Results of a randomized, placebo-controlled, first-in-human trial of topical CY-002 in patients with cutaneous warts

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LETTER TO THE EDITOR

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Editor

Cutaneous wart treatments focus on destruction of epithelium rather than specifically targeting HPV-infected keratinocytes.[1] Clearance in treatment-naïve patients varies between 24 and 40%, with side effects including pain and blistering, prompting need for treatments with improved specificity and efficacy.[2] CY-002 is the topical formulation of a novel 27-amino acid alpha-helical tumour membrane-targeting peptide that aims to achieve an HPV-oriented, immune-targeted treatment. CY-002 selectively induces cell death in tumour and HPV-transformed cell lines, whilst sparing normal cells by targeting membrane charge instability.[3] The objectives of this first-in-human proof-of-concept clinical study were to explore safety, tolerability and efficacy of topical CY-002 in adults with cutaneous warts.

This was a randomized, placebo-controlled, double-blind, single-centre Phase I trial with a clinical safety run-in. Enrolled patients were otherwise healthy, above 18 years old and had ≥1, ≥3 mm cutaneous wart on the hand. Washout of wart-removing products was 30–60 days, depending on the therapy. Patients visited the clinical research unit weekly during at-home treatment of 28 days, followed by 6- and 12-weeks follow-up. One droplet of 15–30 mg CY-002 1% or placebo cream was applied once daily, followed by overnight occlusion. Dose selection was based on extrapolation of pre-clinical systemic and topical safety and pharmacodynamic profiles by allometric scaling. Treatment compliance was monitored using a mobile e-diary application.[4] Safety and efficacy were followed during weekly visits.

In total, 55 patients were treated of which 52 patients completed treatment, 49 finished follow-up and 3 were replaced for incompliance. Baseline and disease characteristics were comparable (Table 1), although placebo patients were more treatment-naïve than CY-002 (67.9% vs. 33.3%, $P = 0.009$). Mean home treatment compliance was 27 from 28 planned doses (96.4%) in both groups. Adverse events were similar between groups, with 2 patients reporting mild application site irritation. No systemic CY-002 exposure was found. After CY-002 treatment, 2 patients (7.7%) achieved full clearance and 4 (15.4%) had clearance ≥1 of treated lesions (Table 2). After placebo, full clearance was observed in 1 (3.8%) patient and 3 (11.5%) patients had clearance ≥1 of treated lesions. Three (3) out 4 CY-002-responders had unsuccessfully used salicylic acid previously, while all placebo responders had treatment-naïve warts. Partial to complete clearance, that is ≥50% lesion volume reduction, was observed in 21 CY-002-treated warts (41%) and 13 lesions (25%) following placebo ($P = 0.0962$). Predominant HPV types were 27 and 57. HPV viral load decreased within the first week after treatment initiation, with no significant differences between the groups due to high variability.

Table 1 Baseline characteristics

Characteristic	Ambulatory trial	
	CY-002 (*n* = 27)	Placebo (*n* = 28)
Age (years), mean (SD)	28.1 (11.4)	25.1 (9.9)
Sex, *n* (%)		
Male	14 (51.9)	12 (42.9)
Female	13 (48.1)	16 (57.1)
Fitzpatrick skin type, *n* (%)		
I	2 (7.4)	3 (10.7)
II	13 (48.1)	12 (42.9)
III	7 (25.9)	8 (28.6)
IV	4 (14.8)	3 (10.7)
V	0 (0)	2 (7.1)
VI	1 (3.7)	0 (0)
BMI (kg/m^2), mean (SD)	23.1 (3.0)	23.8 (3.3)
Wart age (years), mean (SD)	2.32 (1.54)	1.92 (1.26)
Total warts per patient (*n*), mean (SD)	3.56 (3.26)	3.04 (2.3)
HPV type of target wart, *n* (%)		
HPV2/2var	3 (11.1)	5 (17.8)
HPV4†	2 (7.4)	4 (14.3)
HPV27	8 (29.6)	8 (28.6)
HPV57	8 (29.6)	6 (21.4)
Other‡	5 (11.1)	3 (10.7)
Missing	2 (7.4)	2 (7.1)
Previous wart treatment, *n* (%)		
Cryotherapy or surgical excision, *n* (%)	11 (40.7)	8 (28.6)
Salicylic acid	10 (37.0)	4 (14.3)
Other§	0 (0)	0 (0)
No previous wart treatment	9 (33.3)	19 (67.9)

†HPV65 was found as a co-infection with HPV4 in 2 patients from the placebo group.
‡Other HPV types reported included HPV3, HPV10, HPV65, HPV88 and HPV95.
§Homeopathic topical formulation. Display of the 55 patients who initiated the clinical trial.
HPV, Human papillomavirus.

Table 2 Exploratory efficacy measures

	CY-002 *N* = 26 Treated warts = 51	Placebo *N* = 26 Treated warts = 51	*P*-value
Subjects with clearance of all treated warts at EOS, *N* (%)	2 (7.7)	1 (3.8)	0.6092
Subjects with clearance of at least 1 wart at EOS, *N* (%)	4 (15.4)	3 (11.5)	0.7019
Treated warts completely cleared at EOT (Day 28), *N* (%)	0 (0)	1 (2)	1.0000
Treated warts completely cleared at EOS (Day 112), *N* (%)	6 (12)	4 (8)	0.5162
Treated warts with partial to complete clearance at EOT (Day 28), *N* (%)	21 (41)	13 (25)	0.0962
Treated warts with partial to complete clearance at EOS (Day 112), *N* (%)	22 (43)	15 (29)	0.0940
Target wart HPV load change from baseline at EOT, %	−74.4%	+6.2%	0.1009
Target wart HPV load change from baseline at EOS, %	−80.2%	−78.4%	0.9209

Partial to complete clearance was defined as >50% reduction in wart volume. Analysis performed on the 52 patients who completed treatment. EOT, End of Treatment, EOS, End of Study.

Relatively high placebo responses could be explained by the CY-002 group comprising of significantly fewer treatment-naïve patients than the placebo group. Warts exposed to unsuccessful prior therapy appear more resistant to other treatments.[5] In comparison, recent trials investigating topicals reported 0–11.6% clearance in placebo-treated warts.[6,7] This study's main strength is a two-tiered, first-in-human trial design to a novel topical compound investigating safety without compromising on exploring efficacy parameters. The putative limitation of this study is the lack of clinical confirmation that CY-002 reaches HPV-infected keratinocytes. Overnight occlusion was included to enhance dermal penetration. Preclinically, CY-002 penetrated the stratum corneum (data on file). Transdermal drug delivery always poses a key question in dermatology, which is further complicated in this study by the calloused nature of cutaneous warts.[8,9] Even salicylic acid requires erosive intervention.[10] However, potential confounding can occur from abrasions enhancing drug delivery to cutaneous warts.

In conclusion, topical CY-002 is safe and tolerable for topical daily use for 4 weeks. A high placebo response was observed in this study and the difference between CY-002 and placebo did not reach statistical significance. Considering different drug delivery strategies may aid the development of CY-002 for cutaneous warts.

Conflicts of interest

M.N.C. de Koning, employed by, and <1% equity holder of the Viroclinics group of companies, Rotterdam, the Netherlands reports no conflict of interest. L. Prestegarden, employed by and stockholder of Cytovation AS, Bergen, Norway, as mentioned in the affiliations, reports no other conflicts of interest. The other authors have no conflicts of interest to declare.

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Data availability statement

The study is registered at ClinicalTrials.gov (NCT03846648) and EudraCT (2018-002733-38). Other files are available from the authors upon request.

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