Retrospective Analysis of a Randomized Study and Open-Label Study to Evaluate the Safety and Efficacy of OK-432 in Patients with Lymphatic Malformations

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BACKGROUND

- Lymphatic malformations (LM) are rare and congenital anomalies that most commonly arise in the head and neck in children[1]
- LM rarely resolve spontaneously, and currently there are no FDA-approved therapies for the treatment of LM in the United States (US)
- OK-432 is an immunotherapeutic derived from non-viable cells of Streptococcus pyogenes [Group A, Type 3] Su strain treated with benzyl-penicillin used in the treatment of LM
- OK-432 was approved for the treatment of LM in 1995 and is currently the standard of care for LM in Japan and Taiwan

PURPOSE

- The purpose of the randomized study and open-label study was to assess the efficacy and safety of OK-432 in patients with LM

METHODS

- The randomized study conducted in the US enrolled subjects between 1998 and 2005, and the open-label study conducted in the US enrolled subjects between 2005 and 2017
- In the randomized study, subjects were randomized 2:1 to receive treatment immediately (immediate treatment group [ITG]) or delayed by 6 months (delayed treatment group [DTG])
- In the open-label study, subjects were enrolled for compassionate use access to OK-432 and were treated immediately
- Subjects received 4 doses of OK-432 approximately 6-8 weeks apart
- In the randomized study, efficacy was assessed 2 weeks post-treatment; in the open-label study, efficacy was assessed 1 to 6 months post-treatment
- Subjects were followed up for safety throughout the study duration
- The between-treatment group difference in proportion of clinical success or spontaneous resolution was analyzed by a logistic regression model
- Data were analyzed as observed

REFERENCE

1. Lymphatic Malformations. *NORD*. 2020. Accessed March 29, 2022: https://rarediseases.org/rare-diseases/lymphatic-malformations/

RESULTS

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

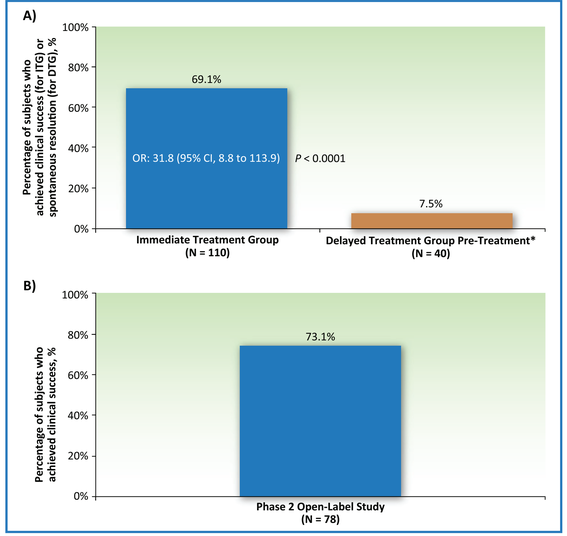
Characteristics	Phase 2 Randomized Study		Phase 2 Open-Label Study
	Immediate Treatment N = 171	Delayed Treatment N = 75	N = 275
Age (years)			
n1	169	73	273
Mean (SD)	4.576 (6.9834)	4.468 (5.0597)	5.481 (6.6382)
Median	2.000	2.000	3.000
Min, max	0.08, 73.00	0.08, 17.00	0.01, 43.00
Age Group, n (%)			
n1	169	73	273
< 6 months[1]	5 (3.0%)	2 (2.7%)	20 (7.3%)
6 months to 18 years	163 (96.4%)	71 (97.3%)	235 (86.1%)
> 18 years[2]	1 (0.6%)	0 (0.0%)	18 (6.6%)
Gender, n (%)			
n1	170	74	274
Male	88 (51.8%)	37 (50.0%)	123 (44.9%)
Female	82 (48.2%)	37 (50.0%)	151 (55.1%)
Race/Ethnicity, n (%)[3]			
n1	158	69	266
White	113 (71.5%)	49 (71.0%)	36 (13.5%)
Black or African American	18 (11.4%)	11 (15.9%)	2 (0.8%)
Asian	8 (5.1%)	1 (1.4%)	191 (71.8%)
Hispanic or Latino	20 (12.7%)	8 (11.6%)	29 (10.9%)
American Indian or Alaska Native	1 (0.6%)	0 (0.0%)	10 (3.8%)
Other	3 (1.9%)	0 (0.0%)	7 (2.6%)
Clinical Stage, n (%)			
n1	118	36	87
Stage I: Unilateral Infrahyoid	16 (13.6%)	2 (5.6%)	18 (20.7%)
Stage II: Unilateral Suprahyoid	27 (22.9%)	8 (22.2%)	6 (6.9%)
Stage III: Unilateral Infra and Suprahyoid	54 (45.8%)	19 (52.8)	51 (58.6%)
Stage IV: Bilateral Suprahyoid	10 (8.5%)	3 (8.3%)	-
Stage V: Bilateral Infra and Suprahyoid	7 (5.9%)	2 (5.6%)	2 (2.3%)
Stage VI: Bilateral Infrahyoid	1 (0.8%)	0 (0.0%)	-
Modifiers Only[4]	3 (2.5%)	2 (5.6%)	10 (11.5%)
Mediastinal Involvement	14 (11.9%)	4 (11.1%)	11 (12.6%)
Stage VII: Retropharyngeal Involvement	19 (16.1%)	6 (16.7%)	11 (12.6%)
Laterality, n (%)			
n1	147	55	210
Unilateral	133 (90.5%)	50 (90.9%)	203 (96.7%)
Bilateral	14 (9.5%)	5 (9.1%)	7 (3.3%)
Lymphatic Malformation Type, n (%)			
n1	141	47	123
Macrocystic	71 (50.4%)	18 (38.3%)	72 (58.5%)
Microcystic	10 (7.1%)	4 (8.5%)	-
Mixed cystic	39 (27.7%)	16 (34.0%)	27 (22.0%)
Not assigned	21 (14.9%)	9 (19.1%)	24 (19.5%)
Prior Surgery			
n1	158	72	264
Yes	19 (12.0%)	10 (13.9%)	23 (8.7%)
No	139 (88.0%)	62 (86.1%)	241 (91.3%)

ABBREVIATIONS: LM = lymphatic malformation, +M = mediastinal involvement, max = maximum, min=minimum, +RP = retropharyngeal involvement, SD = standard deviation.

NOTE: Clinical staging based on modified de Serres (1995) LM clinical staging proposal. Clinical stage modifiers +M (mediastinal involvement) and Stage VII, +RP (retropharyngeal involvement) were added to subjects with lesions that displayed such characteristics. Mixed cystic LM was defined as a combination of both macrocystic and microcystic LM (with ≥ 50% macrocystic disease). For LM type, the 'Not Assigned' category included subjects who were not assigned an LM Type or had a misdiagnosis (e.g., ranula, chyle duct). There were 3 subjects enrolled in the study but not assigned a treatment group. Percentages were based on n. [1] The age at enrollment was < 6 months and subjects were 6 months or almost 6 months of age at the time of injection. [2] The age group was > 18 years to < 65 years for the OK-432-003-OPEN (Safety Population). [3] Subjects could be in more than one category. [4] Included only subjects with mediastinal involvement and/or retropharyngeal involvement who did not fall into Stage I to VI.

- The retrospective analysis of source verified data included 246 randomized subjects and 275 open-label subjects, with the majority of subjects 6 months to 18 years of age with macrocystic and mixed cystic LM (**Table 1**)

FIGURE 1. CLINICAL SUCCESS OR SPONTANEOUS RESOLUTION BY TREATMENT GROUP FOR THE A) PHASE 2 RANDOMIZED STUDY B) PHASE 2 OPEN-LABEL STUDY.



*Reflects data prior to dosing with OK-432.

ABBREVIATIONS: DTG = delayed treatment group, ITG = immediate treatment group, LM = lymphatic malformation.

NOTE: Clinical success was defined as having either a complete (90%-100%) or substantial (60%-89%) reduction in LM volume after treatment. Clinical success in the ITG and OLG was determined with post-treatment imaging. Spontaneous resolution (or regression) was defined as the resolution of the LM without treatment during the 6 months following enrollment as determined by the investigator. Spontaneous resolution in the DTG was determined by investigator judgement prior to treatment. For subjects who were treated with < 4 injections, the post-injection response was evaluated at ~2 weeks after the final injection. If subjects were treated with > 4 injections, the post-injection response was evaluated at ~2 weeks after the 4th injection.

- In the randomized study, the primary efficacy endpoint was clinical success (defined as complete [90%-100%] or substantial [60%-89%] reduction in LM volume measured radiographically) in the ITG versus the spontaneous resolution of the LM in the DTG
  - In randomized subjects with data available for primary endpoint evaluation (N=150), 69.1% of subjects demonstrated clinical success in the ITG and 7.5% of subjects showed spontaneous resolution in the DTG ($p < 0.0001$; **Figure 1A**)
  - With eventual treatment of subjects in the DTG, clinical success rates were similar between the ITG and DTG (69.1% vs 65.6%, respectively)
- In the open-label study, the primary efficacy endpoint was clinical success (defined as complete [90%-100%] or substantial [60%-89%] reduction in LM volume measured radiographically)
  - In the open-label subjects with data available for primary efficacy endpoint evaluation (N=78), 73.1% of subjects achieved clinical success (**Figure 1B**)

TABLE 2. SUMMARY OF SUBJECT DIARY REACTIONS*

Characteristics	Phase 2 Randomized Study N = 219	Phase 2 Open-Label Study N = 275
Subjects with Observed Study Diary Data, N1	162	114
Subjects with Any Study Diary Reactions	161 (99.4%)	112 (98.2%)
Local Reactions	161 (99.4%)	112 (98.2%)
Swelling	158 (97.5%)	112 (98.2%)
Pain	142 (87.7%)	110 (96.5%)
Redness	141 (87.0%)	101 (88.6%)
Systemic Side Effects	153 (94.4%)	102 (89.5%)
Fever	126 (77.8%)	72 (63.2%)
Decreased appetite	105 (64.8%)	63 (55.3%)
Fatigue	93 (57.4%)	66 (57.9%)
Other	85 (52.5%)	39 (34.2%)
Nausea/vomiting	66 (40.7%)	35 (30.7%)
Chills	62 (38.3%)	21 (18.4%)
Headache	50 (30.9%)	32 (28.1%)
Joint pain	32 (19.8%)	18 (15.8%)
Rash	20 (12.3%)	7 (6.1%)
Joint Swelling	9 (5.6%)	3 (2.6%)

*N is the total of subjects who received at least one OK-432 injections.

NOTE: Percentages were based on N1. For the Phase 2 Randomized Study, data were combined for the immediate and delayed treatment groups. Local Reactions and systemic side effects were collected via subject diaries for 14 days after each injection. Fever was defined as body temperature ≥ 38°C (100.4°F). Redness (measured in the largest diameter): Mild= <1" or <2.5cm, Moderate= 1-2" or 2.5-5cm, Severe= >2" or >5cm. Swelling (measured in the largest diameter from baseline): Mild= <1" or <2.5cm, Moderate= 1-2" or 2.5-5cm, Severe= >2" or >5cm. Pain (mild= minor reaction to touch, moderate= cries or protests to touch, severe= cries or reports pain with any movement). Side Effects (mild= easily tolerated, moderate= obviously discomforting, severe= incapacitating).

- The most commonly reported local reactions after treatment with OK-432 were swelling, injection-site pain, and redness (**Table 2**)
- The commonly reported systemic reactions were fever, decreased appetite, and fatigue (**Table 2**)
- Overall, local reactions were more frequently reported as compared to systemic reactions (**Table 2**)
- Local and systemic reactions peaked in the first few days and resolved within 2 weeks

TABLE 3. SUMMARY OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS*

Characteristics	Phase 2 Randomized Study N = 219	Phase 2 Open-Label Study N = 27
Subjects with any TESAEs	20 (9.1%)	11 (4.0%)
Subjects with any TESAEs related to study drug	10 (4.6%)	5 (1.8%)
Subjects with any TESAEs leading to study discontinuation	1 (0.5%)	0 (0.0%)

*N is the total of subjects who received at least one OK-432 injections.

ABBREVIATIONS: SAE = serious adverse event, TESAE = treatment-emergent serious adverse event.

NOTE: Adverse events for this study were defined as any deviations from the expected response to OK-432. Only serious AEs were collected per protocol. TESAEs related to the study drug included SAEs with causality as "Possible", "Probable", or "Definite." For the Phase 2 Randomized Study, data were combined for the immediate and delayed treatment groups. Adverse event terms were coded using MedDRA version 23.0. TESAEs were defined as SAEs that occur after the first injection and within 35 days of the final injection.

- In the randomized and open-label studies, 10 of 219 (4.6%) and 5 of 275 (1.8%) subjects were reported to have treatment emergent serious adverse events (TESAEs) that were assessed by the investigator as related to study drug, respectively (**Table 3**)
- Overall, subjects were followed for up to 3 years post treatment with no new safety concerns

CONCLUSIONS

- In these studies, OK-432 was efficacious and favorably safe in treating macro-cystic and mixed-cystic LM
- Results are consistent with approximately 30 years of OK-432 experience in published studies

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