Summary Report

ZFUZE TLIF Study (693)

medicalmetrics INC.

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SIGNATURE PAGE

By signing this document, the individuals named below agree that they have reviewed and approved this Summary Report. MMI confirms that the document has passed review and meets all quality expectations.

Study Title	ZFUZE TLIF Study	
Treatment Name(s)	ZFUZE™ Cage	
SR Revision / Date	Rev B / 29-Aug-2022	
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HISTORY OF REVISIONS

The following table summarizes the history of revisions to this Summary Report:

Revision	Release Date	Significant Revisions Since Previous Version
A	14-Jul-2022	N/A
B	29-Aug-2022	• Updated the data in the report based on an updated deliverable.

ABBREVIATIONS

CIP. *Clinical Investigational Plan*

FOV. *Field of View*

Ind. *Indeterminate*

MI-TLIF. *Minimally Invasive Transforaminal Lumbar Interbody Fusion*

NA. *Not Applicable*

NR. *Not Required*

PEEK. *Poly- ether-ether-ketone*

PE-TLIF. *Percutaneous Endoscopic Transforaminal Lumbar Interbody Fusion*

PLF. *Posterior Lumbar Fusion*

REP. *Radiographic Evaluation Protocol*

SR. *Summary Report*

TLIF. *Transforaminal Lumbar Interbody Fusion*

UA. *Unable to Assess*

1 INTRODUCTION

This summary report is intended to provide a comparison of lumbar fusion rates between the imaging-based results for MMI Project 693 - ZFUZE TLIF Study and published data from the literature. Images and data were collected per the processes defined in the Radiographic Evaluation Protocol (REP), Revision A (10-Feb-22). The data used in the subsequent summary analysis were taken from the 26-Aug-22 data deliverable provided to DIFUSION.

1.1 Overview of Study Design

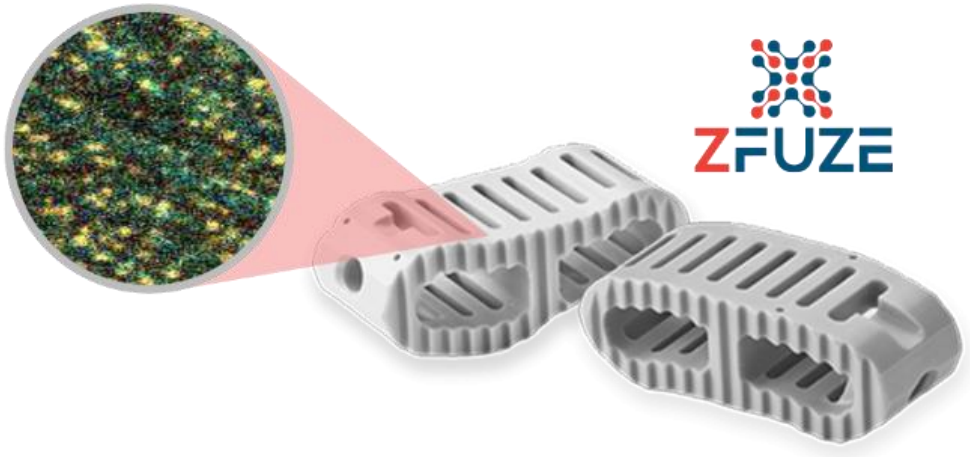
The study was designed to be an unregulated, US-based, single-arm, single-site, retrospective lumbar spinal fusion study. This pilot study used 8 month post-operative CT scans of the lumbar spine of 1 or 2 treated levels that were previously obtained for clinical reasons. The images were retrospectively reviewed to assess radiographic outcomes.

Additional study details can be found in the clinical investigational plan (CIP).

1.2 Device Description

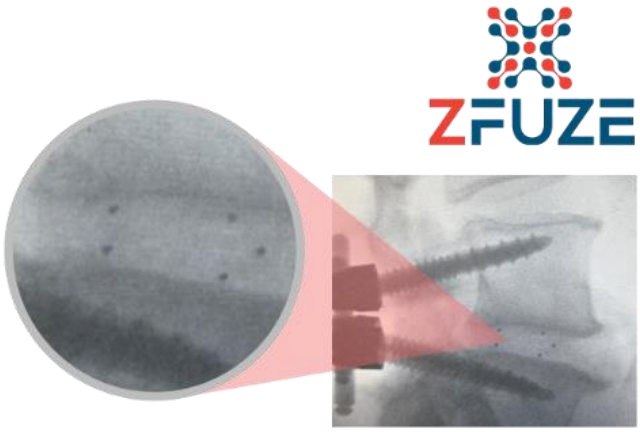
ZFUZE™ is a proprietary blend of Poly- ether-ether-ketone (PEEK) and a material know as a zeolite, a microporous aluminosilicate used in a variety of commercial purposes (**Figure 1**). Added to PEEK in an early stage of manufacturing, this zeolite imparts a negative charge to the final product, and markedly increases the biologic receptiveness of all exposed surfaces of the material. Mechanically, the material functions nearly identically to PEEK. Biologically, surface adherence of bone and in-vitro osteoblast formation are substantially increased. Fibrous rind, typically encountered in PEEK revisions, appears not to form. This material has achieved FDA clearance in late 2019, and is currently commercially available throughout the United States. The first clinical usage was in January in of 2020. ZFUZE™ cage is radiotranslucent with 5 tantalum markers identify implant limits (**Figure 2**).

Figure 1: ZFUZE™ Cage with negatively charged, hydrophilic ceramic Zeolite as shown under scanning electron microscope[1].



[1] https://www.difusiontech.com/fusion-system/. Accessed 01-Feb-22.

Figure 2: Radiotranslucent ZFUZE™ Cage with 5 tantalum markers to identify implant limits[1].



1.3 Imaging Schedule

The imaging schedule for this study is presented in **Table 1**.

Table 1: Imaging Schedule (Count of Levels).

Modality	Month 8	Unscheduled Visits[1]
CT	35[2]	9[3]

[1] Imaging collected at intervals that are not Month 8 were added to the study database as an "Unscheduled Visit" (UV), including two additional visits of a Month 9 visit and a Month 18 visit that were added into the study additionally.
[2] Including 15 single level subjects, 7 two level subjects and 2 three level subjects.
[3] Including 5 single level subjects, and 2 two level subjects.

2 METHODS

2.1 Reviewer Paradigm

All study imaging assessments were performed by a single independent imaging reviewer. The reviewer is a board-certified, fellowship-trained, licensed musculoskeletal radiologist with no financial interest in DIFUSION.

2.2 Assessment Schedule

The following assessments were performed by the reviewer using CT images at the time points indicated in **Table 2**.

Table 2: Schedule of Reviewer Assessments.

Assessments	*Location*	*Time Points*
Interbody Bridging Bone	Index	M8, UV

Assessments	*Location*	*Time Points*
Extent of Osseous Integration - Superior Interface	Index	M8, UV
Extent of Osseous Integration - Inferior Interface	Index	M8, UV
Device Subsidence	Index	M8, UV
Device Migration	Index	M8, UV
Additional Observations	-	M8, UV

In cases where an assessment cannot be made from the available images due to technical factors, sub-optimal image quality, obscured anatomy, obstructed view or other imaging artifacts, the assessment were graded as 'Ind' (Indeterminate). If an assessment cannot be made due to missing images or inadequate FOV, it was graded as 'UA' (Unable to Assess). In cases where an assessment was not applicable to the subject/visit it was graded as 'NA' (Not Applicable). Assessments that are not required at select time points were reported as 'NR' (Not Required).

This summary report focuses on the assessment of Interbody Bridging Bone as described in section 2.3. Additional details on the classification systems for the other assessments can be found in the REP.

2.3 Lumbar Fusion Assessment

The study used the following classification system of Interbody Bridging Bone to assess lumbar fusion.

Interbody Bridging Bone was graded at each index level in accordance with the following definitions:

0. **Absent:** No evidence of continuous bridging bone from endplate to endplate.
1. **Present:** Presence of continuous bridging bone from endplate to endplate.

All available CT were used to determine the presence of bridging bone. Bridging is defined as mature, bony continuity from endplate to endplate with no intervening fractures or discontinuities. Continuous bridging bone occurs as a result of osseous remodeling and incorporation of the interbody graft with the vertebral endplates and/or formation of new bone adjacent to the graft that spans the interbody space.

3 RESULTS

3.1 Interbody Bridging Bone Assessment Summary

The study result of interbody bridging bone assessment at all time points is summarized in **Table 3**. The imaging was generally of good to excellent quality for analysis. One time point was graded "UA" for an unscheduled visit with comments from the reviewer indicating the labeled index level was not treated. The study result

of interbody bridging bone assessment at Month 8 is summarized in **Table 4** with a fusion rate of 91.4% for a total of 35 treated levels.

Table 3: Study Result of Interbody Bridging Bone at All Timepoints.

Interbody Bridging Bone Assessment	*Result at All Timepoints*		
	Absent (0)	*Present (1)*	*UA*
Count of Levels	3[1]	39[2]	2[3]
Percentage	6.8%	88.6%	4.5%

[1] Including 1 single level subject and 2 two level subjects.
[2] Including 18 single level subjects, 8 two level subjects and 2 three level subjects.
[3] Including 1 single level subject, and 1 two level subject.

Table 4: Study Result of Interbody Bridging Bone at Month 8.

Interbody Bridging Bone Assessment	*Result at Month 8*		
	Absent (0)	*Present (1)*	*UA*
Count of Levels	3[1]	32[2]	0
Percentage	8.6%	91.4%	0%

[1] Including 1 single level subject and 2 two level subjects.
[2] Including 14 single level subjects, 7 two level subjects and 2 three level subjects.

3.2 Lumbar Fusion Rate Data from the Scientific Literature

A literature search was conducted to review lumbar fusion studies that met the following criteria: 1) included Transforaminal Lumbar Interbody Fusion (TLIF) or Minimally Invasive Transforaminal Lumbar Interbody Fusion (MI-TLIF) procedures, 2) at least ten subjects per treatment group, 3) fusion assessment with radiographs and/or CT, and 4) at least 6 months follow up post-surgery. **Table 5** provides a summary on lumbar fusion rates from selected studies that report relevant information.

Table 5: Lumbar Fusion Rate Data from the Scientific Literature.

Study and Treatment	Assessment Method and Fusion Criteria	Sample Size	Fusion Rate
Park, 2011[2], MI-TLIF	Flexion-extension lateral X-ray and CT by Park et al. [2]	66 subjects	• Solid fusion rate is 77% (N = 51) at mean of 36 months
Kasliwal, 2012[3], MI-TLIF	CT	40 subjects (45 treated levels)	• CT fusion rate is 67.5% at mean of 22 months

[2] Park Y, Ha JW, Lee YT, Sung NY. **The effect of a radiographic solid fusion on clinical outcomes after minimally invasive transforaminal lumbar interbody fusion.** *Spine J*. 2011;11(3):205-212
[3] Kasliwal MK, Deutsch H. **Clinical and radiographic outcomes using local bone shavings as autograft in minimally invasive transforaminal lumbar interbody fusion.** *World Neurosurg*. 2012;78(1-2):185-190.

Study and Treatment	Assessment Method and Fusion Criteria	Sample Size	Fusion Rate
Girasole, 2013[4], TLIF	CT by Girasole et al.[4]	44 subjects in the 6-month follow-up arm and 38 patients in the 12-month follow-up arm.	• 6-month fusion rate: grade III or IV - 93.2% including grade IV fusion - 31 (70.5%), grade III fusion - 10 (22.7%), grade II fusion - 2 (4.5%), and grade I fusion - 1 (2.3%). • 12-month fusion rate: grade III or IV - 97.4% including grade IV fusion - 28 (73.7%), grade III fusion - 9 (23.7%), grade II fusion - 0 (0%), and grade I fusion - 1 (2.6%).
Massie, 2018[5], MI-TLIF	X-ray and CT	44 subjects (48 treated levels)	• CT bony fusion rate at 6 months: 54%. • CT bony fusion rate at 1 year: 96%. • CT bony fusion rate at 2 year: 100%.
McEntire, 2020[6], TLIF	X-ray and CT by Burkus et al.[7]	100 subjects (50 per cohort)	• Rate of bone bridging between the endplates by 12-month CT: PEEK cage - 42%; Si_3N_4 cage - 57%. • Segmental fusion assessment at 24 months[8]: PEEK cage - 88.2% (N = 30); Si_3N_4 cage - 80.6% (N = 29). • Segmental fusion assessment at 24 months[9]: PEEK cage - 46.7% (N = 21); Si_3N_4 cage - 57.8% (N = 26).
Ao, 2020[10], MI-TLIF and Percutaneous endoscopic transforaminal lumbar interbody	Flexion-extension lateral X-ray and CT[11]	75 subjects	• Clinical fusion rate at 12 months: PE-TLIF 100% (34/34), MI-TLIF 100% (39/39). • CT fusion rate at 12 months: PE-TLIF 85.3% (29/34), MI-TLIF 92.3% (36/39).

[4] Girasole G, Muro G, Mintz A, Chertoff J. **Transforaminal lumbar interbody fusion rates in patients using a novel titanium implant and demineralized cancellous allograft bone sponge.** *Int J Spine Surg*. 2013;7(1):e95-e100.

[5] Massie LW, Zakaria HM, Schultz LR, Basheer A, Buraimoh MA, Chang V. **Assessment of radiographic and clinical outcomes of an articulating expandable interbody cage in minimally invasive transforaminal lumbar interbody fusion for spondylolisthesis.** *Neurosurg Focus*. 2018;44(1):E8.

[6] McEntire BJ, Maslin G, Bal BS. **Two-year results of a double-blind multicenter randomized controlled non-inferiority trial of polyetheretherketone (PEEK) versus silicon nitride spinal fusion cages in patients with symptomatic degenerative lumbar disc disorders.** *J Spine Surg*. 2020;6(3):523-540.

[7] Burkus JK, Foley K, Haid RW, LeHuec JC. **Surgical Interbody Research Group--radiographic assessment of interbody fusion devices: fusion criteria for anterior lumbar interbody surgery.** *Neurosurg Focus*. 2001;10(4):E11. Published 2001 Apr 15.

[8] Kersten RF, van Gaalen SM, Arts MP, et al. **The SNAP trial: a double blind multi-center randomized controlled trial of a silicon nitride versus a PEEK cage in transforaminal lumbar interbody fusion in patients with symptomatic degenerative lumbar disc disorders: study protocol.** BMC Musculoskelet Disord. 2014;15:57: criteria for fusion: <2° angular motion and <0.5 mm translational motion.

[9] US FDA. **Guidance Document for the Preparation of IDEs for Spinal Systems. Device Evaluation Office United States**. 2000:1-32.: criteria for fusion: evidence of bridging bone, <5° angular motion, and <3 mm translational motion.

[10] Ao S, Zheng W, Wu J, et al. **Comparison of Preliminary clinical outcomes between percutaneous endoscopic and minimally invasive transforaminal lumbar interbody fusion for lumbar degenerative diseases in a tertiary hospital: Is percutaneous endoscopic procedure superior to MIS-TLIF? A prospective cohort study.** *Int J Surg*. 2020;76:136-143.

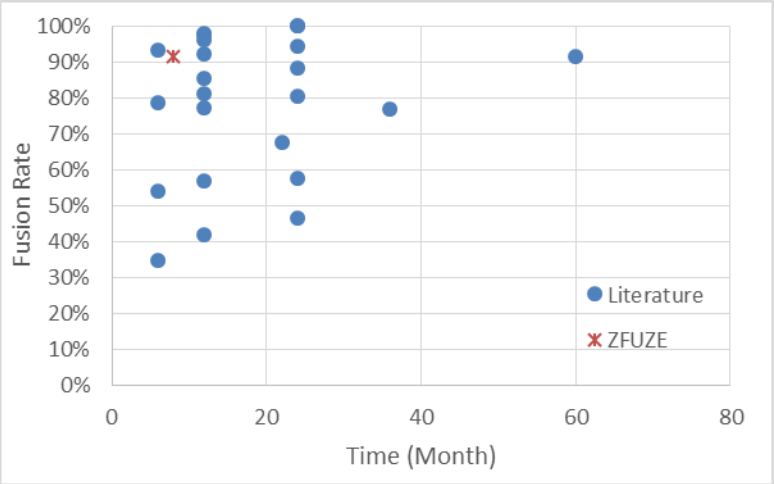
[11] Clinical fusion was considered successful if there was no mechanical low-back pain and segmental movement was less than 4° at the fused levels on flexion–extension dynamic radiographs. CT Fusion was considered successful if there was bridging trabecular bone between the vertebral bodies in multiplanar-reconstruction CT, irrespective of the status of facet fusion

Study and Treatment	Assessment Method and Fusion Criteria	Sample Size	Fusion Rate
fusion (PE-TLIF)			
Roh, 2022[12], MI-TLIF	X-ray and CT by modified Bridwell[13]	107 subjects	• Rate of Bridwell grades 1 and 2 (fused): 77.1% (27 segments) at 1 year, 91.4% (32 segments) at 5 years, and 94.3% (33 segments) at 10 years.
Gray, 2022[14], Posterior Lumbar Fusion (PLF) and TLIF	X-ray by Lenke 5-point modified intertransverse fusion scale[15]	99 subjects (17 in the PLF group and 82 in the TLIF + PLF group)	• Fusion rate at 6 months: PLF – 35%, TLIF – 78.7%. • Fusion rate at 12 months: PLF – 81.3%, TLIF – 97.9%. • Fusion rate at 24 months: PLF – 94.4%, TLIF – 100%.

3.3 Lumbar Fusion Rate Comparison

Lumbar fusion rate results from **Table 4** for the ZFUZE study TLIF and **Table 5** from the literature are plotted in **Figure 3** for comparison. Note that efforts have been made to identify studies from the literature with similar study design as the ZFUZE TLIF study, however different studies may use different criteria to determine fusion.

Figure 3: Fusion Rate Comparison: ZFUZE vs. Literature.



4 CONCLUSIONS

Overall, the lack of literature data on fusion rate at the timepoint of 8 months makes it not a straightforward comparison with the study result. However, the study fusion rate at 8

[12] Roh YH, Lee JC, Hwang J, et al. **Long-Term Clinical and Radiological Outcomes of Minimally Invasive Transforaminal Lumbar Interbody Fusion: 10-Year Follow-up Results.** *J Korean Med Sci*. 2022;37(13):e105.

[13] Bridwell KH, Lenke LG, McEnery KW, Baldus C, Blanke K: **Anterior fresh frozen structural allografts in the thoracic and lumbar spine. Do they work if combined with posterior fusion and instrumentation in adult patients with kyphosis or anterior column defects?** *Spine* 1995, **20**(12):1410-1418.

[14] Gray MT, Davis KP, McEntire BJ, Bal BS, Smith MW. Transforaminal lumbar interbody fusion with a silicon nitride cage demonstrates early radiographic fusion. *J Spine Surg*. 2022;8(1):29-43.

[15] Lenke LG, Bridwell KH, Bullis D, Betz RR, Baldus C, Schoenecker PL. **Results of in situ fusion for isthmic spondylolisthesis.** *J Spinal Disord*. 1992;5(4):433-442.

months of 91.4% is higher than most available imaging-based fusion rate data at 6 months and 12 months from the literature as indicated in **Table 5**.