



Original article

rhBMP-2 (Recombinant Human Bone Morphogenetic Protein-2) in real world spine surgery. A phase IV, National, multicentre, retrospective study collecting data from patient medical files in French spinal centres



Ange François Vincentelli^a, Marc Szadkowski^b, Dominique Vardon^c, Stéphane Litrico^d, Stéphane Fuentès^e, Jean-Paul Steib^{f,g}, Jean-Charles Le Huec^h, Jean Huppert^{i,j}, Gilles Dubois^k, Thibaut Lenoir^l, Frédéric Sailhan^m, Norbert Passuti^{n,*}

^a Neurochirurgie, Générale de Santé - Hôpital Privé Clairval, Serarl Neuro Val Redon, 317, boulevard du Redon, Marseille 13009, France

^b Chirurgie Orthopédique et Traumatologie, Hôpital Privé Jean-Mermoz, Ramsay Générale de Santé, 24, avenue Paul-Santy, Lyon 69008, France

^c Chirurgie Orthopédique et Traumatologie, Clinique Médipole Garonne, 45, rue de Gironis, CS 13624, Toulouse 311036, France

^d Neurochirurgie, CHU Nice - Hôpital Pasteur, BP 69, Nice 06002, France

^e Neurochirurgie, Service de Neurochirurgie la Timone, PR Dufour, 264, rue Saint Pierre, 13385 Marseille, France

^f Service de Chirurgie du rachis, Hôpitaux Universitaires de Strasbourg - HautePierre, 2, avenue Molière, Strasbourg 67200, France

^g Hôpital Civil, Pavillon chirurgical B, 1, place de l'hôpital, BP 426, Strasbourg 67091200, France

^h Polyclinique bordeaux nord aquitaine, lab deterca univ bordeaux, 15–35, rue Boucher, Bordeaux 33000, France

ⁱ Ortho-rachis 2, CHU Pellegrin tripode, Bordeaux 33076, France

^j Neurochirurgie, Clinique Du Parc, 9bis, rue de la Piot, Saint-Priest en Jarez 42270, France

^k Neurochirurgie, Nouvelle Clinique de l'Union, boulevard de Ratalens-Saint-Jean, BP 36, Saint-Jean 31240, France

^l Neurochirurgie, Clinique Ambroise-Paré, 25–27 boulevard Victor Hugo, Neuilly-sur-seine 92200, France

^m Neurochirurgie, Hôpital Cochin, 27, rue du Faubourg Saint-Jacques, Paris 75014, France

ⁿ Chirurgie Orthopédique et Traumatologie, CHU Nantes - Hôpital Saint-Jacques, 85, rue Saint-Jacques, Nantes Cedex 44093, France

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ABSTRACT

Background: This is a Phase IV, national, multicentre, retrospective study to observe the real-world use of rhBMP-2 in France.

Hypothesis: There was no statistical hypothesis, the statistical analyses were descriptive in nature.

Patients and methods: Data was collected from patient medical files in 10 French spinal centres. Primary objectives were to understand which patients were treated with rhBMP-2, commercialised in Europe as InductOs™ and how rhBMP-2 was used during spinal fusion surgery in France between 2011 and 2012.

Results: Four hundred patients (634 levels) treated with rhBMP-2 were included in the analysis. The most frequent primary diagnostic indication for rhBMP-2 use was degenerative disc disease (DDD; 129/400; 32.3% of patients) followed by spondylolisthesis (119/400; 29.8%), deformity (59/400; 14.8%) and pseudoarthrosis (29/400; 7.3%). The most frequently treated level was L4–L5 (33.8% of levels in 53.5% of patients); followed by L5–S1 (29.8%, 47.3%), L3–L4 (16.7%, 26.5%), and L2–L3 (7.3%, 11.5%), all other levels (less than 5% of patients). No interbody fusion device was used in 42.7% of levels. Wetted matrix of rhBMP-2 was placed in the interbody space in 58.4% of levels (370/634). The most common procedure for rhBMP-2 treatment was posterior lumbar fusion (PLF) (221/634; 34.9% of levels), followed by anterior lumbar interbody fusion (ALIF) (188/634; 29.7%), posterior lumbar interbody fusion (PLIF) (111/634; 17.5%), lateral lumbar interbody fusion (LLIF) (106/634; 16.7%), transforaminal lumbar interbody fusion (TLIF) (4/634; 0.6%) and 'other' (4/634; 0.6%). Thirty-one adverse events of Interest (AEI) were recorded in 27 patients. One AEI was considered related to rhBMP-2. Unplanned secondary spine interventions at index level treated with rhBMP-2 were required in 4 patients.

* Corresponding author.

E-mail address: norbert.passuti@chu-nantes.fr (N. Passuti).

Discussion: In years 2011 and 2012 when the surgeries captured in this retrospective study were done, rhBMP-2 was indicated for single level (L4–S1) anterior lumbar spine fusion as a substitute for autogenous bone graft in adults with DDD. The most common procedure for the treatment with rhBMP-2 was PLF (off-label use), followed by ALIF (on-label use). The safety findings confirm a predictable and manageable safety profile.

Level of evidence: IV.

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1. Introduction

Degenerative Disc Disease (DDD) is a common disorder of the spine caused by degeneration of the intervertebral discs. For some people, it can lead to pathologic conditions [1,2]. When non-operative treatments for DDD are unsuccessful, lumbar spinal fusion is considered [1–3]. Postoperative fusion rates typically range from 88%–97% at 2 years when used with autogenous bone [3]. Standard surgical practice consists of harvesting bone from the iliac crest which may cause significant pain and other complications [4]. Alternatives include the use of allografts, osteoinductive growth factors and synthetic osteoconductive compounds. Diboterminal alfa (recombinant human bone morphogenetic protein-2, rhBMP-2) is an osteoinductive bone growth factor belonging to the transforming growth factor- β superfamily. The efficacy and safety of rhBMP-2 was established in patients with DDD undergoing standalone anterior lumbar interbody fusion (ALIF) [3,5–12]. rhBMP-2 is commercialised in Europe as InductOs™ and was indicated for Anterior approaches as a substitute for autogenous bone graft at the time the surgeries captured in this retrospective study were done. rhBMP-2 is presented in a pack including 12 mg of rhBMP-2 and an absorbable collagen sponge matrix made from bovine Type I collagen. Since 2014, the indication for rhBMP-2 has been extended to single-level lumbar interbody spine fusion [3,5–12].

The aim of this phase IV, multicentre, retrospective study was to observe the real-world use of rhBMP-2 in France, more specifically which patients were treated, and how rhBMP-2 was used during spinal fusion surgery.

2. Patients and methods

Data was collected through a retrospective review of medical records of patients who had undergone a spinal fusion procedure with rhBMP-2 according to the regular operative technique.

2.1. Site selection

The French Spine Surgery Society (SFCR) sent a feasibility questionnaire to 54 spine hospitals in France. From the 24 sites which responded and agreed to participate, 10 were randomly selected in subgroups (5 private and 5 public hospitals) among sites which had used a minimum of 20 rhBMP-2 packs in spine surgery between 2011 and 2012, had documented primary endpoint parameters and agreed to comply with the protocol and applicable regulations. To limit site selection bias no consideration was given to the type of surgery or the interbody devices used.

2.2. Patient selection

A target number of patients were defined for each site to ensure that the patients enrolled were representative (relative patient volume to be contributed by each site to reach the enrolment of 400 patients). Each site sent a registered non-objection letter to eligible patients, most recently treated first, until reaching site target enrolment.

Patients were eligible for the study if they were treated with rhBMP-2 between 1st January 2011 and 31st December 2012, over 18 years old at the procedure, had medical records documenting the required information and had received the non-objection letter.

Patients were not eligible if: patient declined participation within 3 weeks of receipt of the non-objection letter, was a vulnerable patient unable to understand the non-objection letter or unable to exercise free decision to refuse to participate to the study, had died since procedure or was participating in a concurrent interventional trial.

2.3. Assessments

The primary objectives of this study were to understand which patients are treated with rhBMP-2 during spinal fusion surgery in France and how rhBMP-2 is used in these surgeries. Age, gender, primary diagnostic indication, medical history and fusion-related risk factors such as smoking and diabetes at pre-operative visit (≤ 60 days from surgery) were considered. Surgical data was collected for the number of levels treated and procedure type for the implantation of rhBMP-2 (ALIF, posterior lumbar interbody fusion [PLIF], transforaminal lumbar interbody fusion [TLIF], lateral lumbar interbody fusion [LLIF], including direct lumbar interbody fusion [DLIF] and eXtreme lateral interbody fusion [XLIF]), posterolateral fusion (PLF) and other type). The rhBMP-2 wetted matrix placement was classified as posterior lateral or interbody space. Fixation and instrument(s) used to stabilise were collected if applicable.

The secondary objectives were to summarise the occurrence of adverse events of interest through 12 months (AEI); describe the occurrence of secondary spine surgery; index level treated with rhBMP-2 and to evaluate the fusion rate assessed by the investigator. Fusion was defined as evidence of bridging trabeculae; no evidence of motion as defined by ≤ 3 mm difference on translation the lateral flexion/extension radiographs and $< 5^\circ$ difference in angular motion between flexion and extension; no evidence of radiolucency surrounding $> 50\%$ of the interbody fusion device. A partial fusion was recorded as a non-fusion. A case was considered as fusion success if all treated levels were a success, and a fusion failure if at least one level was a failure. If at least one level's fusion status could not be determined while all the rest of levels were successes, then the patient level was considered not determined.

2.4. Statistical analysis

All statistical analyses were planned prior to study conduct. There was no statistical hypothesis, the analyses were descriptive in nature. For patients who had secondary surgeries at index level treated with rhBMP-2, all effectiveness endpoints before the secondary surgery were carried to the later time periods. Missing data was not imputed. Patient demographics and characteristic categorical variables were analysed by descriptive statistics. The statistical program used was SAS, version 9.2 or later.

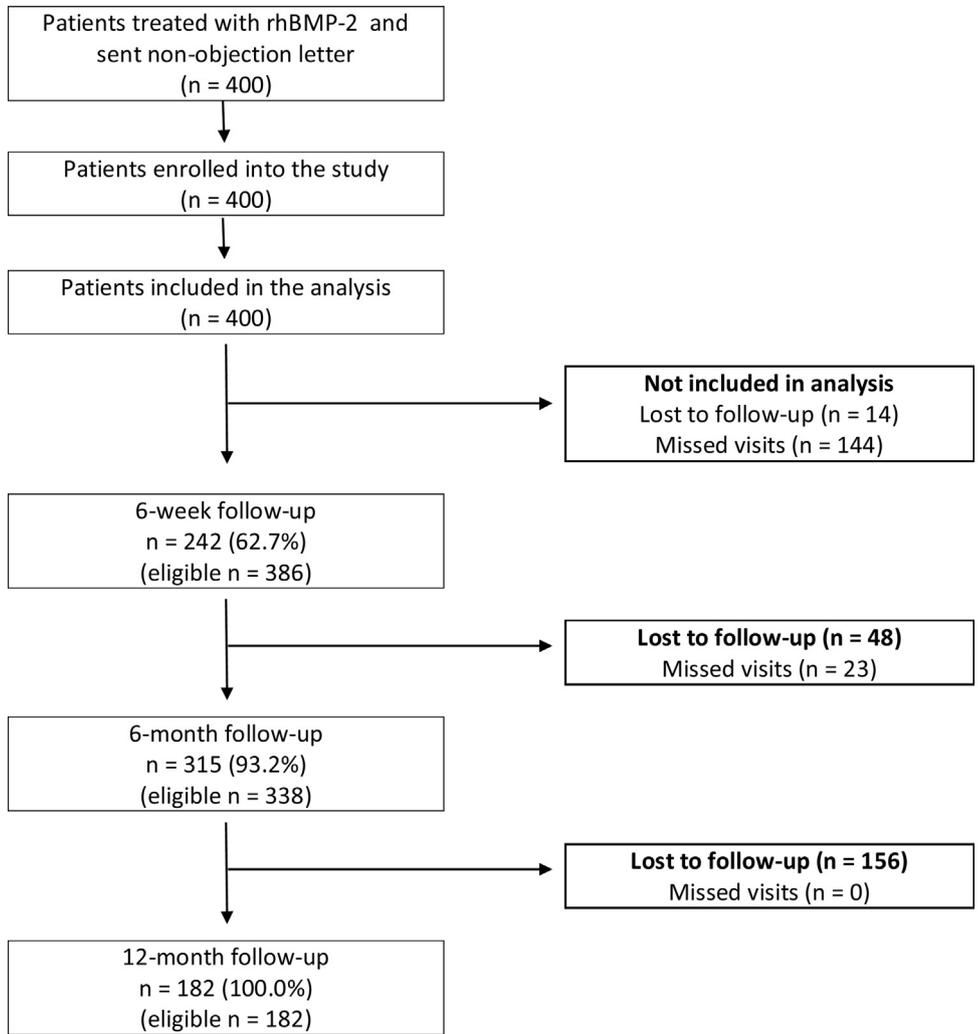


Fig. 1. Study Flowchart.

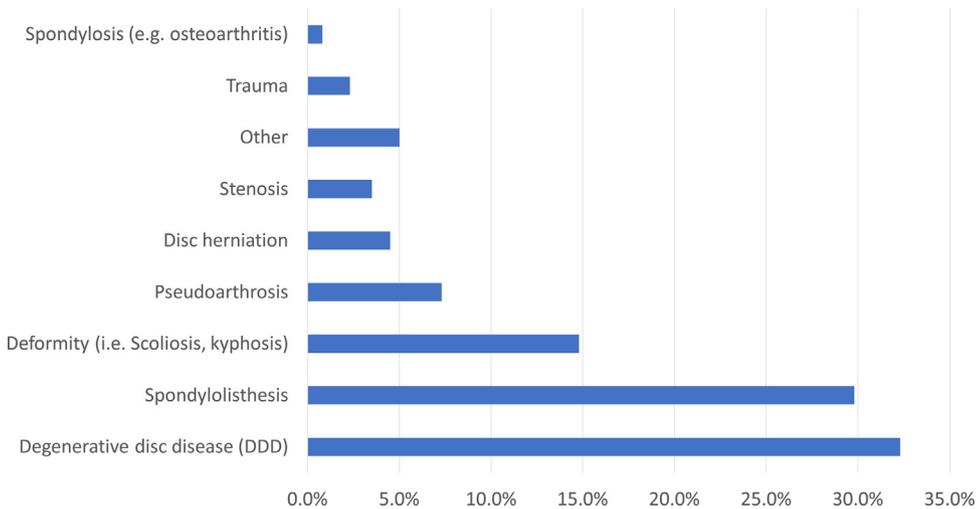


Fig. 2. Primary diagnostic Indication (n = 400 patients).

3. Results

3.1. Primary endpoints

3.1.1. Patient demographics

Four hundred patients met eligibility criteria (Fig. 1). The primary indication for rhBMP-2 use was DDD as observed in 32.3% of patients (129/400), followed by spondylolisthesis (29.8%; 119/400), deformity (14.8%; 59/400) and pseudoarthrosis (7.3%; 29/400) (Fig. 2). The sums of percentages do not equal 100% because multiple answers were possible.

Patient characteristics are provided in Table 1. A total of 46.3% of patients (185/400) had prior surgery of which 85.9% were on the index level.

Previous treatments with rhBMP-2 were reported by 6 patients and rhBMP-7 in 2 patients.

3.1.2. Surgery Data

The level most frequently treated with rhBMP-2 was L4–L5 (33.8%, 214/634 levels) in 53.5% (214/400) of patients; followed by L5–S1 in 29.8% (189/634 levels; 47.3% 189/400 patients), and L3–L4 (16.7%, 106/634 levels; 26.5%, 106/400 patients); and L2–L3 (7.3%, 46/634 levels; 11.5%, 46/400 patients). All other levels were treated in less than 5% of patients (Fig. 3).

The procedures utilising rhBMP-2 treatment were PLF (34.9% of levels; 221/634), followed by ALIF (29.7% of levels; 188/634), PLIF (17.5% of levels; 111/634) and LLIF (16.7% of levels; 106/634) with TLIF and other in 0.6% (4/634) levels each (Fig. 4). No interbody fusion device was used in 42.7% of levels (271/634).

Wetted matrix containing rhBMP-2 was placed in the interbody space in 58.4% (370/634) of levels; further defined as inside the cage in 90.5% (335/370) of these levels, between the cages in 16.2% (60/370) and outside the cage in 5.9% (22/370). Matrix was positioned in the posterior lateral space in 42.6% (270/634) of levels and 'other' for 3.2% (20/634) of levels. Sum of percentages may be higher than 100% because multiple answers were possible.

Stabilisation was performed in 84.4% (535/634) of levels of which 74.6% (399/535) posterior and 37.4% (200/535) anterior. No stabilisation was performed in 15.6% (99/634) of levels.

Grafting material was used in combination with rhBMP-2 in 62.5% (396/634) of levels as follows: (73.7% (292/396) local bone autograft, 14.9% (59/396) iliac crest bone autograft, 6.6% (26/396) allograft, 4.5% (18/396) ceramic/synthetic material and

Table 1
Patient characteristics.

Variable	N = 400
Gender (Male/Female)	163 (40.8%)/237 (59.3%)
Age (years, Mean ± SD, range)	54.5 (±14.8, 18–87)
BMI (Mean ± SD, range)	26.04 (± 4.27, 17.1–42.2)
Smoking status, n (%)	
Current smoker	110 (27.5%)
Not currently smoking	267 (66.8%)
Never smoked	133 (33.3%)
Past smoker who stopped smoking	67 (16.8%)
Unknown if past or never	67 (16.8%)
Not available	23 (5.8%)
Diabetes	
Type I	2 (0.5%)
Type II	24 (6.0%)
Diabetes Type Unknown	3 (0.8%)
Diabetes Type I + II + Unknown	29 (7.3%)
Time to surgery since onset of primary diagnostic indication (Days)	
Mean (± SD, range)	299.1 (± 845, 0–7386)
Patients with prior spine surgery	
Yes	185 (46.3%)
No	205 (51.3%)
Unknown	10 (2.5%)

BMI: Body Mass Index; SD: Standard Deviation.

0.3% (1/396) 'other'. No grafting material was used in 36.6% (232/634) and 'not available' in 0.9% (6/634) of levels respectively.

3.2. Secondary endpoints

3.2.1. Adverse events of interest (AEI)

Thirty one AEI were reported in 27 patients (Table 2). The most commonly reported AEI included 7 patients with device (implant) displacement and 5 with fluid collection at site of implant. AEI are reported in Table 3. No AEI were categorised as Exuberant Bone Formation or Heterotopic Bone Growth.

Sixteen AEI were considered related to study procedure, 3 AEI were considered related to device/other, and one case of radiculitis at one-month post-surgery was considered related to rhBMP-2.

No patients were pregnant at the time of study procedure and pregnancy was reported in one patient at the 12-month visit. The pregnancy outcome was elective abortion. No additional information about the pregnancy was available. One patient had died 69 days after the procedure and was not enrolled into the study as

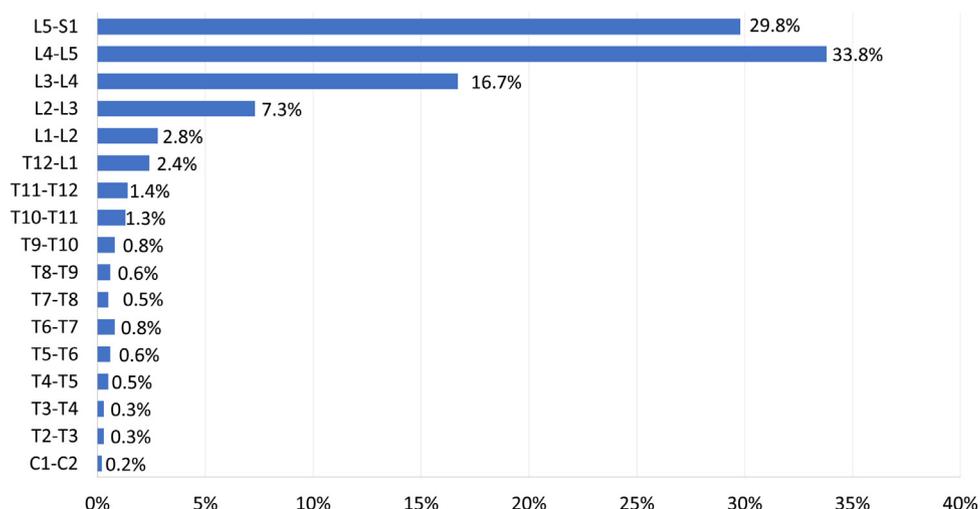


Fig. 3. Levels treated with rhBMP2 (n = 634 levels).

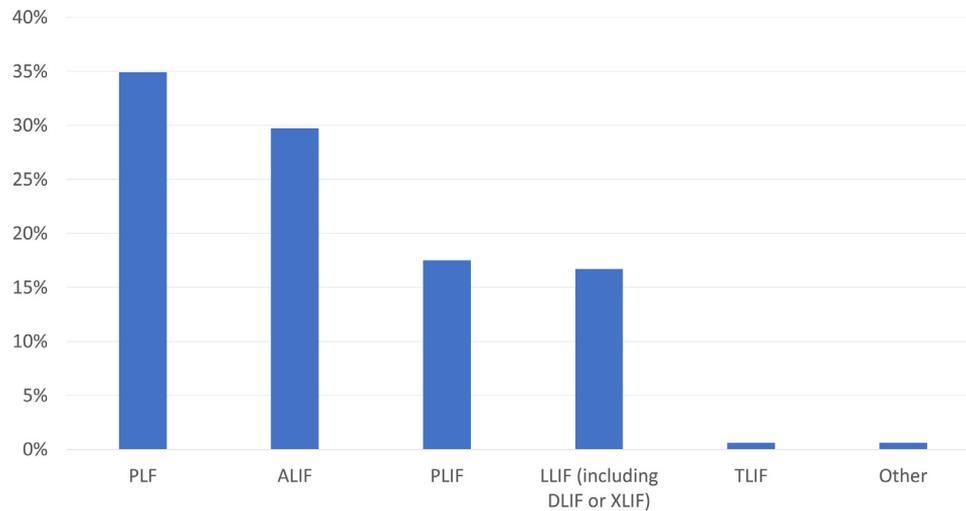


Fig. 4. Procedure for rhBMP-2 treatment.

Table 2
Classification of Adverse Events of Interest (AEI).

Full Analysis Set (N=400)	
	Cumulative
Number of AEIs	31
AEI Classification	% (n/cumulative)
Life-threatening ^a	6.5% (2/31)
Required in-patient hospitalization or prolongation of an existing hospitalization	64.5% (20/31)
Resulted in persistent or significant disability or incapacity	22.6% (7/31)
Was a congenital anomaly/birth defect	0.0% (0/31)
Was suspected to be a transmission of an infectious agent via a medicinal product	3.2% (1/31)
Events medically judged as important	38.7% (12/31)
Event leading to a revision surgery at the index level	22.6% (7/31)
Total	100% (31/31)

Note: One AEI could be classified in one or more categories.

^a Intestinal obstruction and Post procedural haematoma.

Table 3
Adverse Events of Interest (AEI).

Full Analysis Set (N=400)	
AEI Categories	Cumulative
Number of AEI	31
Device (implant) displacement	22.6% (7/31)
Fluid collection at the site of implant	16.1% (5/31)
Nerve compression or nerve root disorders	9.7% (3/31)
Excessive bone resorption	3.2% (1/31)
Allergic reactions or inflammation	3.2% (1/31)
Male fertility problems	3.2% (1/31)
Neoplasms, Benign, Malignant and Unspecified (including Cysts and polyps)	3.2% (1/31)
Exuberant Bone Formation or Heterotopic Bone Growth	0.0% (0/31)
Other Adverse Event of interest	38.7% (12/31)
Total	100% (31/31)

Note: One AEI could be classified in one or more categories.

per protocol exclusion criteria. The description of the event was unknown, with unknown relation to rhBMP-2.

3.2.2. Secondary spine surgeries

Following study procedure there were three planned secondary spine surgeries (three patients) and nine unplanned interventions (nine patients).

Median time from index surgery to first unplanned secondary surgery was 156 days (range 26–455 days) and the reason was AE in

5 patients and other in 4 patients. The type of unplanned secondary spine surgery was fusion in 85.0% (17/20) of levels (7/9 of patients) and 'other' in 15.0% (3/20) of levels (3/9 patients).

Four patients had unplanned secondary spine interventions at index level treated with rhBMP-2. The reason was the occurrence of an AE in 2 patients, and other in 2 patients.

3.2.3. Fusion rates

Fusion results were available for 386 patients, with successful fusion at last assessment determined in 48.4% (187/386) of all patients and fusion failure reported in 13.7% (53/386) of patients, 12.4% (48/386) unable to determine, and 25.4% (98/386) had no assessment done (Table 4). When considering the assessment performed at 12-months, fusion rate per patient was reported as successful for 94.5% (120/127) of patients and failure for (7/127) of patients. At 12-months, fusion assessment was done by radiograph in 65.7% patients (94/143), CT scan in 37.8% (54/143), and other in 4.9% patients (7/143).

Other results: surgery data

The majority (64.5%, 258/400) of patients were treated with rhBMP-2 at 1 level, patients were treated up to 16 levels (Table 5).

When available, the most frequent amount of matrix is 2/6 (approximately 4 mg) in 35.2% (223/634) of levels (Fig. 5).

4. Discussion

This retrospective study allowed the description of real-world use of rhBMP-2 in France. In years 2011 and 2012 when the surgeries captured in this retrospective study were done, rhBMP-2 was indicated for single level (L4–S1) anterior lumbar spinal fusion as a substitute for autogenous bone graft in adults with DDD who had undergone at least 6 months of non-operative treatment for their condition. Since 2014, rhBMP-2 is indicated for single-level lumbar interbody spinal fusion as a substitute for autogenous bone graft, for use with an approved (CE-marked) lumbar interbody fusion device in adults with DDD who have had at least 6 months of non-operative treatment for this condition [13].

Approximately one-third of patients had DDD as a primary diagnosis while around half of the cohort received rhBMP-2 as a part of a revision procedure. One-third of patients were treated at more than one level, which was outside the current indication of rhBMP-2. The most common procedure for the treatment with rhBMP-2

Table 4
Fusion rate and fusion success rate.

Full Analysis Set (N = 400)				
Fusion	6 weeks	6 months	12 months	Fusion rate at last assessment
n available	242	315	182	386
No	38.4% (93/242)	29.8% (94/315)	3.8% (7/182)	13.7% (53/386)
Yes	2.9% (7/242)	33.0% (104/315)	65.9% (120/182)	48.4% (187/386)
Unable to determine	25.2% (61/242)	21.6% (68/315)	9.9% (18/182)	12.4% (48/386)
Assessment not done	33.5% (81/242)	15.6% (49/315)	20.3% (37/182)	25.4% (98/386)
Fusion success rate ^a				
n available	100	198	127	
No	93.0% (93/100)	47.5% (94/198)	5.5% (7/127)	
Yes	7.0% (7/100)	52.5% (104/198)	94.5% (120/127)	

^a Fusion success rate was based on the images that were determined to be either success or no success

Table 5
Number of levels treated with rhBMP-2 per patient.

Number of Levels Treated per patient (all levels)	% (n/N)
1 Level	258 (64.5%)
2 Levels	105 (26.3%)
3 Levels	23 (5.8%)
4 Levels	7 (1.8%)
5 Levels	2 (0.5%)
8 Levels	2 (0.5%)
13 Levels	1 (0.3%)
14 Levels	1 (0.3%)
16 Levels	1 (0.3%)

was PLF (off-label use), followed by ALIF (label use). These observations warrant the need for future studies investigating the use of rhBMP in PLF. A study is currently ongoing on Posterior Fixation for PLF Treatment (NCT03118505).

Fusion has been assessed as a success at last assessment for approximately half of the enrolled patients; Fusion was a success in 94.5% of patients followed-up at 12-months. These results should be interpreted with care, as fusion was assessed at different timepoints, with different images types and in addition by the investigational sites and not by an independent radiologist.

Despite a significant proportion of patients being treated off-label at the time of data collection [13], the safety profile of rhBMP-2 was favourable: Thirty-one AEI were reported in 27/400 patients. Unplanned secondary spine interventions at index level treated with rhBMP-2 were required in 4 patients. This observation supports the safety profile established in prospective controlled trials

and meta-analyses [14,15]. However, safety data was retrospectively collected.

This study had the following limitations: Even though there was a desire to limit bias in the site selection, we cannot exclude that there was no bias related to centre effect. Due to the retrospective nature of the study, the patient follow-up schedule and duration have been very different depending on the site standard of care. This explains why more than half of patients were lost to follow-up at 12-months.

In summary, this study provides insight into which patients are treated with rhBMP-2, and how rhBMP-2 is used during spine fusion surgery in France. The findings confirm a predictable and manageable safety profile.

Ethical review committee statement

The study was conducted according to the Declaration of Helsinki and French regulation. According to the latter, the study did not need a notification to the Ethics Committee due to its retrospective and non-interventional status. Data retrieved for this clinical study was handled as per the EU Data Protection Directive (95/46/EC).

Disclosure of interest

V.D. reports personal fees from Medtronic during the conduct of the study; personal fees from Medtronic outside the submitted work; L.S. reports personal fees from Medtronic during the conduct of the study; personal fees and non-financial support from Medtronic, LDR Medical and Safe Orthopaedics outside the

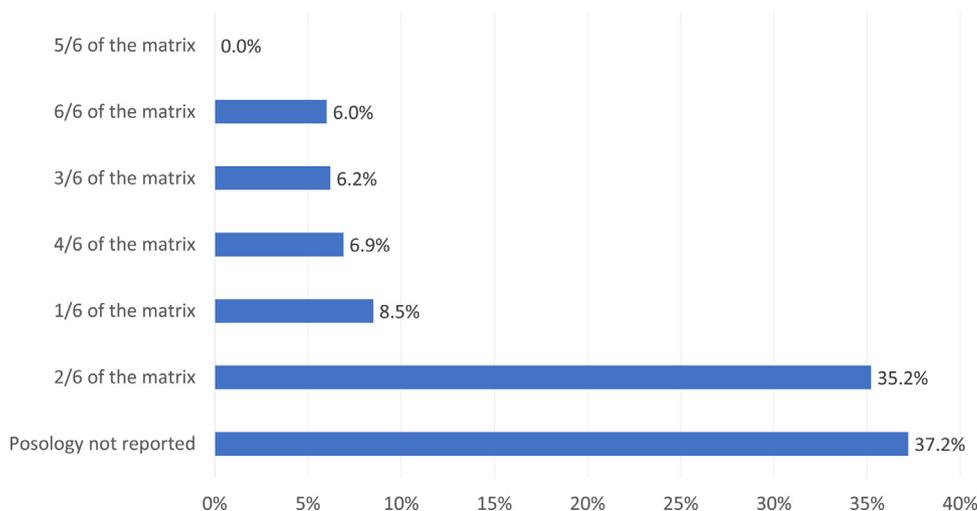


Fig. 5. Quantity of rhBMP-2 impregnated matrix used per level (All patients).

submitted work; S.-J.P. reports personal fees from Medtronic during the conduct of the study; financial support from Clariance, LDR Medical (Zimmer-Biomet), Medtronic and non-financial support from Clariance, LDR Medical (Zimmer-Biomet) outside the submitted work; H.J. reports personal fees from Medtronic during the conduct of the study.

The other authors declare that they have no competing interest.

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Authors' contribution

All authors were investigators in the study and contributed equally to the development of this manuscript.

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