Randomized Phase Ib Clinical Trial of DB-020 Intratympanic Injections to Reduce High-Dose Cisplatin Ototoxicity

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About the article

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Introduction | Methods | Results | Discussion | Reference

Introduction

- **Cisplatin**: widely used for a broad range of solid tumors
- **Incidence** of cisplatin-induced ototoxicity in adult patients with cancer: **36%***
- Previous efforts to reduce cisplatin ototoxicity with IT steroid injections **failed** to demonstrate benefit.*
- **DB-020 (Sodium thiosulfate pentahydrate)**: chelating and inactivating cisplatin locally in the cochlea

*Chattaraj, A., Syed, M. P., Low, C. A., & Owonikoko, T. K. (2023). Cisplatin-Induced Ototoxicity: A Concise Review of the Burden, Prevention, and Interception Strategies. JCO oncology practice, 19(5), 278–283. https://doi.org/10.1200/OP.22.00710

The status quo

- **IV sodium thiosulfate high dose (16-20 g/m2):**
  Approved by FDA for use in pediatric patients to reduce the risk of cisplatin-associated ototoxicity

- No FDA-approved drugs for adults against Cisplatin ototoxicity.

- IT injection offers the potential to reduce ototoxicity without diminishing the intended anti-tumor effects provided by systemic cisplatin exposure

Previous trial – Phase Ia*

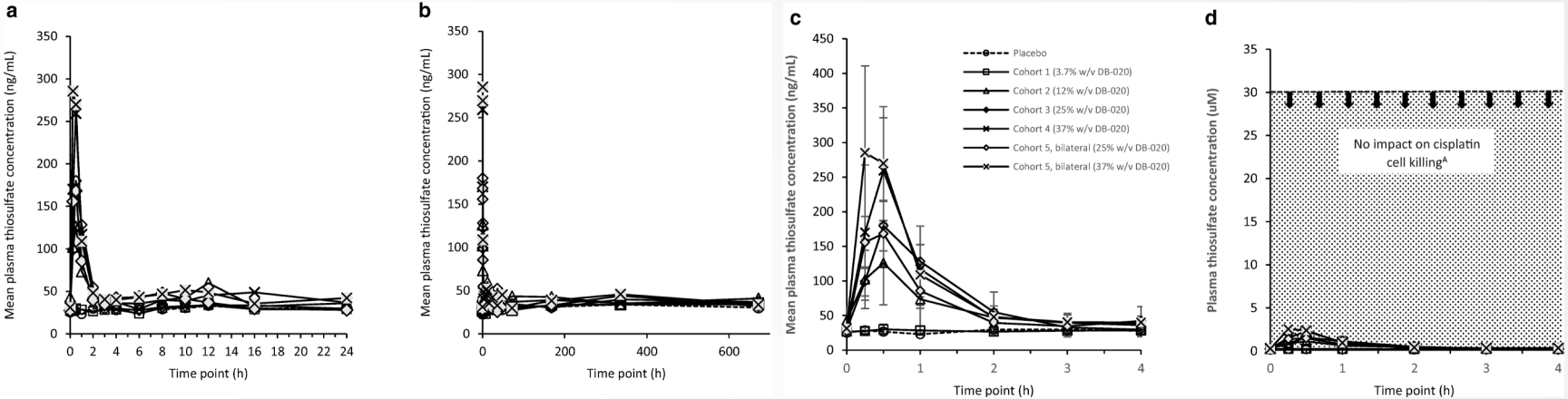
Phase I study in healthy volunteers (DB-020-001)

No serious treatment-emergent adverse events (TEAEs)

No discontinuations occurred due to adverse events (AEs)

*Viglietta, V. et al. (2020). Phase 1 study to evaluate safety, tolerability and pharmacokinetics of a novel intra-tympanic administered thiosulfate to prevent cisplatin-induced hearing loss in cancer patients.

Previous trial – Pharmacokinetics*,**



*Viglietta, V. et al. (2020). Phase 1 study to evaluate safety, tolerability and pharmacokinetics of a novel intra-tympanic administered thiosulfate to prevent cisplatin-induced hearing loss in cancer patients.
**Berglin, C. et al. (2011). Prevention of cisplatin-induced hearing loss by administration of a thiosulfate-containing gel to the middle ear in a guinea pig model.

Endpoints

Primary endpoint: evaluate safety and tolerability:

- Incidence of AEs
- Vital signs
- Electrocardiogram results
- Clinical laboratory assessments
- Otoscopy examination results
- Follow-up disease status

Endpoints

Secondary endpoint:
Evaluation of efficacy in DB-020–treated compared with placebo-treated ears using

- Incidence of American Speech-Language-Hearing Association (ASHA)–defined ototoxicity
- Changes in pure tone audiometry
- Tympanometry…

Study design

Phase Ib, randomized, double-blind, placebo-controlled clinical trial
Sites: five medical centers in **Australia** and the **United States**

Patients:
Including:

- over 18 years of age
- scheduled to receive a total cumulative cisplatin dose of ≥280 mg/m2 over at least three cycles (once every 21 days or once every 28 days)
- cancer of any type and any stage
- anticipated survival of >1 year
- Normal otoscopic findings…

Excluding

- investigational agents and/or radiation >35 Gy involving the cochlear region
- Patients with hearing loss of >45 dB averaged over 6 and 8 kHz in either ear
- Prior Cisplatin treatment…

Treatment

Bilateral IT injections

- DB-020 in one ear
- Placebo: (sodium hyaluronate in 0.9% sodium chloride) in the other

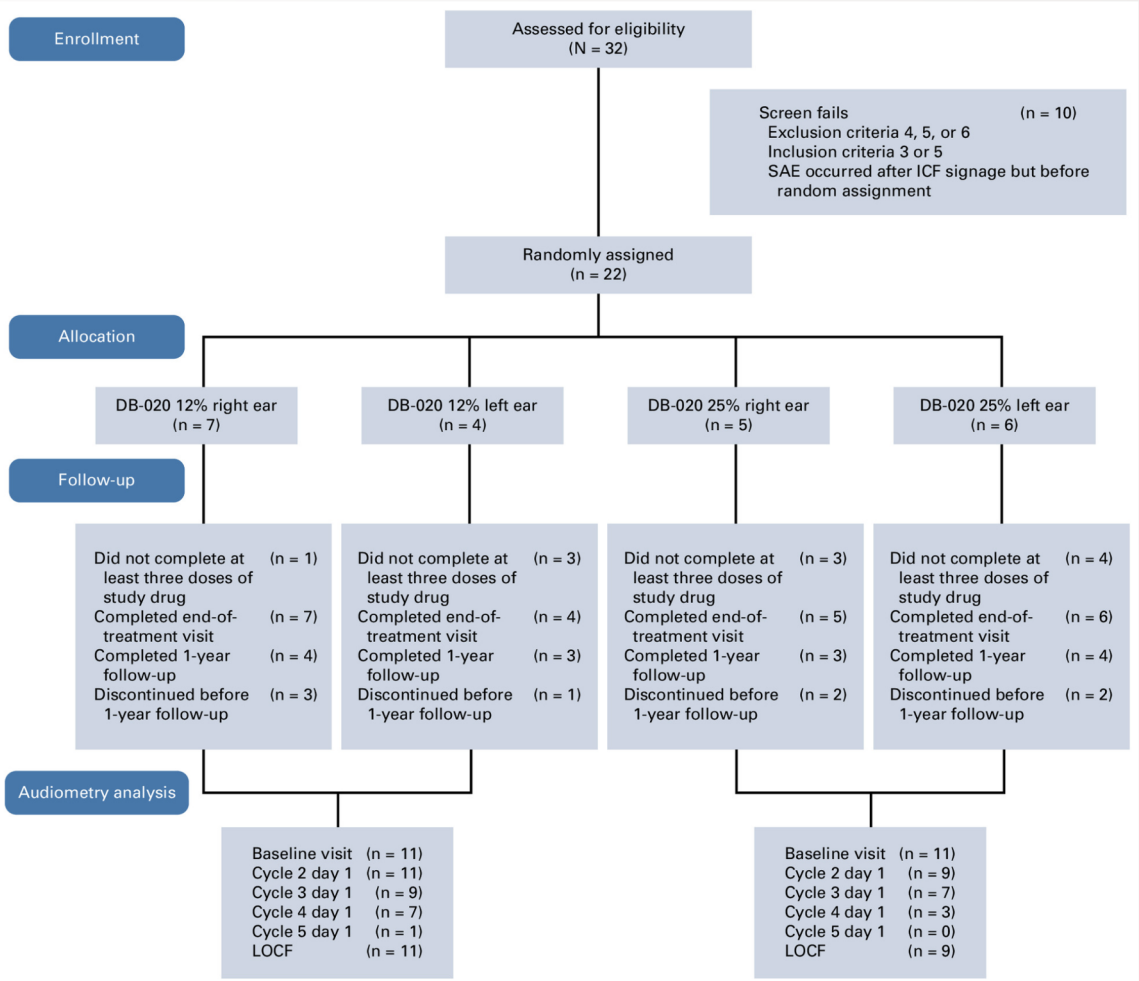
Randomization

- DB-020 12% w/v (0.5 M) in the right ear
- DB-020 12% w/v (0.5 M) in the left ear
- DB-020 25% w/v (1 M) in the right ear
- DB-020 25% w/v (1 M) in the left ear
- Placebo assigned to the non–DB-020 ear for each patient

Metrics: Ototoxicity

ASHA criteria

- Ototoxic change if one of the following criteria are met:
  a. **≥20-dB** increase in audiometric threshold at any **one** test frequency
  b. **≥10-dB** increase in threshold at any **two adjacent** frequencies, or
  c. **loss of response** at **three consecutive** frequencies where responses were previously obtained
- Severe ototoxicity was defined as a **≥20-dB** increase in measured threshold at any **two adjacent frequencies**


Enrollment
Assessed for eligibility
(N = 32)
Screen fails (n = 10)
Exclusion criteria 4, 5, or 6
Inclusion criteria 3 or 5
SAE occurred after ICF signage but before random assignment
Randomly assigned
(n = 22)
Allocation
DB-020 12% right ear
(n = 7)
DB-020 12% left ear
(n = 4)
DB-020 25% right ear
(n = 5)
DB-020 25% left ear
(n = 6)
Follow-up
Did not complete at least three doses of study drug (n = 1)
Completed end-of-treatment visit (n = 7)
Completed 1-year follow-up (n = 4)
Discontinued before 1-year follow-up (n = 3)
Did not complete at least three doses of study drug (n = 3)
Completed end-of-treatment visit (n = 4)
Completed 1-year follow-up (n = 3)
Discontinued before 1-year follow-up (n = 1)
Did not complete at least three doses of study drug (n = 3)
Completed end-of-treatment visit (n = 5)
Completed 1-year follow-up (n = 3)
Discontinued before 1-year follow-up (n = 2)
Did not complete at least three doses of study drug (n = 4)
Completed end-of-treatment visit (n = 6)
Completed 1-year follow-up (n = 4)
Discontinued before 1-year follow-up (n = 2)
Audiometry analysis
Baseline visit (n = 11)
Cycle 2 day 1 (n = 11)
Cycle 3 day 1 (n = 9)
Cycle 4 day 1 (n = 7)
Cycle 5 day 1 (n = 1)
LOCF (n = 11)
Baseline visit (n = 11)
Cycle 2 day 1 (n = 9)
Cycle 3 day 1 (n = 7)
Cycle 4 day 1 (n = 3)
Cycle 5 day 1 (n = 0)
LOCF (n = 9)

Demographics

Demographic Characteristic	DB-020 12% Right Ear (n = 7)	DB-020 12% Left Ear (n = 4)	DB-020 25% Right Ear (n = 5)	DB-020 25% Left Ear (n = 6)	Overall (N = 22)
Age at consent, years					
Mean (SD)	56.7 (12.76)	56.0 (6.78)	53.4 (6.23)	54.0 (12.95)	55.1 (10.12)
Median	62.0	53.5	54.0	53.0	54.0
Min, max	37, 71	51, 66	46, 62	35, 69	35, 71
Sex, No. (%)					
Male	5 (71.4)	4 (100)	5 (100)	5 (83.3)	19 (86.4)
Female	2 (28.6)	0	0	1 (16.7)	3 (13.6)
Race, No. (%)					
White	7 (100)	4 (100)	5 (100)	6 (100)	22 (100)

Demographics

Neoplasms benign, malignant, and unspecified, No. (%)	6 (85.7)[a]	4 (100)	5 (100)	6 (100)	21 (95.5)
Tonsil cancer	3 (42.9)	2 (50.0)	4 (80.0)	3 (50.0)	12 (54.5)
Squamous cell carcinoma of the tongue	1 (14.3)	1 (25.0)	1 (20.0)	1 (16.7)	4 (18.2)
Oropharyngeal squamous cell carcinoma	0	1 (25.0)	0	1 (16.7)	2 (9.1)
Squamous cell carcinoma	1 (14.3)	0	0	1 (16.7)	2 (9.1)
Basal cell carcinoma	0	0	0	1 (16.7)	1 (4.5)
Lung neoplasm malignant	1 (14.3)	0	0	0	1 (4.5)
Malignant melanoma	0	0	0	1 (16.7)	1 (4.5)
Oral cavity cancer metastatic	0	0	0	1 (16.7)	1 (4.5)
Oropharyngeal cancer	1 (14.3)	0	0	0	1 (4.5)

Safety

All patients experienced **at least one TEAE*.**
The most common TEAEs by preferred term were

- **ear pain** (n = 18, 81.8%)
- **nausea** (n = 16, 72.7%)
- **constipation** (n = 13, 59.1%)
- **tinnitus** (n = 11, 50.0%)
- **dysgeusia** (n = 9, 40.9%)

*TEAE: Treatment Emergent Adverse Events

Safety

Preferred Term, n (%)	DB-020 12% Right Ear (N = 7)	DB-020 12% Left Ear (N = 4)	DB-020 25% Right Ear (N = 5)	DB-020 25% Left Ear (N = 6)	Overall (N = 22)
Subjects with ≥1 TEAE	7(100.0)	4(100.0)	5(100.0)	6(100.0)	22(100.0)
Ear pain	5 (71.4)	3 (75.0)	5 (100)	5 (83.3)	18 (81.8)
Nausea	6 (85.7)	3 (75.0)	4 (80.0)	3 (50.0)	16 (72.7)
Constipation	4 (57.1)	2 (50.0)	3 (60.0)	4 (66.7)	13 (59.1)
Tinnitus	5 (71.4)	0	2 (40.0)	4 (66.7)	11 (50.0)
Dysgeusia	4 (57.1)	0	3 (60.0)	2 (33.3)	9 (40.9)
Fatigue	3 (42.9)	1 (25.0)	0	2 (33.3)	6 (27.3)

Safety

Ear pain: DB-020-treated ears (77.3%) > Placebo-treated ears (13.6%)
Tinnitus: Placebo-treated ears (50.0%) > DB-020-treated ears (13.6%)

Preferred Term	Placebo (N = 22), No. (%)	DB-020 12% (n = 11), No. (%)	DB-020 25% (n = 11), No. (%)	DB-020 (N = 22), No. (%)
Ear pain	3 (14)	8 (73)	9 (82)	17 (77)
Tinnitus	11 (50)	0 (0)	3 (27)	3 (14)

Safety

Serious adverse events (SAEs)

- Acute kidney injury (n=2, 9.1%)
- Aspiration Pneumonia (n=1, 4.1%)
- Pulmonary embolism (n=1, 4.1%)
- Radiation mucositis (n=1, 4.1%) ...
- Otoscopy results showed **no** tympanic membrane perforations.
- **No AEs led to death** during this study.

Exposure

Mean total cumulative cisplatin dose: **255 mg/m2**
Mean number of cisplatin cycles: **2.3 cycles**

Assessment Timepoint, n (%)	DB-020 12% (N = 11)	DB-020 25% (N = 11)	Overall (N = 22)
Cycle 1 day 1	11 (100)	11 (100)	22 (100)
Cycle 2 day 1	9 (81.8)	7 (63.6)	16 (72.7)
Cycle 3 day 1	7 (63.6)	4 (36.4)	11 (50.0)
Cycle 4 day 1	1 (9.1)	0	1 (4.5)
Cycle 5 day 1	0	0	0
Cycle 6 day 1	0	0	0

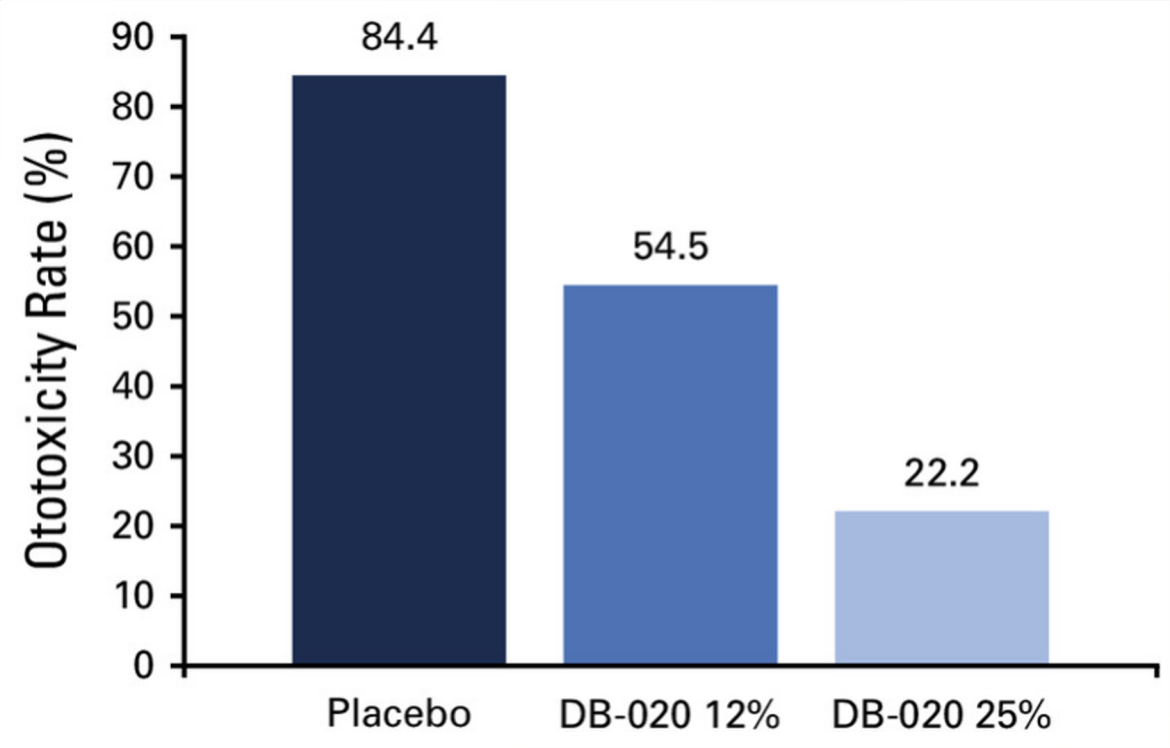
Pharmacokinetics

Mean endogenous thiosulfate plasma concentrations
Before administration vs. **After** administration
(15 minutes before cisplatin dose)
DB-020 12%: 400 ng/mL **vs.** 393 ng/mL
DB-020 25%: 570 ng/mL **vs.** 530 ng/mL

☒ DB-020 did not affect endogenous thiosulfate plasma concentrations

Mean unbound cisplatin concentrations on cycle 1 day 1
DB-020 12%: 1928 ng/mL
DB-020 25%: 2061 ng/mL

Ototoxicity

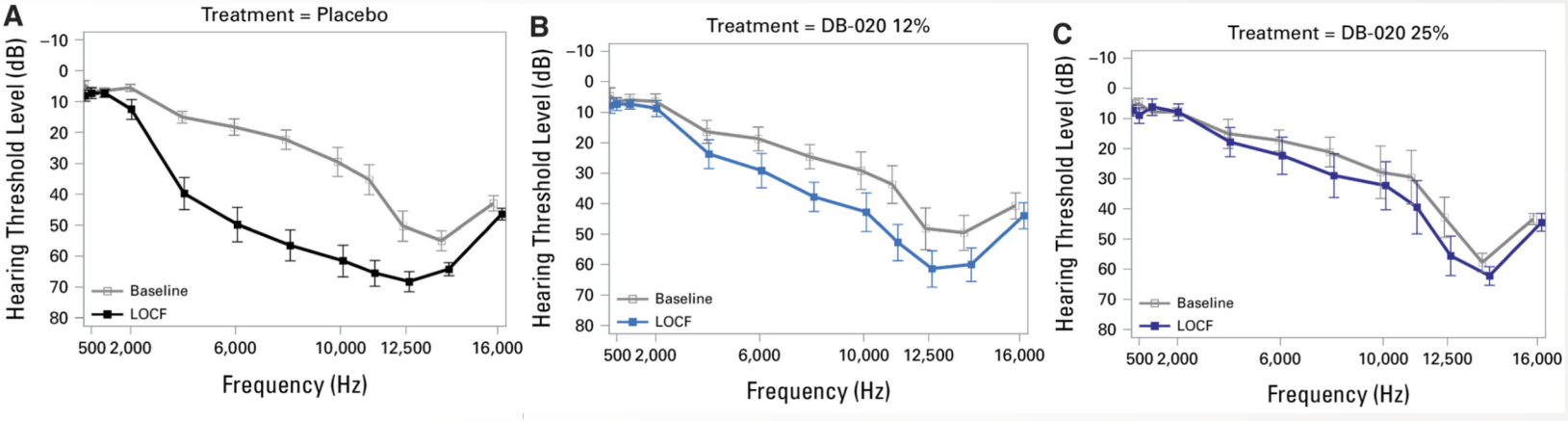


Ototoxicity

Assessment	Placebo Ears (N = 20)	DB-020 Ears (N = 20)	*P* DB-020 *v* Placebo
Ototoxicity (250-8,000 Hz), %	85	40	.0027
Ototoxicity (9,000-16,000 Hz), %	90	60	.0143
Severe ototoxicity (250-8,000 Hz), %	70	15	.0009
Severe ototoxicity (9,000-16,000 Hz), %	80	35	.0027
Average threshold shift (4,000-8,000 Hz), LS mean dB	30.22	7.99	<.0001
Average threshold shift (9,000-16,000 Hz), LS mean dB	21.38	9.19	.0022
Speech intelligibility index, LS mean	−0.15	−0.03	.0001

☒ Significantly lower incidences of ototoxicity

Ototoxicity



Results

	LS Mean (SE)			DB-020 12% *v* Placebo			DB-020 25% *v* Placebo		
Timepoint	**Placebo**	**DB-020 12%**	**DB-020 25%**	**Difference (SE)**	**95% CI**	***P*-value**	**Difference (SE)**	**95% CI**	***P*-Value**
4,000–8,000 Hz									
LOCF	30.22 (4.317)	10.24 (3.433)	5.23 (1.784)	–19.98 (5.40)	–30.93, –9.02	.007	–24.99 (4.78)	–34.68, –15.29	<.0001
250–8,000 Hz									
LOCF	15.02 (2.374)	5.41 (1.730)	2.60 (1.191)	–9.61 (2.92)	–15.53, –3.70	.0002	–12.43 (2.65)	–17.81, –7.05	<.0001
9,000–16,000 Hz									
LOCF	21.38 (3.215)	11.68 (2.682)	6.15 (1.901)	–9.70 (4.19)	–18.19, –1.21	.0263	–15.23 (3.78)	–22.90, –7.57	.0003

Tympanometry Category Shifts

Treatment	Baseline Category[a]	LOCF Category, n (%)				
		B	C	As	A	Ad
Placebo (N = 22)	B	0	0	0	0	0
	C	0	0	0	0	0
	As	0	0	1 (4.5)	0	0
	A	0	1 (4.5)	0	17 (77.3)	0
	Ad	0	0	0	0	0
DB-020, 12% (N = 11)	B	0	0	0	0	0
	C	0	0	0	0	0
	As	0	0	0	0	0
	A	0	1 (9.1)	1 (9.1)	8 (72.7)	0
	Ad	0	0	0	0	0
DB-020, 25% (N = 11)	B	0	0	0	0	0
	C	0	0	0	0	0
	As	0	0	0	0	0
	A	0	1 (9.1)	0	8 (72.7)	0
	Ad	0	0	0	0	0
DB-020 (N = 22)	B	0	0	0	0	0
	C	0	0	0	0	0
	As	0	0	0	0	0
	A	0	2 (9.1)	1 (4.5)	16 (72.7)	0
	Ad	0	0	0	0	0

HHIA Category Shifts

Supplemental Table 13. HHIA Category Shifts at End of Treatment

Treatment Group	Baseline Category[a]	End-of-Treatment Category, n (%)		
		No Handicap	Mid-Moderate Handicap	Significant Handicap
DB-020, 12% (= 11)	No handicap	9 (81.8)	0	0
	Mid-moderate handicap	0	0	0
	Significant handicap	0	0	0
DB-020, 25% (n = 11)	No handicap	5 (45.5)	1 (9.1)	0
	Mid-moderate handicap	1 (9.1)	0	0
	Significant handicap	0	0	0
Overall (N = 22)	No handicap	14 (63.6)	1 (4.5)	0
	Mid-moderate handicap	1 (4.5)	0	0
	Significant handicap	0	0	0

Safety - Adverse events

Ear pain: DB-020-treated ears (77.3%) > Placebo-treated ears (13.6%)
Tinnitus: Placebo-treated ears (50.0%) > DB-020-treated ears (13.6%)

Preferred Term	Placebo (N = 22), No. (%)	DB-020 12% (n = 11), No. (%)	DB-020 25% (n = 11), No. (%)	DB-020 (N = 22), No. (%)
Ear pain	3 (14)	8 (73)	9 (82)	17 (77)
Tinnitus	11 (50)	0 (0)	3 (27)	3 (14)

- Tinnitus was more common in placebo-treated ears than in DB-020–treated ears, suggesting tinnitus was related to ototoxicity
- Ear pain related to injections lasted a median duration of 10 minutes after injection

Safety - Serious Adverse Events

Serious adverse events (SAEs)

- Acute kidney injury (n=2, 9.1%)
- Aspiration Pneumonia (n=1, 4.1%)
- Pulmonary embolism (n=1, 4.1%)
- Radiation mucositis (n=1, 4.1%) ...

→ The 14 SAEs were all determined to be unrelated to study drug, with 9 occurring in DB-020 12%-treated patients and 5 in DB-020 25%-treated patients.

Affecting Cisplatin level

- Sodium thiosulfate threshold: **30μM (7445 ng/mL)***
- Concentrations under IT injections **(≤570 ng/mL)** were significantly lower than concentrations seen with systemic administration **(approximately 2 million ng/mL)**
- Free cisplatin levels in this study were consistent with values expected in the absence of a cisplatin-chelating agent

→ DB-020 had **no systemic impact** on cisplatin plasma concentrations.

*Viglietta, V. et al. (2020). Phase 1 study to evaluate safety, tolerability, and pharmacokinetics of a novel intra-tympanic administered thiosulfate to prevent cisplatin-induced hearing loss in cancer patients. Investigational New Drugs, 38(5), 1463–1471. https://doi.org/10.1007/s10637-020-00918-1

Strength and Limitations

Strength

Each patient was their own control with one ear treated with DB-020 and the other with placebo

Limitation

No patients received placebo in both ears.

Summary

- Clear and meaningful reductions in cisplatin ototoxicity
- Low plasma concentration of thiosulfate
- No apparent impact on plasma concentrations of free cisplatin
- safety profile that supports continued development of the highest dose, DB-020 25% (1.0M)

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