CLINICAL DEVELOPMENT DEPARTMENT

Randomised, double-blind, placebo-controlled Phase II proof-of-concept study of APD515 solution for oromucosal and oral administration for relief of xerostomia in patients with cancer.

Sponsor Study No.: DX10008

Final report

Phase of study: II
Clinical Phase (screening) Started On: 02 November 2011
Clinical Phase (Last Patient Last Visit) Completed On: 20 December 2012

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Report Status:	Final 1.0
Date of Report:	25 October 2013

The study was conducted according to ICH guideline E6 (Guideline for Good Clinical Practice (GCP) 1996) and all applicable regulatory requirements.

SYNOPSIS

Name of Sponsor: Acacia Pharma Ltd	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: APD515	**Volume:**	
Name of Active Ingredient: bethanechol chloride	**Page**	
Title of Study: Randomised, double-blind, placebo-controlled Phase II proof-of-concept study of APD515 solution for oromucosal and oral administration for relief of xerostomia in patients with cancer		
Principal Investigator: Dr Andrew Davies MD FRCP, Consultant in Palliative Medicine, Royal Surrey County Hospital, Egerton Road, Guildford, GU2 7XX, UK		
Investigators and study centre(s): The following 8 investigators, based at study centres across the UK and Denmark, enrolled patients during the study: **UK:** Dr Andrew Davies (site 01, 6 patients) Dr Paul Perkins (site 02, 6 patients) Dr Andrew Wilcock (site 05, 3 patients) Dr Alpna Chauhan (site 06, 1 patient) Dr Miriam Johnson (site 07, 3 patients) Dr Daniel Munday (site 08, 1 patient) **Denmark:** Dr Siri Beier Jensen (site 11, 11 patients) Dr Eva Harder (site 13, 1 patient)		
Publication (reference): No abstracts have been published on the results of this study.		
Study period: 02 November 2011 – 20 December 2012	**Phase of development:** II	
Objectives: **Primary**: To evaluate the efficacy of APD515, given by oromucosal application followed by oral ingestion, compared to placebo at relieving the subjective symptom of dry mouth in adult cancer patients. **Secondary**: • To characterise further the efficacy profile of APD515 in adult cancer patients with xerostomia. • To assess the safety of APD515 compared to placebo in adult cancer patients with xerostomia.		

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Name of Finished Product: APD515	**Volume:**	
Name of Active Ingredient: bethanechol chloride	**Page**	

Study Design: This was a multi-centre, double-blind, randomised, placebo-controlled, cross-over study.

Number of Patients:

Planned: 30 evaluable patients in each cohort (maximum 60 evaluable patients in total, if two dose-level cohorts enrolled) were planned. Following an interim analysis, a second cohort was not enrolled in this study.

Enrolled: 32 patients (17 patients [APD515/placebo treatment sequence] and 15 patients [placebo/APD515 treatment sequence]); all 32 patients were randomised.

Analysed: 31 (safety [SAF] analysis set); 30 (intent-to-treat [ITT] analysis set); 26 (per protocol [PP] analysis set).

Main Criteria for Inclusion:
Males and females (aged ≥ 18 years) with confirmed primary neoplasm at any site (apart from non-melanoma skin cancers), for which first-line cytotoxic therapy had been completed more than one month prior to study entry and who had a subjective complaint of dry mouth, ongoing for at least two weeks prior to study entry, were eligible. Patients also had: a demonstrated capacity for salivary stimulation (stimulated whole saliva rate > unstimulated whole saliva flow rate); a Karnofsky performance score ≥ 60% or Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate renal and hepatic function and hydration status; serum urea < 1.5 x ULN and serum urea:creatinine ratio < 100; plasma sodium ≤ ULN; adequate haematological function. Ongoing palliative, hormonal, cytostatic or 'targeted' therapy was permitted provided that the risk of oral mucositis in the patient was not judged to be significant. All patients had to use adequate contraception throughout the study and for 14 days afterwards or in the case of females, were post-menopausal or surgically sterile.

Patients were not eligible if they had: a confirmed diagnosis of Sjögren's syndrome; prior radiotherapy for head and neck cancer, or other substantial doses of radiation delivered to the area of the mouth or salivary glands; significant, symptomatic disease of the oral cavity; intestinal or urinary obstruction; used of oral or topical (including ocular) pilocarpine or cevimeline in the two weeks prior to enrolment; concomitant use of procainamide, quinidine or ganglionic blocking agents.

Investigational Medicinal Product:
APD515 (bethanechol chloride solution for oromucosal and oral administration) for topical administration to the oromucosal surface and oral ingestion, at a dose of 20 mg.

Bulk batches of active and placebo investigational medicinal product (IMP) were manufactured twice in separate manufacturing campaigns, and each of the four batches was given a distinct batch number which are provided here. The bulk IMP was then dispensed into bottles and packed into patient kits – both the bottles and patient kits were assigned batch numbers.

Name of Sponsor: Acacia Pharma Ltd	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: APD515	**Volume:**	
Name of Active Ingredient: bethanechol chloride	**Page**	

Batch numbers for APD515 (bulk): ACA/11/0014 and ACA/11/0050.

Comparator Product
Placebo: identical to IMP except for the absence of bethanechol.
Batch numbers for placebo (bulk): ACA/11/0013 and ACA/11/0051.

Duration of Treatment:
Patients were randomised to receive active APD515 or placebo for one week followed by the reverse for one week, with a one-week wash-out period between.

Criteria for Evaluation:
Primary:

- Subjective measure of oral dryness as recorded on a 100 mm visual analogue scale (VAS).

Secondary:

- Subjective measure of oral comfort, difficulty in speaking and difficulty in swallowing, as recorded on a 100 mm VAS.
- Improvement or otherwise in subjective sensation of oral dryness, oral comfort and difficulty in speaking and swallowing, on direct questioning.
- Subjective assessment of overall value of treatment and theoretical willingness to continue.
- Subjective differentiation of active and placebo.
- Unstimulated whole saliva flow rate.
- Usage of non-pharmaceutical preparations for xerostomia relief.
- Nature and frequency of oromucosal lesions and other adverse events.

Statistical Methods:
The ITT analysis set was used for the primary efficacy analysis and included all patients who received at least one dose of IMP (APD515 or placebo), and who had at least one post-dosing VAS score. The PP analysis set comprised all patients who completed both treatment periods, (with ≥ 80% dosing compliance) in each treatment period and no other major deviations. The SAF comprised all patients who received at least one dose of IMP (APD515 or placebo).

The primary efficacy analysis was between the post-dosing means for the VAS measurement of oral dryness over the active and placebo treatment periods. This comparison was evaluated within a mixed effects analysis of variance (ANOVA) model. A secondary analysis using ANOVA of the same VAS measurement was performed within the PP analysis set. Further secondary analyses included comparisons of the UWSFR using the same ANOVA model for both the ITT and PP analysis sets. The questionnaire responses were compared by treatment using the Mainland-Gart test. The patients were classified into three categories; preference for period 1 treatment, no preference in both periods, preference for period 2 treatment. Patients

Name of Sponsor: Acacia Pharma Ltd	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: APD515	Volume:	
Name of Active Ingredient: bethanechol chloride	Page	

showing no preference were considered as non-informative and therefore their data were excluded from the analysis. The association between the preference and the treatment sequence was examined using Fisher's exact test.

Listings and summary statistics were presented for all efficacy endpoints.

All safety evaluations were performed on the SAF set unless specified otherwise.

The total number of treatment-emergent adverse events (TEAEs) and the total number of patients with TEAEs, the total number of serious TEAEs and the total number of patients with serious TEAEs, the total number of patients with TEAEs leading to withdrawal, the total number of patients with TEAEs leading to death, the number of patients with TEAEs by severity and relationship were tabulated by treatment group.

The number and percentage of patients experiencing TEAEs were summarised and presented by system organ class (SOC) and preferred term (PT); SOC, PT and severity; SOC, PT and relationship with SOC and PT presented in decreasing frequency of patients by treatment group.

For clinical laboratory parameters, a shift in clinical significance from baseline were summarised by treatment group. All safety assessments were listed.

Efficacy Results: The primary and secondary objectives of this study were achieved in relation to the efficacy endpoints, with the results demonstrating a better outcome for patients following treatment with APD515 compared with placebo. In relation to the primary endpoint, a clinically significant difference (ie., a difference greater than 10 mm) and statistically significant difference ($p = 0.0005$) were observed between the APD515 and placebo treatment groups in relation to the VAS scores for question 1 ("How dry is your mouth today?) in favour of APD515. There was good correlation between the patients' perception of xerostomia relief, obtained through the VAS and questionnaire analyses, and the objective measure of salivary flow rates.

Safety and Tolerability Results: During this study, APD515 was well-tolerated, with a safety profile that was similar to placebo. A similar proportion of patients experienced TEAEs in the APD515 treatment group and placebo treatment group, with the greatest percentage of patients experiencing TEAEs of mild severity and TEAEs that were unrelated/remotely related to the IMP. Of the patients who experienced TEAEs, the highest percentage experienced gastrointestinal (GI) disorders in both treatment groups. There were no deaths or SAEs. There were no changes of significant clinical concern observed in the other safety parameters that were assessed.

Conclusions: In conclusion, APD515 performed well with respect to all endpoints, indicating that APD515 provides adult cancer patients with effective xerostomia relief, which is well tolerated and without the systemic cholinergic side effects seen with other pharmacologically active agents used against xerostomia.

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Date of report: 25 October 2013		