2. SYNOPSIS

Sponsor RXi Pharmaceuticals Corporation	
Investigational Product DPCP Ointment (Samcyprone™)	
Active ingredient Diphenylcyclopropenone	
Title of study - A Prospective, Phase 2a Study to Evaluate the Effectiveness and Safety of DPCP Ointment (Samcyprone™) on the Clearance of Verruca Vulgaris (Common Warts) in Subjects Ages 18 – 65 Years	
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Publication - Not applicable	
Study Period Date of First Subject First Visit: December 23, 2015 Date of Last Subject Last Visit: January 4, 2018	**Phase of development** Phase 2a
Primary Objectives • To evaluate the effectiveness of Sensitizing DPCP Ointment (0.4%) in eliciting a sensitization response in healthy subjects with common warts • To evaluate the effectiveness of Treatment DPCP Ointment (0.04%) in the clearance of common wart lesions over a 10-week treatment period with once weekly treatments **Secondary Objectives** • To evaluate the safety and tolerability of a treatment regimen for common warts consisting of a sensitization dose with Sensitizing DPCP Ointment and 10 weekly treatments with Treatment DPCP Ointment • To evaluate pharmacokinetics (PK) of DPCP after topical administration of the Sensitization DPCP Ointment in a subset of subjects (up to 8 subjects total)	
Methodology This was a Phase 2a, prospective, open label, multi-dose study. Healthy subjects with common warts were enrolled into one of two cohorts. The study was divided into two phases (the Sensitization Phase and the Treatment Phase). There was also an option for subjects to participate in a third part, the Extension Phase. Differences between Cohort 1 and Cohort 2 are the inclusion of a vehicle dose administration in the sensitization phase of Cohort 1, the timing of a second sensitization dose with DPCP (if	

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required), and the different amount of DPCP applied to warts during the Sensitization Phase and the Treatment Phase (and optional Extension Phase).

Subjects who exhibited a sensitization response on an inner arm site continued into the Treatment Phase. After the initial 10-week Treatment Phase, any subject, whose treated warts did not clear, but who presented with partial eradication, and met Extension Phase criteria, was given the option to enter a 10-week Extension Phase.

Number of subjects - The study allowed enrollment up to 160 generally healthy subjects with common warts with approximately 40 evaluable subjects in each of two cohorts. A total of 106 subjects were screened and 88 subjects were enrolled in the study. The data from 83 subjects were analyzable for the full analysis and the data from 54 subjects were analyzable for the per protocol analysis.

Diagnosis and main criteria for inclusion - Male and female subjects were between the ages of 18 and 65 years of age (inclusive), presented with at least one verruca vulgaris (common cutaneous, plantar, and periungual wart) that had been present for at least 4 weeks, that measured between 3 and 20 mm and were located on hands, feet, limbs and/or trunk. A maximum of 4 cutaneous single warts or one area of clustered or adjacent warts up to 80 mm were treated.

Test product - DPCP Ointment (Samcyprone™)

Duration of treatment

Sensitization Phase: up to 2 sensitization doses, 2 weeks apart for Cohort 1 and 1 week apart for Cohort 2.

Main Study Treatment Phase: weekly treatment for 10 weeks or until wart eradication, whichever comes first.

Optional Extension Treatment Phase: weekly treatment for 10 weeks or until wart eradication, whichever comes first.

Reference therapy - Not applicable

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CRITERIA FOR EVALUATION

Primary endpoints

- Investigator assessment of Immunotherapeutic Skin Response Scores (Text Table 10) as an assessment of the sensitization rate and level achieved
- Investigator assessment of wart clearance with DPCP Ointment and vehicle treatment as measured by measurement of wart surface area over time and Investigator Global Assessment Score (IGAS; Text Table 11) assessment of wart clearance

Secondary endpoints

- Incidence and severity of AEs, graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
- Significance of changes in clinical laboratory testing results

Exploratory endpoints

- Patient reported outcome (PRO) of wart clearance and treatment tolerability for DPCP will be evaluated
- PK parameters on a subset of subjects including C_{max}, T_{max}, and other parameters, if possible, to determine the disposition of DPCP in plasma

Statistical methods

No hypothesis testing was pre-defined and none was performed. Graphical displays and tabulations are the primary tools used for the data analysis. Where appropriate, confidence intervals are provided. Data analysis was performed using appropriate statistical methods and software (e.g. JMP or SAS). Descriptive statistics are presented as means, standard deviations, medians and ranges for the continuous variables and as counts and percentages for categorical variables. An alpha level of 5% is used for all analyses, unless otherwise stated. Demographics are tabulated.

Full Analysis Set: All subjects that received at least one treatment dose of Treatment DPCP Ointment and from whom at least one measurement of the primary endpoint was obtained are included in the efficacy analysis. Subjects were analyzed according to cohort.

Modified Full Analysis Set (mFAS): The modified FAS (mFAS) analysis includes all subjects who completed the study (i.e. for whom end of study assessment was performed).

Per-Protocol Analysis Set: All subjects from the full analysis set population without any major deviations related to the assessment of the primary endpoint. Subjects were analyzed by cohort.

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Safety Analysis Set: All subjects receiving at least one dose of DPCP Ointment or vehicle are included in the safety analyses.

RESULTS SUMMARY & CONCLUSIONS

Efficacy results

Immunotherapeutic response (successful sensitization): Of the 88 subjects enrolled in the study, 86 subjects received at least one sensitization dose of 0.4% DPCP ointment, and a DTH response, defined as a skin reaction score > 2+ at the sensitization site, was observed in 84 subjects (Cohort 1: 38/39, Cohort 2: 46/47), resulting in a 97.7% success rate of 0.4% DPCP ointment in eliciting the required immunotherapeutic response.

Wart clearance: From the 54 subjects included in the PPAS dataset, 51.9% experienced total wart clearance in the full study duration (*i.e.* in the main study phase and the extension phase combined). The total clearance was slightly higher in Cohort 2 compared to Cohort 1 (52.8% versus 50.0%). In addition, subjects in Cohort 2 also experienced more clearance of at least one wart as compared to Cohort 1 subjects in the full study duration (58.3% versus 50.0%).

From the 87 warts included in the PPAS dataset, 54.0% achieved full clearance over the full study duration. With more lesions achieving full wart clearance in Cohort 1 compared to Cohort 2 (58.6% versus 51.7%). The potential progression towards wart clearance, wart response to the treatment, defined as a reduction of wart size of more than 50%, was assessed for each wart. In the full study duration, 59.8% lesions were considered responders, with again more responders in Cohort 1 compared to Cohort 2 (65.5% versus 56.9%).

The location of the lesions (*i.e.* plantar or non-plantar) was found to have an influence on the complete clearance. In the PPAS dataset, 58.3% of the non-plantar lesions achieved complete clearance in the full study duration, compared to 33.3% of the plantar lesions. In addition, the type of lesion (*i.e.* singular or cluster) was also found to influence the complete clearance rate. In the full study duration, 33.3% of the wart clusters achieved complete clearance compared to 55.6% of the singular lesions. The wart response rates for non-plantar versus plantar warts and singular versus wart clusters followed a similar trend.

Plantar wart ease of ambulation: None of the patients in Cohort 2 considered their ability to walk to be negatively impacted at any point in the study, *i.e.* scored “no impact” at all time points. Two (2) out of 6 or 33.3% Cohort 1 patients with plantar warts considered their ease of ambulation

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mildly impacted at screening, and the other 4 subjects (66.7%) scored "no impact". After 10 weeks this was 1 patient (16.7%) and 5 patients (83.3%), respectively. At the end of the extension phase, 1 out of 2 subjects in Cohort 1 (50.0%) reported moderate impact and the other (50.0%) no impact. The results suggest that the treatment with DPCP does not negatively impact ease of ambulation.

Patient reported tolerability: From all subjects, 68.5% (37/54) reported the treatment to be highly tolerable (Cohort 1: 12/18 or 66.7%; Cohort 2: 25/36 or 69.4%), 29.6% (16/54) reported the treatment to be somewhat tolerable (Cohort 1: 6/18 or 33.3%; Cohort 2: 10/36 or 27.8%), and 1.9% (1/54) reported the treatment to be intolerable (Cohort 1: 0%; Cohort 2: 1/36 or 2.8%). The location of the lesion on the subject who experienced the treatment to be intolerable was plantar.

Pharmacokinetics: PK samples were collected from a subset of subjects (N=5) from Cohort 1 to determine plasma levels of DPCP. The analytical results show that the measured concentrations of DPCP in plasma was below the quantification limit of the assay (BQL of 0.1 ng/ml) for all samples. Therefore, no further analysis of maximum observed concentration (C_{max}), time of C_{max}, time of last measurable concentration (T_{last}), concentration corresponding to T_{last}, and area under the concentration curve (AUC) was performed.

Safety results

A total of 84 AEs were reported. In Cohort 1, 57 AEs were reported in 23 subjects. In Cohort 2, 27 AEs were reported in 20 subjects.

There were 47/84 (56.0%) AEs that were considered related (possibly, probably, or definite) to the study drug. In total, 33/84 (39.3%) of these AEs were definite related to the study drug, of which 18, 12 and 3 were considered mild, moderate and severe, respectively. Seven (7) AEs (7/84; 8.3%) were considered possible related to the study drug, of which 6 were mild and 1 was moderate. The remaining 7 AEs (7/84; 8.3%) were probable related to the study drug, of which 3, 3 and 1 were considered respectively mild, moderate and severe. There were 37/84 (44.0%) AEs which were considered unrelated to the study drug (28 mild, 7 moderate and 2 severe).There were no DLTs reported for this study. There were no laboratory results that were determined by the Investigator to be clinically significant and related to the study drug.

There were no deaths reported during this study. Two SAEs were reported for one study subject, see Section 12.3, but neither of the SAEs were considered to be related to study drug. An Independent Safety Monitor (ISM) was used to adjudicate AE causality, DLTs, MedDRA coding,

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SAE reportability as a SUSAR, aggregate SAE/AE review for unreasonable risk, and protocol deviation adjudication for impact on data integrity and safety.

Conclusion

Efficacy: Sensitizing DPCP ointment (0.4%) showed to be highly effective (97.7% success rate) in eliciting a sensitization response in generally healthy subjects with common warts, which is a prerequisite for a therapeutic response. Of the 83 subjects that were included in the FAS population, a difference was observed in the number of sensitizing doses required to get a DTH response between the cohorts. Only one dose was sufficient in 94.7% of the subjects in Cohort 1, whereas in Cohort 2 this was the case in 52.2% of the subjects.

The therapeutic efficacy results, based on wart measurements, showed that the treatment resulted in complete clearance of 54.0% of all included warts. In line with literature and clinical practice experience, the efficacy was lower for plantar warts and wart clusters. Of note is the markedly higher complete wart clearance rate for non-plantar wart lesions in Cohort 1 (71.4%) vs. Cohort 2 (52.9%). Based on these results it appears that, similarly to the sensitization phase, there may be a dose response effect, considering the amount of DPCP ointment used on the wart lesions in Cohort 2 was half of that in Cohort 1.

Patient reported outcomes showed no impact on the ease of ambulation in the subjects of Cohort 2 and in Cohort 1 only 1 subject reported moderate impact on ambulation. The results suggest that the treatment with DPCP does not negatively impact ease of ambulation. Regarding the tolerability of the treatment, 1 subject with a plantar wart from Cohort 2 reported the treatment to be intolerable. Overall, 68.5% of all subjects reported the treatment to be 'highly tolerable', and only 1 subject (one with plantar wart) found the treatment intolerable.

Safety: Drug-related adverse events reported in the study were mostly local reactions due to the sensitization and challenge responses in the skin which are to be expected for a topical immune response modifier such as DPCP. There were no drug related SAEs, and no DLTs. The most commonly reported AEs were application site reactions and most of these reactions were mild to moderate. The few instances of severe application site reactions occurred almost exclusively in Cohort 1. There was no measurable systemic exposure of DPCP after topical administration with 0.4% DPCP ointment and there were no clinical significant laboratory results. Overall, the use of

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the 0.4% and 0.04% DPCP ointment as per this study protocol results in a satisfactory safety profile.	
Date of the report 21 February 2019	