a valid dossier.

	CTA assessment - National Phase CA				
	Dossier			Approval	
	Deadline	Sent	Valid dossier	Deadline	Received
AT	07/07/2009	01/07/2009	07/07/2009	17/07/2009	17/07/2009
BE	07/07/2009	30/06/2009	01/07/2009	11/07/2009	06/07/2009
DE	07/07/2009	30/06/2009	20/07/2009	30/07/2009	20/07/2009
ES	07/07/2009	02/07/2009	20/07/2009	28/09/2009	Pending
FR	07/07/2009	30/06/2009	17/07/2009	27/07/2009	17/07/2009
IT					
NL	07/07/2009	02/07/2009	06/07/2009	16/07/2009	15/07/2009
UK	07/07/2009	30/06/2009	02/07/2009	12/07/2009	07/07/2009

Table 2

We have four comments.

1- During the national phases, we have received requests from France, Germany and Spain to modify the information on the Investigational Medicinal Product in the clinical trial application (EudraCT form, sections D1/D2 and D3.8/D3.10). We think that this should have happened during the VHP, in the aims of harmonizing the EudraCT form. The other countries did not make any requests. Hence, we have four different EudraCT forms.

2- The Spanish Competent Authorities were very helpful. In the aim of being in the timeframe set by the VHP we submitted the dossier at the same time as the other countries (hence within the timeframe of 20 days) and received a document stating that the dossier was accepted and the final decision pending upon the receipt of the EC approval. Their approval will be given with 10 days upon the receipt of the EC approval instead of 60 days.

3- The Dutch Competent Authorities (CCMO) were apparently not fully aware of the VHP – This was a personal communication made to EORTC by the Dutch National Coordinator.

4- In Italy, the Director-Generals of the public health facilities at which the Clinical Trial will be conducted have not delegated their responsibilities as Competent Authorities to their respective Ethics Committees. The Study dossier has been submitted to the Ethics Committees and it is still under evaluation.