A first-in-human proof-of-concept trial of intravaginal artesunate to treat cervical intraepithelial neoplasia 2/3 (CIN2/3)

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Abstract

- Current **treatment options for CIN2/3** are either **excisional** or **ablative** and require sequential healthcare visits.
- **Artesunate** is a compound that is **WHO-approved** for treatment of acute malaria and has extensive **safety data** in multiple populations via various administration routes.
- Artesunate has **cytotoxic effect on squamous cells** transformed by HPV.

Objectives

To assess the safety and efficacy of self-administered artesunate vaginal inserts in biopsy-confirmed CIN2/3.

Methods

- **Study Design:** First-in-human Phase I dose-escalation.
- **Study Population:** Adult, immunocompetent women with a diagnosis of CIN2/3, visible residual lesion, detectable HPV.
- **Study Drug: a**rtesunate suppositories (Frantz Viral Therapeutics, LLC).
- **Definitions:** Efficacy: histologic regression to ≤CIN1; viral clearance : absence of HPV genotype detected at baseline
- **Procedures:** Patients assigned sequentially to treatment groups

Table 1. Treatment groups

Treatment group	ID	Dose (mg)	Number of treatment cycles
1	ART50_1	50	1 (week 0)
2	ART200_1	200	1 (week 0)
3	ART200_2	200	2 (weeks 0, 2)
4	ART200_3	200	3 (weeks 0, 2, 4)

Each treatment cycle consisted of vaginal inserts self-administered on five consecutive nights

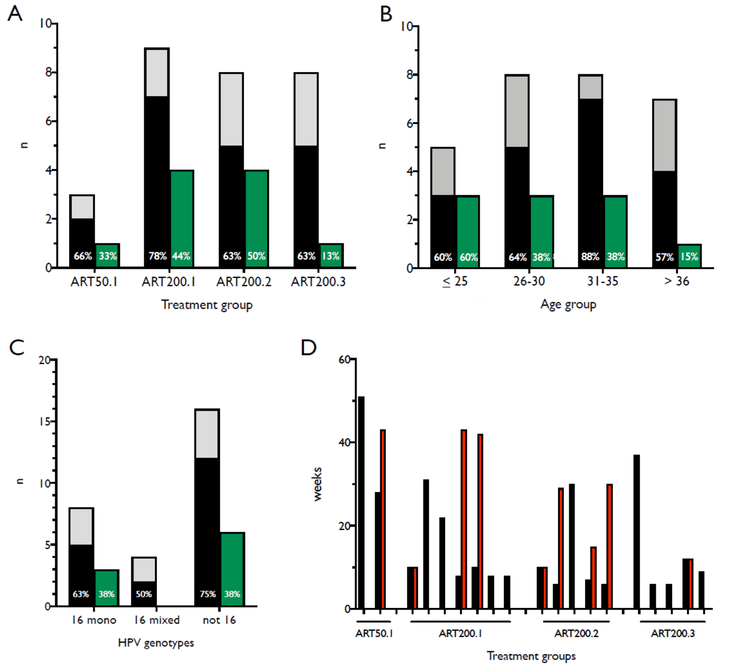
- Suppositories self-administered at bedtime, 5 consecutive nights
- Daily diary card symptom report
- Colposcopy – Weeks 6, 9, 15, 28, 41
- **Standard-of-care resection** performed at week 15 or later for residual HSIL

Analyses:

- Safety analyses - based on patients receiving at least one dose; assessed by severity, frequency, duration of reported events.
- Tolerability - percent of patients able to complete regimen.
- Modified intention-to-treat analyses for efficacy and viral clearance were based on patients who received at least one dose for whom endpoint data were available.

Results

Figure 1: Histologic regression and viral clearance. (A) by treatment group, **(B)** by age group, **(C)** by HPV genotypes; (total subjects --grey; histologic regression - black, viral clearance –green) **(D)** time to histologic regression (black), time to viral clearance (red), by treatment group



Modified intention-to-treat analysis:

- Histologic regression was observed in **19/28 (67.9%)** subjects
- Clearance of HPV genotypes detected at baseline occurred in **9/19 (47.4%)** subjects whose lesions underwent histologic regression

Table 2. Patient characteristics

ID	Race	Age	HPV at study entry	TTHR (wks)		TTVC (wks)	
Treatment Group 1 (50mg insert x 5 doses)							
ART50_1_1	W	29	52, 67	HR	51	X	X
ART50_1_2	W	37	31	X	X	X	X
ART50_1_3	W	25	51	HR	28	VC	43
Treatment Group 2 (200mg insert x 5 doses)							
ART200_1_1	W	31	16	HR	10	VC	10
ART200_1_2	W	35	33, 58	HR	22	X	X
ART200_1_3	W	35	16	HR	31	X	X
ART200_1_4	B	23	16, 35, 42, 52	X	X	X	X
ART200_1_5	W	27	54, 73	HR	8	VC	43
ART200_1_6	W	33	52	HR	10	VC	42
ART200_1_7	W	28	16, 18, 62	HR	8	X	X
ART200_1_8	W	29	16	X	X	X	X
ART200_1_9	B	26	58, 68	HR	16	X	X
Treatment Group 3 (200mg insert x 5 doses at weeks 0, 2)							
ART200_2_1	W	32	51	HR	10	VC	10
ART200_2_2	B	26	52, 59	X	X	X	X
ART200_2_3	W	32	16, 53	HR	30	X	X
ART200_2_4	W	29	16, 31, 42	X	X	X	X
ART200_2_6	A	37	58	X	X	X	X
ART200_2_7	W	23	82	HR	6	VC	29
ART200_2_8	W	43	16	HR	7	VC	15
ART200_2_9	W	27	42, 66	HR	6	X	X
Treatment Group 4 (200mg insert x 5 doses at weeks 0, 2, 4)							
ART200_3_1	B	39	33, 83	HR	6	X	X
ART200_3_2	W	32	16	HR	38	X	X
ART200_3_3	W	50	16	X	X	X	X
ART200_1_4	W	32	16	X	X	X	X
ART200_3_5	W	24	52	X	X	X	X
ART200_3_6	B	39	51, 83, IS39	HR	6	X	X
ART200_3_7	W	25	16	HR	12	VC	12
ART200_3_8	A	42	33	HR	9	X	X

A = Asian; **B** = Black; **W** = White

TTHR = time to histologic regression (wks); **TTVC** = time to viral clearance (wks)

Table 3. Reported adverse events

	Treatment group (number of subjects)				
Parameter	**1 (3)**	**2 (9)**	**3 (10)**	**4 (8)**	**Total (30)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥1 AE	2 (66.7)	9 (100)	100 (80)	8 (100)	**27 (90)**
≥1 Related AE	2 (66.7)	6 (66.7)	8 (80)	8 (100)	**24 (80)**
≥1 Serious AE	0	0	1 (10)	0	**1 (3.3)**
≥ 1 Related Serious AE	0	0	0	0	**0**
Total occurrences	**n**	**n**	**n**	**n**	**n**
Deaths	0	0	0	0	**0**
All AEs	14	42	50	55	**161**
All Related AEs	12	27	42	51	**132**
All Serious AEs	0	0	1	0	**1**
All Related Serious AEs	0	0	0	0	**0**

Conclusions

- Self-administered vaginal artesunate inserts were **safe and well-tolerated**.
- We observed **histologic regression in two-thirds** of patients and **viral clearance in nearly half** of those who had histologic regression.
- This regression rate is **clinically relevant**, compared to a 20-29% expected regression rate.
- Effective self-administered treatment could provide an **alternative to surgical treatment** in high-resource settings, and substantially impact **access and barriers to care** in low-resource settings

Future Directions

- Validation in Phase IIb clinical trial (CIN) (NCT04098744)
- Clinical trials for pre-invasive HPV lesions in the anus (**AIN2/3**) (NCT03100045) and vulvar intraepithelial neoplasia (**VIN2/3**) (NCT03792516)

Reference

Trimble CL et al, "A first-in-human proof-of-concept trial of intravaginal artesunate to treat cervical intraepithelial neoplasia 2/3 (CIN2/3)" Gynecol Oncol 2020 Jan 28 Epub ahead of print