EudraCT Clinical Trial Results: Secondary Endpoint (Determination of the Steady State Concentration of AMG 319 in Blood)

EudraCT number	2014-004388-20
Protocol number	CRUKD/15/004
Protocol title	A Cancer Research UK randomised, double-blind, placebo-controlled Phase IIa trial of AMG 319 given orally as a neoadjuvant therapy in patients with human papillomavirus (HPV) positive and negative head and neck squamous cell carcinoma (HNSCC)
Sponsor	Cancer Research UK, Centre for Drug Development 407 St John Street, London, United Kingdom, EC1V 4AD
End of Trial date	03 May 2018

For the purpose of posting clinical trial results for the Cancer Research UK clinical trial CRUKD/15/004 to the European Clinical Trials Database (EudraCT), the following text, table and figure summarising the pharmacokinetic (PK) data from the trial has been extracted from the approved Clinical Study Report (Version 1.0, dated 09 April 2019):

Secondary endpoint: Determination of the Steady State Concentration of AMG 319 in Blood

AMG 319 levels were measured in plasma in all patients who received AMG 319 or placebo. Data was obtained from 30 patients. Of these 30 patients, 22 patients were randomised at the AMG 319 400 mg (or placebo) level and eight patients were randomised at the AMG 319 300 mg (or placebo) level. The analysis was performed in a blinded manner and from the blinded results, 20 patients were assumed to have received AMG 319 and nine patients were assumed to have received placebo. The treatment arm of one patient could not be determined due to errors in sample processing at the clinical site.

Comparison with the treatment allocation following unblinding showed that all patients who received AMG 319 (except the one patient whose allocation was not determined) had quantifiable plasma levels (≥10 ng/mL) of AMG 319 in at least one sample; patients who received placebo did not.

Of the patients who received AMG 319, ten patients had received at least 80% of trial medication (per protocol [PP] population). A summary of plasma AMG 319 concentrations for samples obtained from patients on the trial are given in Table 1; the Day 8 plasma AMG 319 concentration measurements for two patients were markedly higher than others and were considered as potential outliers and excluded from the summary.

All six patients who received AMG 319 in the AMG 319 300 mg treatment arm achieved their maximum plasma AMG 319 concentration on Day 8 of trial treatment. Two patients who received AMG 319 in the AMG 319 400 mg arm achieved their maximum plasma AMG 319 concentration on Day 22 of trial treatment.

Table 1 Summary of plasma AMG 319 concentrations (outliers excluded)

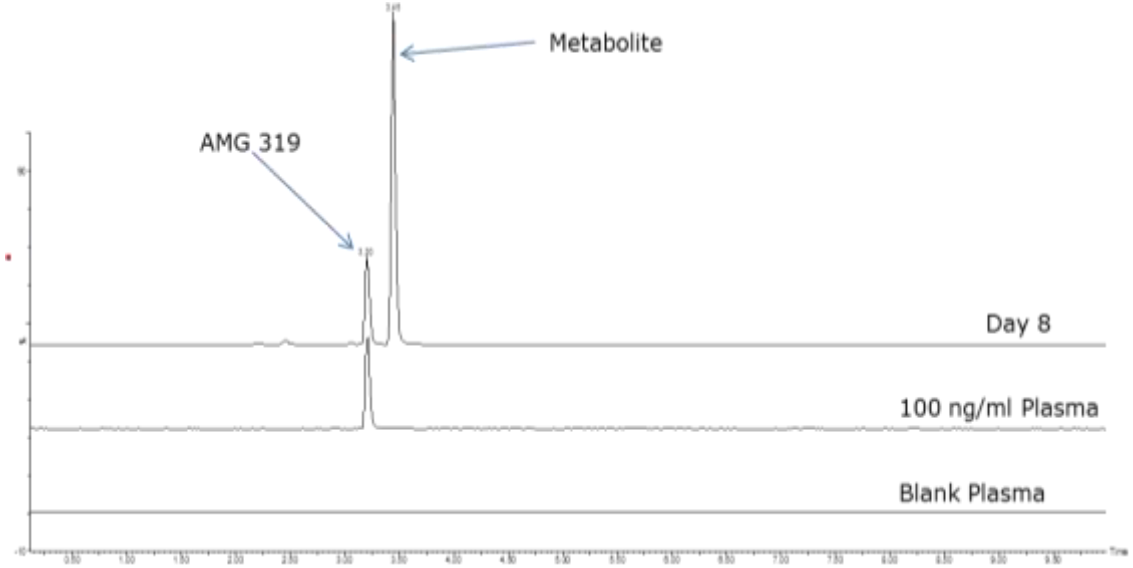
	All Patients			Per Protocol Population		
	AMG 319	AMG 319 400mg	AMG 319 300 mg	AMG 319	AMG 319 400mg	AMG 319 300 mg
Day 8						
Number	18*	12*	6	9*	6*	3*
Mean (sd)	165 (133)	149 (112)	198 (175)	121 (65.4)	98.9 (37.3)	164 (96.7)
Median	118	110	168	117	102	204
Min	37.4	37.4	42.7	37.4	37.4	54.0
Max	518	439	518	235	146	235
Day 15						
Number	12	9	3	9	6	3
Mean (sd)	42.1 (42.0)	35.7 (38.5)	61.2 (55.0)	55.2 (40.6)	52.2 (37.3)	61.2 (55.0)
Median	34.0	17.3	51.3	51.3	52.8	51.3
Min	1.41	1.41	11.9	11.9	12.6	11.9
Max	120	116	120	120	116	120
Day 22						
Number	13	10	3	10	7	3
Mean (sd)	73.6 (64.6)	72.0 (71.0)	78.9 (47.7)	94.5 (58.7)	101 (65.1)	78.9 (47.7)
Median	81.4	51.4	101	104	108	101
Min	2.43	2.43	24.1	15.5	15.5	24.1
Max	179	179	112	179	179	112

**Outliers excluded.*

When outliers have been excluded, mean plasma concentrations in the Intention to Treat population (±standard deviation [sd]) of AMG 319 on Day 8 were 149 (±112) ng/mL and 198 (±175) ng/mL for the 400 mg and 300 mg dose cohorts respectively. When data was assessed from patients who had taken AMG 319 at a compliance level of at least 80% (PP population), the mean concentrations reduced to 98.9 (±37.3) ng/mL and 164 (±96.7) ng/mL respectively. AMG 319 concentrations were variable with % CV values of 74.9% and 88.6% for 400 mg and 300 mg dose cohorts.

In 95% of plasma samples with quantifiable levels of AMG 319, an unidentified peak, assumed to be a metabolic product was observed. This peak was at least equivalent to the AMG 319 content of the samples, and in some cases was significantly more (up to 10 times higher). Mass spectrometry studies show the unidentified peak had a molecular weight of +16 atomic mass units compared to the AMG 319 suggesting a hydroxylation or methylation of AMG 319. Figure 1 shows multiple reaction monitoring chromatogram from analysis of samples from one patient; these were representative of the peaks observed in other patients.

Figure 1 Representative multiple reaction monitoring chromatograms of AMG 319 and metabolite



The bottom chromatogram shows the results from a blank plasma extract, the middle shows a 100 ng/mL calibration extract, while the top shows the plasma extract from one patient on Day 8. As expected, no peaks are detected in the blank and a single peak in the expected, validated retention time range of 3.3±0.3 minutes (3.20 minutes) is observed in the calibration extract. A peak with the expected retention time for AMG 319 is detected in the patient extract, but an additional peak is also seen with a retention time of 3.45 minutes.