Phase 2 Study of TAVT-119 (Amlodipine Besylate) Gel in Patients with Chronic Anal Fissure

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Background

- First line treatments for anal fissure (AF) include:
  - Topical nitrates (limited by headache / tolerability)[1-3]
  - Topical calcium channel blockers (not FDA approved; compounded)[1,4]
- TAVT-119 is a novel amlodipine formulation in development to treat anal fissure pain

Objectives

- To assess the efficacy, safety, and tolerability of TAVT-119 gel in patients with AF

Methods

Study Design

- Phase 2, 6-week, double-blind, placebo-controlled trial (Part 1), with a 6-week open-label extension (Part 2)
- Conducted at 3 sites in Hungary (EUDRACT: 2019-000853-30)

Key Eligibility

- **Part 1:** Aged ≥18 years; single, chronic AF (≥6 weeks); moderate to severe anal pain (50–100 mm on a 100 mm visual analog scale [VAS] over past 2 weeks)
- **Part 2:** Not completely healed at the end of Part 1

Assessments

- Anal pressure (manometry)
- Investigator-assessed healing (grade 0 [none], grade 1 [partial], or grade 2 [complete])
- Pain (VAS 0–100 mm; 0 = no pain)
- Bleeding (anal bleeding score [ABS], 2–9; 2 = lowest frequency and amount)
- Complete response (composite of healing [grade 2] and pain [30% decrease])
- Safety (vitals and treatment-emergent adverse events [TEAEs])

Analyses

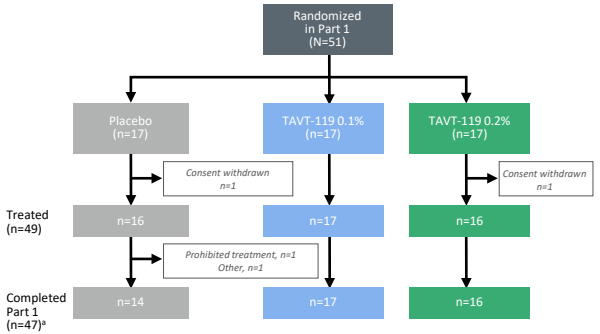
- Changes from baseline in resting anal pressure (primary endpoint at Day 42), anal pain, and bleeding analyzed using mixed model repeated measures
- Secondary endpoints were summarized descriptively
- The responder analyses included number of patients with ≥30% reduction in pain (pre-specified), ≥50% reduction in pain (post hoc), and no anal bleeding (ABS=2; post hoc)
- Interim assessment for conditional powering of primary endpoint when 50% of patients completed Part 1

Results

Study Status/Patients

- Of the 90 planned patients, 51 were randomized between 7 Aug 2019 and 10 Jun 2020 **(Figure 1)**
  - Recruitment was stopped early in Mar 2020 as sites closed due to COVID-19; terminated in Jun 2020 due to interim assessment
- The groups were well-matched demographically **(Table 1)**

Figure 1. Patient disposition



[a]A total of 43 patients continued into Part 2 of the study, to all receive TAVT-119 0.2% twice daily (BID) TAVT-119 0.1% gel BID was equivalent to 1 mg amlodipine daily; TAVT-119 0.2% gel BID was equivalent to 2 mg amlodipine daily; all patients received best supportive care during the study

Table 1. Patient demographics and baseline disease characteristics (safety population)

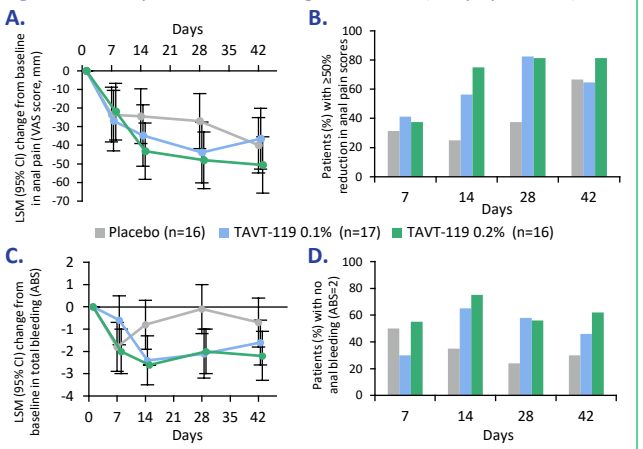
Parameter	Statistic	Placebo (n=16)	TAVT-119 0.1% (n=17)	TAVT-119 0.2% (n=16)	Overall (N=49)
Sex, male	n (%)	10 (62.5)	11 (64.7)	9 (56.3)	30 (61.2)
Age (years)	Mean (SD)	46.1 (12.8)	46.5 (13.1)	41.6 (13.8)	44.8 (13.2)
Race, White	n (%)	16 (100)	17 (100)	16 (100)	49 (100)
Resting anal pressure (mmHg)	Mean (SD)	100.9 (20.8)	95 (24.2)	101.3 (26.2)	–
Anal pain intensity (mm)	Mean (SD)	76.2 (23.3)	69.9 (22)	71.8 (25.7)	–
Total bleeding score	Mean (SD)	5.3 (2)	5.4 (2.1)	5.7 (2.8)	–

SD, standard deviation

Efficacy

- At Day 42, there were no significant differences between active treatment and placebo in anal pressure, and no clinically significant differences for complete healing or complete response rates **(Table 2)**
- However, positive trends were noted for anal pain and bleeding in patients treated with TAVT-119 vs placebo gel **(Figures 2A-D)**

Figure 2. Anal pain and bleeding outcomes (ITT population)



In the TAVT-119 0.1% group, one patient had a missing score at Day 14. ABS, anal bleeding score; CI, confidence interval; ITT, intent to treat; LSM, least-squares mean; VAS, visual analog scale

Table 2. Efficacy results at day 42 (ITT population)

	Placebo (n=16)	TAVT-119 0.1% (n=17)	TAVT-119 0.2% (n=16)
LSM change in anal pressure from baseline, mmHg (95% CI)	-42.3 (-53.6, -31.1)	-43.5[a] (-55.3, -31.6)	-36.1[a] (-47.0, -25.2)
Complete response, n (%)	4[b] (26.7)	6 (35.3)	3 (18.8)
Complete healing, n (%)	4[b] (26.7)	6 (35.3)	3 (18.8)
≥30% reduction in anal pain, n (%)	13[b] (86.7)	13 (76.5)	14 (87.5)

[a]No significant difference vs placebo. [b]n=15 at Day 42
CI, confidence interval; ITT, intent to treat; LSM, least-squares mean

Safety

- In Part 1, TAVT-119 was generally well tolerated, with TEAEs in 13 placebo patients (81.3%), and 10 (58.8%) and 11 (68.8%) patients receiving TAVT-119 0.1% and 0.2%, respectively
- There were no serious AEs, and the most common TEAEs are shown in **Table 3**

Table 3. Most frequent TEAEs (safety population)

Number (%) of patients	Placebo (n=16)	TAVT-119 0.1% (n=17)	TAVT-119 0.2% (n=16)	Overall (N=49)
Anorectal discomfort	5 (31.3)	1 (5.9)	2 (12.5)	8 (16.3)
Constipation	2 (12.5)	2 (11.8)	1 (6.3)	5 (10.2)
Oropharyngeal pain	1 (6.3)	2 (11.8)	2 (12.5)	5 (10.2)
Diarrhea	3 (18.8)	1 (5.9)	0	4 (8.2)
Nasopharyngitis	1 (6.3)	2 (11.8)	0	3 (6.1)
Headache	0	2 (11.8)	1 (6.3)	3 (6.1)
Hypertension	0	3 (17.6)	0	3 (6.1)

Study Limitations

- Small sample size due to early termination of the study
- Anal pressure assessed 12 hours post-dose (later than other studies[5,6]), and may have limited clinical relevance
- Six weeks may not be long enough to compare effects on healing

Conclusions

- TAVT-119 gel was generally well tolerated in AF patients, with the 0.2% strength showing promise in reducing anal pain. Further evaluation of TAVT-119 gel is planned.

References

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