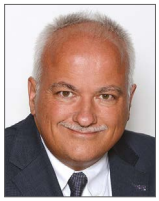
Safety and performance of the second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) in patients with de novo coronary lesions: three-year clinical results and angiographic findings of the BIOSOLVE-II first-in-man trial



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KEYWORDS

- bioresorbable scaffolds
- myocardial infarction
- stable angina
- stent thrombosis

Abstract

Aims: We aimed to evaluate the safety and performance of a magnesium-based sirolimus-eluting metal scaffold at three-year follow-up to assess vessel response two years beyond scaffold resorption.

Methods and results: BIOSOLVE-II is an international, multicentre first-in-man study, including 123 patients with *de novo* lesions. Predilatation was mandatory and post-dilatation was left to the discretion of the investigators. Dual antiplatelet therapy was recommended for six months. At three years, 91.1% of patients were angina-free and 8.0% were on dual antiplatelet therapy. The target lesion failure rate was 6.8% (n=8: two cardiac deaths, one target vessel myocardial infarction and five target lesion revascularisations). No probable or definite scaffold thrombosis was observed. Imaging follow-up was voluntary and serial angiographic assessment at 6, 12, and 36 months was available in 25 patients. In these, a slight increase in in-segment and in-scaffold late lumen loss and diameter stenosis was observed between 12 and 36 months (by 0.11±0.28 mm and 0.13±0.30 mm for late lumen loss, and by 3.8±10.1% and 4.1±10.2% for diameter stenosis).

Conclusions: Two years beyond the resorption period of a sirolimus-eluting bioresorbable metal scaffold built from a proprietary magnesium alloy, complication rates remained low. In the patients with serial angiographic assessment, late lumen loss and diameter stenosis did not increase substantially beyond the resorption period.

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Abbreviations

CD-TLR	clinically driven target lesion revascularisation
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DREAMS 2G	drug-eluting absorbable metal scaffold second generation
IVUS	intravascular ultrasound
LLL	late lumen loss
OCT	optical coherence tomography
TLF	target lesion failure

Introduction

Bioresorbable scaffolds have been developed to overcome the limitations of permanent drug-eluting stents (DES); however, initial enthusiasm was dashed after studies raised concerns about the safety and efficacy of the polymeric Absorb™ scaffold (Abbott Vascular, Santa Clara, CA, USA) prior to its bioresorption, in particular elevated scaffold thrombosis and myocardial infarction rates[1-3]. Attempts to mitigate these risks resulted in modified implantation techniques and prolongation of dual antiplatelet therapy (DAPT), but currently it is unclear to what extent these risk mitigation measures will impact on outcomes[3].

In *ex vivo* porcine carotid jugular arteriovenous shunt models, magnesium-based scaffolds have shown reduced thrombogenicity compared to the Absorb scaffold and to a stainless steel stent, suggesting that the magnesium-based metal scaffold may have inherent properties that reduce thrombogenicity[4,5]. No scaffold thrombosis has been reported for the second-generation drug-eluting absorbable magnesium scaffold (DREAMS 2G, commercial name Magmaris®; Biotronik AG, Bülach, Switzerland) in 184 patients studied up to 24 months, which is beyond its degradation time of approximately 12 months[6-8]. We now report three-year outcomes of BIOSOLVE-II (BIOTRONIK – Safety and Clinical PerFormance of the Drug Eluting Absorbable Metal Scaffold in the Treatment of Subjects with *de NOvo* Lesions in NatiVE Coronary Arteries) to assess vessel response up to two years post resorption.

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Methods

STUDY DESIGN AND POPULATION

Study methods have been described in detail previously[6,9]. In brief, BIOSOLVE-II is an international, multicentre, first-in-man study assessing the safety and performance of the DREAMS 2G scaffold (Magmaris) in 123 patients enrolled in 13 centres worldwide. Patients with a maximum of two *de novo* lesions with a reference vessel diameter of 2.2–3.7 mm, vessel length ≤21 mm and stable or unstable angina or documented silent ischaemia could be enrolled. Main exclusion criteria were myocardial infarction within 72 hours prior to the index procedure, unprotected left main disease, three-vessel coronary artery disease, and heavily calcified lesions. The full list of inclusion and exclusion criteria is available at ClinicalTrials.gov: NCT01960504. In a subgroup of 30 consecutive patients, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) was conducted pre and post procedure and at six months. Angiographic follow-up was scheduled at six months and, if the subject consented, at one and three years. If a reintervention was performed within three to six months post procedure or within the time window of the three-year follow-up, the angiographic assessment prior to the intervention was used for analysis. Lesions with reinterventions were then precluded from further imaging follow-up assessment. Additional imaging assessments outside the protocol had to be documented and were evaluated by the core laboratory. Follow-up was scheduled for up to three years.

The endpoints at three years were (a) target lesion failure (TLF), defined as a composite of cardiac death, target vessel myocardial infarction, coronary artery bypass grafting and clinically driven target lesion revascularisation (CD-TLR), and (b) stent thrombosis. Cardiac death, CD-TLR and scaffold thrombosis were defined according to the Academic Research Consortium guidelines, periprocedural myocardial infarction according to SCAI definitions and non-periprocedural myocardial infarction according to the extended historical definition[10-12].

The study was performed according to the Declaration of Helsinki and ISO14155, was approved by the ethics committees and competent authorities, and all patients provided consent. Monitoring encompassed 100% source document verification, all events were adjudicated by a clinical events committee, and all images were assessed by a core laboratory.

DEVICE AND PROCEDURE

The Magmaris is a magnesium-based scaffold coated with bioresorbable poly-L-lactide acid which incorporates sirolimus, the same drug-polymer combination that is used for the Orsiro stent (Biotronik)[13]. During degradation, the magnesium alloy is first converted to hydrated magnesium oxide and, in a second phase, the magnesium oxide is converted to magnesium phosphate which is consecutively replaced by amorphous calcium phosphate. At one year, the degradation is almost fully complete (95%)[9,14]. The Magmaris has a strut thickness of 150 µm, a strut width of 150 µm, and was available in sizes 2.5×20 mm, 3.0×20 mm and 3.5×25 mm during the course of the study.

Predilatation was mandatory. The predilatation balloon ought to be not more than 0.5 mm smaller than the reference vessel diameter and should not exceed the reference vessel diameter. Furthermore, it should not exceed the length of the original lesion. Post-dilatation was left to the discretion of the investigator; however, the diameter of the post-dilatation balloon should not exceed the selected diameter of the scaffold by more than 0.5 mm. DAPT was recommended for at least six months post procedure.

STATISTICAL ANALYSIS

The sample size had been calculated for the primary endpoint, late lumen loss (LLL) at six months[9]. The analysis was based on the intention-to-treat population, defined as patients in whom the scaffold entered the guide catheter. Patients not receiving the scaffold counted towards device and procedure success only. For continuous data, means, standard deviations and 95% confidence intervals (CI)

were calculated, as appropriate. For categorical data, absolute and relative frequencies with 95% CI for proportions were calculated.

For clinical outcomes, the denominator included patients with a respective event and/or follow-up assessment. Student's t-test, Wilcoxon sign test and Fisher's exact test were applied for comparison; p-values of <0.05 represent significance. A *post hoc* analysis was performed to compare outcomes beyond 12 months with those of an unaffected vessel without stenosis to estimate general disease progression. For that purpose, the normalised LLL (LLL divided by reference vessel diameter) in target vessels and similar non-target vessels with comparable dimensions were compared. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Outcomes up to two years have been described previously[6,9,15]. In brief, lesions were 12.6±4.5 mm long with a diameter of 2.68±0.40 mm. Type A, B1, B2 and C lesions were present in 0.8%, 55.7%, 41.8%, and 1.6%, respectively. Post-dilatation was performed in 61.2% of lesions with a mean pressure of 18.0±4.5 atm (95% CI: 17.1-19.0). In two patients, the scaffold could not be implanted; these patients were not included in the angiographic and clinical endpoint analysis according to the clinical investigation plan.

At six months, 90.6% (106/117) of patients were on DAPT, eight patients received anticoagulation therapy for atrial fibrillation, and three patients were on acetylsalicylic acid only. At 12 months, 44.4% (52/117) of patients were on DAPT, and at three years 8.0% (9/112). The ischaemic status at three years was assessed in 112 patients, of whom 91.1% (n=102) were symptom-free and 8.9% (n=10) had stable angina.

Clinical data at three years were available for 117/121 patients (97%; two patient visits were missed and two patients withdrew consent). One additional TLF occurred between two and three years, leading to a three-year TLF rate of 6.8% (n=8 [95% CI: 3.0-13.0]) **(Table 1)**. Clinically driven TLR occurred in five patients (4.3% [95% CI: 1.4-9.7]) **(Supplementary Table 1)**. Except for one periprocedural infarction (0.9% [95% CI: 0.0-4.7]), no target vessel myocardial infarction was observed and there was no definite or probable scaffold thrombosis. Of the five deaths, two were cardiac (one unwitnessed death on day 134 and one on day 395); the others were cancer, pulmonary infection, and intracerebral haemorrhage.

Table 1. Clinical outcomes.

	6 months	12 months	24 months	36 months
TLF	4 (3.3)	4 (3.4)	7 (5.9)	8 (6.8)
Death	2 (1.7)	2 (1.7)	4 (3.3)	5 (4.3)
Cardiac death*	1 (0.8)	1 (0.8)	2 (1.7)	2 (1.7)
Target vessel MI	1 (0.8)	1 (0.8)	1 (0.9)	1 (0.9)
CD-TLR	2 (1.7)	2 (1.7)	4 (3.4)	5 (4.3)
CABG	0	0	0	0
Scaffold thrombosis definite or probable	0	0	0	0

Data are presented as n and frequencies (%). *All unwitnessed deaths. CABG: coronary artery bypass graft; CD-TLR: clinically driven target lesion revascularisation; MI: myocardial infarction; TLF: target lesion failure

Voluntary angiographic assessment at 36 months was performed in 48 patients. There was no significant difference in baseline and procedural characteristics between patients with 36-month angiography and those without, except that patients with 36-month angiography had smaller minimal lumen diameters at baseline and a lower maximum pressure at implantation **(Supplementary Table 2)**. LLL at 36 months was 0.43±0.40 mm in-segment and 0.54±0.38 mm in-scaffold, and diameter stenosis was 28.6±11.6% (range 0.8 to 58.3) and 26.7±11.9% (range 0.8 to 60.0), respectively.

Serial angiographic assessments at 6 and 36 months are available for 47 patients, and pairs for 6, 12, and 36 months are available for 25 patients **(Figure 1, Supplementary Table 3)**. The increase in LLL between one and three years was 0.1±0.28 mm in-segment (range –0.40 to 0.66, p=0.060) and 0.13±0.30 mm in-scaffold (range –0.33 to 0.75, p=0.042). Diameter stenosis increased by 3.8±10.1% in-segment (range –11.5 to 24.1%, p=0.072) and 4.1±10.2% in-scaffold (range –11.5 to 28.5%, p=0.054). Serial OCT (n=12) and IVUS (n=8) assessments are shown in **Figure 2**, **Table 2**, **Supplementary Table 2**, and **Supplementary Table 4**. No intraluminal mass or prolapse was detected by OCT.

In a *post hoc* analysis, the normalised LLL of study scaffolded vessel segments ("target segments") was compared to the corresponding target segments of non-target vessels of similar dimensions **(Figure 3, Table 3)**. In the scaffolded target segments, there was a strong trend towards a higher normalised LLL compared to the corresponding target segments of non-target vessels at 12 months, while beyond 12 months the normalised LLL was not statistically different between target and non-target vessels. When analysing the "long segments" (segments proximal and distal to the target respective to the corresponding target vessel segment), there was no difference between the target compared to the non-target segments in normalised LLL at 12 months and 36 months.

Discussion

The main findings of BIOSOLVE-II at three years are (a) sustained low TLF and TLR rates, (b) absence of definite or probable scaffold thrombosis, and (c) stable lumen dimensions between 12 and 36 months.

TLF and CD-TLR rates were similar to three-year outcomes of the Absorb scaffold and the everolimus-eluting XIENCE® stent (Abbott Vascular) obtained from a recent patient-data pooled meta-analysis[16]. In this meta-analysis, the pooled TLF rate was 11.7% for Absorb and 8.1% for XIENCE compared to 6.8% in our series; the CD-TLR rate was 6.6% for Absorb and 4.4% for XIENCE compared to 4.3% in our series. The three-year CD-TLR rate of Absorb in the ABSORB cohort B trial was 7.0%[17]. To the best of

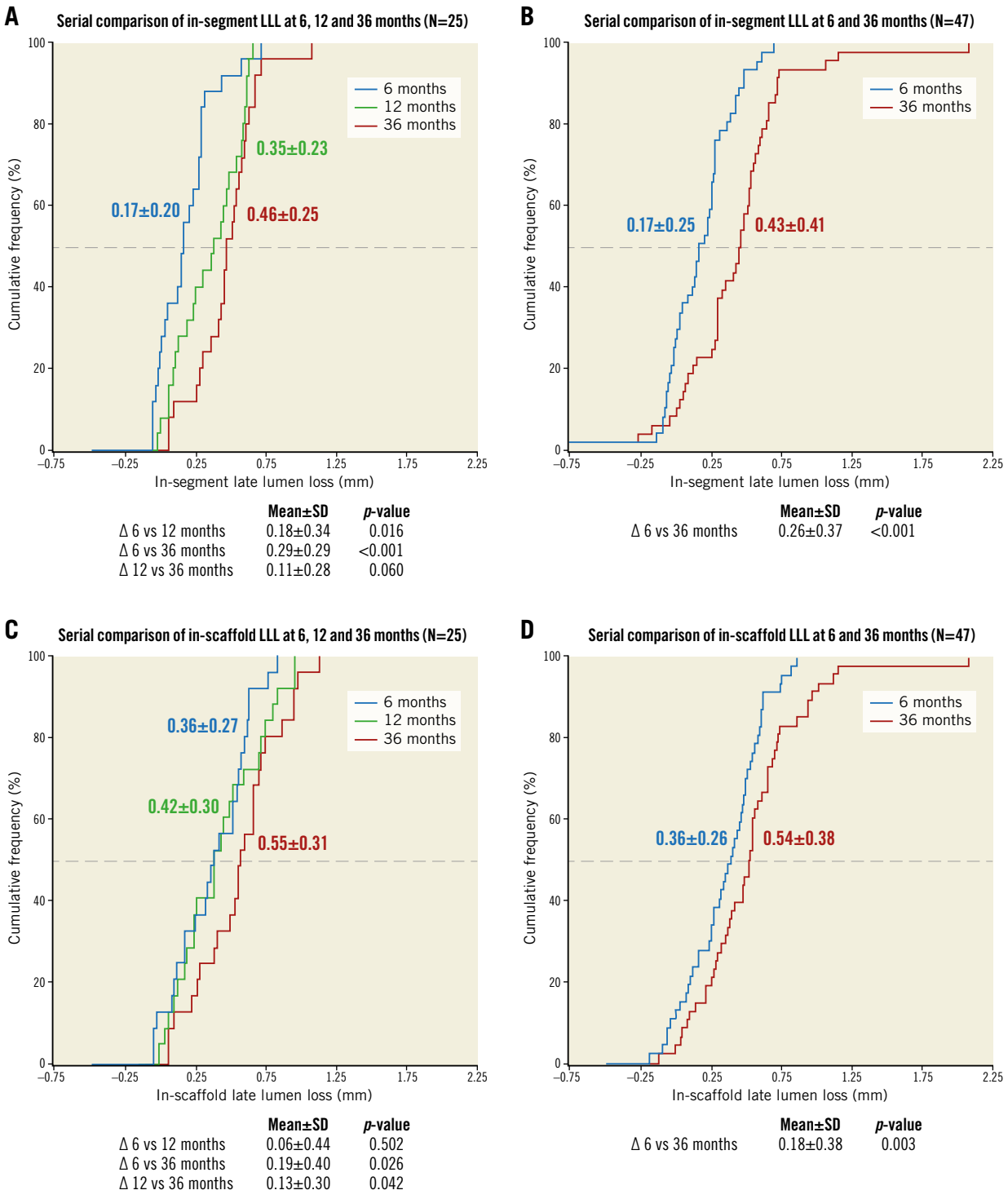

Figure 1. *Cumulative frequency curves for in-segment and in-scaffold late lumen loss up to 36 months. A) & B) Serial in-segment late lumen loss (LLL) at 6, 12, and 36 months in 25 patients and serial LLL at 6 and 36 months in 47 patients. C) & D) Outcomes for in-scaffold LLL. Note: angiographic follow-up was mandatory at 6 months and voluntary at 12 and 36 months.*

our knowledge, no three-year outcomes of other CE-marked scaffolds have been published to date. However, 24-month outcomes of the DESolve® polymeric scaffold (Elixir Medical Corporation, Sunnyvale, CA, USA) were similar to 36-month outcomes in our series (7.4% TLF and 4.1% TLR)[18].

Consistent with previous reports of BIOSOLVE-I, II and III studies[6,9,19], no definite or probable scaffold thrombosis was observed at 36 months compared to 0% for ABSORB cohort B, 2.4% for Absorb and 0.6% for XIENCE in a meta-analysis of randomised trials[16,17], and 0.8% for DESolve at 24 months[18]. These

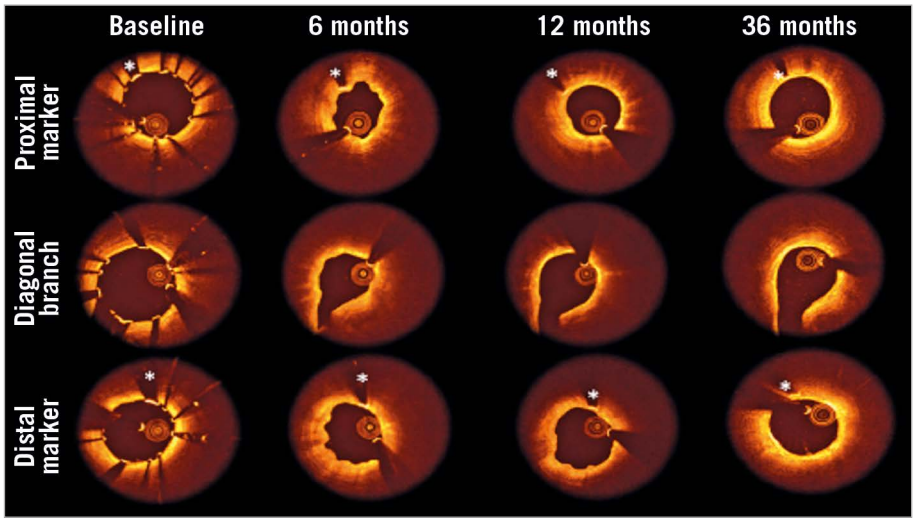

Figure 2. *Serial OCT analysis from post procedure to 6, 12 and 36 months. A representative example of serial OCT assessment proximal, at the origin of the diagonal branch and at the distal end of the scaffold. The frames demonstrate the degradation of the scaffold over time with struts covering the side branch already resorbed at six months. The lumen area slightly decreased during the 12-month degradation of the scaffold. At 36 months, a slight increase in lumen area can be observed. *scaffold marker.*

outcomes were obtained even though only 44.4% of patients were on DAPT at 12 months and 8.0% at 36 months. In contrast, prolonged DAPT covering the resorption period is recommended for Absorb[1,16]; in ABSORB II, DAPT use at three years was 31% for Absorb and 30% for XIENCE[20], and, in ABSORB III, DAPT use was 55.8% and 53.5%, respectively[21]. There are multiple explanations for these outcomes: first, the absorption time of Magmaris/DREAMS 2G is substantially shorter than for Absorb (approximately 12 months versus approximately three years[13,17]); second, Magmaris/DREAMS 2G seems to have fewer issues such

Table 2. Paired optical coherence (OCT) and intravascular ultrasound (IVUS) data.

	Post procedure	12 months	36 months	Δ 12 months vs post proc.	Δ 36 vs 12 months	*p*-value 12 months vs post proc.	*p*-value 36 vs 12 months
OCT, N=12							
No. of analysed struts	201 (192-214)	NA	NA	NA	NA	NA	NA
Scaffold area (mm²)	7.08 (6.35-8.16)	NA	NA	NA	NA	NA	NA
Mean lumen area (mm²)	7.58 (6.78-9.16)	5.68 (4.88-7.81)	5.45 (4.26-7.36)	–1.48 (–2.15- –1.04)	–0.54 (–1.01-0.16)	0.0003	0.096
Minimum lumen area (mm²)	6.28 (5.18-7.81)	4.14 (3.67-5.78)	3.42 (2.84-5.02)	–2.18 (–2.46- –1.29)	–0.63 (–1.61- –0.24)	0.0002	0.020
Malapposed struts (%)	1.93 (0.90-5.26)	NA	NA	NA	NA	NA	NA
Mean incomplete strut apposition area (mm²)	0.05 (0.01-0.09)	NA	NA	NA	NA	NA	NA
IVUS, N=8							
Vessel area (mm²)	14.94 (13.11-16.19)	14.07 (12.99-16.48)	14.86 (12.70-17.37)	–0.31 (–0.96-0.52)	0.10 (–0.02-1.11)	0.458	0.179
Mean scaffold area (mm²)	6.62 (6.03-6.90)	6.14 (5.50-6.56)	NA	–0.40 (–1.02- –0.05)	NA	0.050	NA
Minimum scaffold area (mm²)	5.74 (5.00-6.09)	4.93 (3.96-5.22)	NA	–0.91 (–1.05- –0.77)	NA	<0.001	NA
Neointimal hyperplasia area (mm²)	NA	0.24 (0.11-0.48)	NA	NA	NA	NA	NA
Mean lumen area (mm²)	6.59 (6.03-7.17)	5.92 (5.36-6.68)	5.76 (5.36-6.96)	–0.59 (–1.04- –0.24)	0.09 (–0.33-0.34)	0.011	0.894
Minimal lumen area (mm²)	5.33 (4.99-6.00)	4.73 (3.96-5.22)	4.79 (3.40-5.07)	–0.92 (–1.21- –0.67)	–0.09 (–0.31-0.12)	0.002	0.307
Total plaque area (mm²)	8.25 (6.80-9.30)	8.45 (7.25-9.88)	8.84 (7.34-10.32)	0.51 (0.03-0.84)	0.43 (–0.04-0.90)	0.054	0.060
Patients with incomplete strut apposition in N (%)	2 (25.0)	4 (50.0)	NA	NA	NA	0.414	NA
Malapposition area (mm²)	0.00 (0.00-0.00)	0.00 (0.00-0.05)	NA	0.00 (0.00-0.05)	NA	0.652	NA

Data are presented as median and interquartile range (Q1, Q3) or n (%). IVUS: intravascular ultrasound; NA: not applicable; OCT: optical coherence tomography

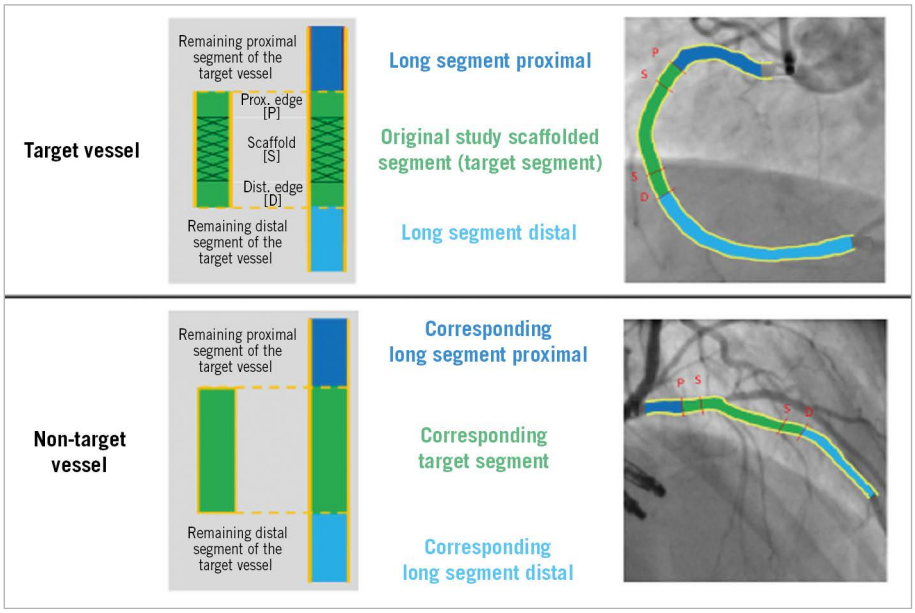

Figure 3. *Comparative angiographic analysis of target vessel versus non-target vessel (without stenosis). Schematic procedure of how the attribution of the normal progression of the disease was estimated within the target and the non-target vessel.*

Table 3. Comparative angiographic analysis by normalised late lumen loss of target vessel versus non-target vessel.

	Target segment/corresponding target segment				Long segment (proximal and distal of target segment/ corresponding target segment)			
	Target (N=25)	Non-target (N=21)	Δ Target vs non-target (N=21)	*p*-value	Target (N=24)	Non-target (N=22)	Δ Target vs non-target (N=21)	*p*-value
Resorption time: Δ baseline vs 12 months	0.123 ±0.094	0.019 ±0.128	0.096 ±0.194	0.051	0.058 ±0.090	0.019 ±0.102	0.023 ±0.103	0.384
Post-resorption time Δ 12 vs 36 months	0.049 ±0.113	0.023 ±0.093	0.015 ±0.142	0.627	–0.017 ±0.082	0.015 ±0.099	–0.019 ±0.102	0.395

Data are presented as mean±SD. Non-target vessels were selected to have similar lengths to the target segment. The short segment refers to the scaffolded segment.

as malapposition, disintegration or discontinuities[6,16]; and third, the Magmaris scaffold itself is associated with reduced thrombogenicity as shown in porcine arteriovenous shunt models in which Magmaris exhibited less thrombogenicity and inflammatory cell deposition compared to the Absorb scaffold and an equivalent 316L stainless steel stent[4,5].

Published three-year angiographic outcomes of contemporary stents in similar populations to BIOSOLVE-II are rare but, if reported, LLL and diameter stenosis were superior to our series (except for a similar in-scaffold diameter stenosis of Absorb). In our series, in-scaffold LLL at 36 months was 0.54±0.38 mm compared to 0.29±0.43 mm in ABSORB cohort B[17], 0.37±0.45 mm for Absorb and 0.25±0.25 mm for XIENCE in ABSORB II[20], and 0.25±0.37 mm for the biodegradable polymer sirolimus-eluting Firehawk® stent (MicroPort Medical, Shanghai, China) and 0.26±0.19 mm for the durable polymer everolimus-eluting XIENCE V stent in the TARGET I trial[22]. In-scaffold diameter stenosis was 26.7±11.9% in BIOSOLVE-II compared to 23.2±14.9% for ABSORB cohort B[17], 25.8±17.3% for Absorb and 15.7±8.3% for XIENCE in ABSORB II[20], and 13.2±11.0% and 12.6±6.8% in TARGET I for Firehawk and XIENCE V stents[22].

In contrast to outcomes of BIOSOLVE-I with the precursor product DREAMS first generation[19], no decrease in mean LLL was observed in BIOSOLVE-II up to three years. This might be a play of chance due to the low number of serial imaging follow-ups in BIOSOLVE-I and BIOSOLVE-II or might be related to different confounding patient and lesion characteristics. However, the lumen size was reported to be preserved between six and 12 months[15]. Most importantly, the LLL between 12- and 36-month follow-up remained stable and was similar between target and non-target segments. Therefore, the change in LLL may be attributed to the overall disease progression rather than very late effects of DREAMS 2G beyond its resorption time. Notably, in serial assessments of permanent DES, it seems that there is a more pronounced increase over time. For instance, in the TARGET I trial, both contemporary stents had an LLL of only 0.05 mm at

nine months, which increased by 0.20 mm and 0.21 mm to 0.25 and 0.26 mm at 36 months, respectively[22], while in BIOSOLVE-II the difference between one and three years was 0.13 mm.

Limitations

BIOSOLVE-II has several limitations which have been reported previously[6,9]. In brief, the trial was not randomised and included patients with more simple lesions. The lack of mandated imaging follow-up beyond six months and the associated low patient number with follow-up assessments is the main limitation of the study; therefore, imaging outcomes should be interpreted with caution. As the imaging follow-up beyond six months was voluntary, there might be a potential selection bias, even though the comparison of baseline and procedural parameters did not reveal any relevant differences among the groups. Furthermore, the comparison of disease progression in target versus non-target vessels should be interpreted considering that it was a *post hoc* analysis and disease progression may vary in different vessels. Even though these data present outcomes two years beyond the resorption time, further follow-up would be interesting to assess how the disease progression will evolve over time. Furthermore, registry data are awaited to report outcomes in a larger patient population.

Conclusions

In BIOSOLVE-II, the drug-eluting metal magnesium-based scaffold DREAMS 2G/Magmaris showed favourable safety outcomes at three years, with low TLF and TLR rates and absence of definite or probable scaffold thrombosis in a patient cohort with common risk characteristics for a first-in-man trial. There was no substantial increase in LLL from one to three years.

Impact on daily practice

Three-year outcomes of BIOSOLVE-II provide additional assurance on the long-term outcomes of DREAMS 2G (Magmaris) with clinical event rates comparable to contemporary permanent DES; the absence of definite and probable scaffold thrombosis two years beyond the resorption period is encouraging. While lumen size was preserved beyond the resorption period, overall angiographic outcomes are somewhat disappointing.

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Details of patients who experienced a clinically driven target lesion revascularisation.

Supplementary Table 2. Comparison of patients' baseline and procedural characteristics amongst the imaging subgroups.

Supplementary Table 3. Angiographic outcomes up to 3 years (paired and unpaired analysis).

Supplementary Table 4. Serial intravascular ultrasound (IVUS) and optical coherence tomography (OCT) analysis up to 3 years in patients who had both assessments (n=6).

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Supplementary data

Supplementary Table 1. Details of patients who experienced a clinically driven target lesion revascularisation.

Event	Post-procedure day	Description
TLR	84	RVD 3.5 mm, lesion length 15.0 mm, predilatation **3.0** x 15 mm **scoring balloon**, scaffold 3.0 x 20 mm, post-dilatation 3.0 x 15 mm NC balloon, 16 atm, and 3.5 x 12 mm NC balloon, 10 atm, post-procedure in-scaffold **DS: 23%.** Event description: angina (on exertion), in-scaffold DS 81%, treatment with 3.5 mm DES, post-dilation with 4.0 and 4.5 mm balloons
TLR	180	RVD 2.6 mm, lesion length 12.7 mm, predilatation 2.5 x 15 mm NC balloon, scaffold 3.0 x 20 mm, **no post-dilatation**, post-procedure DS: 10%. Event description: ongoing angina, DS: 54% treatment with 3.0 x 24 mm DES
TLR	461	RVD 2.6 mm, lesion length 7.8 mm, predilatation 3.0 x 12 mm NC balloon, scaffold: 3.0 x 20 mm, post-dilatation 3.5 x 15 mm NC balloon, 24 atm, post-procedure in-scaffold DS: 18%. Event description: angina, in-scaffold DS 50%, treatment with 3.0 x 24 mm DES
TLR	561	RVD 2.3 mm, lesion length 12.8 mm, predilatation 2.5 x 15 mm **semi-compliant** balloon, scaffold: 3.0 x 20 mm, post-dilatation 3.0 x 12 mm NC balloon, 18 atm, post-procedure in-scaffold DS: 12%. Event description: positive stress test and chest pain, in-scaffold DS: 67%, treatment with 2.25 x 32 mm DES
TLR	1,083	RVD 3.0 mm, lesion length 16 mm, predilatation 3.0 x 15 mm **scoring** balloon, scaffold: 3.0 x 20 mm, **no post-dilatation** Event description: recurrent angina. Amongst others, per core laboratory 70% in-scaffold restenosis in the target vessel, treatment of target vessel with 4 DES (diameter from 2.5 to 3.0 mm and length from 15 to 40 mm)

Predilatation was performed in all subjects. Highlights in bold reflect procedural steps that are not in line with current treatment recommendations.
DAPT: dual antiplatelet therapy; DES: drug-eluting stent; DS: diameter stenosis; NC: non-compliant; RVD: reference vessel diameter; TLR: clinically driven target lesion revascularisation

Supplementary Table 2. Comparison of patients' baseline and procedural characteristics amongst the imaging subgroups.

	3-year angiographic assessment			Serial OCT assessment			Serial IVUS assessment		
	Yes N=48	No N=75	*p*-value	Yes N=12	No N=111	*p*-value	Yes N=8	No N=115	*p*-value
Medical history									
Age (years)	66.1±9.9	64.6±10.5	0.42	67.2±8.7	65.0±10.5	0.55	68.1±8.4	65.0±10.4	0.46
Male	29 (60.4)	49 (65.3)	0.70	5 (41.7)	73 (65.8)	0.12	3 (37.5)	75 (65.2)	0.14
History of MI	13 (27.1)	16 (21.3)	0.52	1 (8.3)	28 (25.2)	0.29	2 (25.0)	27 (23.5)	1.00
Hypertension	39 (81.3)	62 (82.7)	1.00	8 (66.7)	93 (83.8)	0.23	8 (100.0)	93 (80.9)	0.35
Hypercholesterolaemia	27 (56.3)	47 (62.7)	0.48	5 (41.7)	69 (62.2)	0.17	4 (50.0)	70 (60.9)	0.54
Diabetes mellitus	15 (31.3)	21 (28.0)	0.84	2 (16.7)	34 (30.6)	0.51	3 (37.5)	33 (28.7)	0.69
Previous coronary interventions/surgeries	22 (45.8)	30 (40.0)	0.52	5 (41.7)	47 (42.3)	0.96	6 (75.0)	46 (40.0)	0.053
Target lesion									
Lesion class			0.22			0.14			0.014
Type A	1 (2.1)	0		1 (8.3)	0		1 (12.5)	0	
Type B1	30 (62.5)	38 (51.4)		7 (58.3)	61 (55.5)		4 (50.0	64 (56.1)	
Type B2	16 (33.3)	35 (47.3)		4 (33.3)	47 (42.7)		2 (25.0)	49 (53.0)	
Type C	1 (2.1)	1 (1.4)		0	2 (1.8)		1 (12.5)	1 (0.9)	
Moderate to heavy calcification	5 (10.4)	8 (10.8)	1.00	2 (16.7)	11 (10.0)	0.62	2 (25.0)	11 (9.6)	0.20
RVD (mm)	2.70±0.39	2.67±0.40	0.26	2.76±0.23	2.67±0.41	0.73	2.74±0.20	2.68±0.41	0.89
Lesion length (mm)	13.1±4.6	12.3±4.5	0.97	11.6±3.4	12.7±4.6	0.96	12.3±3.4	12.6±4.6	0.50
Diameter stenosis (%)	57.8±10.5	53.5±9.9	0.083	60.5±11.6	54.6±10.1	0.078	59.2±13.7	54.9±10.1	0.061
MLD (mm)	1.13±0.29	1.24±0.33	0.018	1.08±0.33	1.21±0.31	0.061	1.11±0.39	1.20±0.31	0.044
Procedure*									
Scaffold diameter (mm)	3.17±0.26	3.10±0.23	0.15	3.17±0.25	3.12±0.25	0.59	3.06±0.18	3.13±0.25	0.40
Scaffold length (mm)	21.8±2.4	21.2±2.1	0.14	21.7±2.5	21.4±2.2	0.67	20.6±1.8	21.5±2.3	0.31

	3-year angiographic assessment			Serial OCT assessment			Serial IVUS assessment		
	Yes N=48	**No N=75**	***p*-value**	**Yes N=12**	**No N=111**	***p*-value**	**Yes N=8**	**No N=115**	***p*-value**
Maximum pressure applied (atm)	13.4±2.5	14.3±2.3	0.039	13.6±2.2	14.0±2.4	0.53	14.0±1.9	14.0±2.5	0.93
Inflation time (sec)	24.6±15.8	23.7±16.1	0.70	26.3±15.5	23.8±16.0	0.51	28.4±17.4	23.7±15.8	0.47
Post-dilatation performed	25 (52.1)	49 (65.3)	0.19	9 (75.0)	65 (58.6)	0.36	5 (62.5)	69 (60.0)	1.00
Follow-up									
Target lesion failure	2 (4.5%)	6 (8.1%)	0.36	0	8 (7.7%)	1.00	0	8 (7.4%)	1.00
Late lumen loss				N=11	N=37		N=8	N=40	
In-scaffold	0.54±0.38	NA	NA	0.61±0.33	0.52±0.39	0.35	0.50±0.26	0.55±0.40	0.82
In-segment	0.43±0.40	NA	NA	0.44±0.33	0.42±0.43	0.76	0.40±0.27	0.43±0.43	0.93

Data are displayed as n (%) or mean±SD. *n=125 scaffolds were used.

IVUS: intravascular ultrasound; MI: myocardial infarction; MLD: minimum lumen diameter; NA: not applicable; OCT: optical coherence tomography; RVD: reference vessel diameter

Supplementary Table 3. Angiographic outcomes up to 3 years (paired and unpaired analysis).

	Baseline	Post-procedure	6 months	12 months	36 months
Unpaired analysis	**N=123**	**N=123**	**N=113**	**N=45**	**N=48**
RVD (mm)	2.68±0.40				
In-scaffold		2.78±0.36	2.60±0.41	2.63±0.41	2.60±0.49
In-segment		2.69±0.39	2.56±0.41	2.58±0.44	2.58±0.49
MLD (mm)	1.19±0.32				
In-scaffold		2.45±0.32	2.00±0.44	2.11±0.40	1.91±0.50
In-segment		2.16±0.40	1.89±0.43	1.96±0.40	1.85±0.48
Diameter stenosis (%)	55.3±10.3				
In-scaffold		11.7±5.2	22.6±12.9	19.8±8.8	26.6±12.1
In-segment		19.7±8.3	25.9±12.2	24.0±10.7	28.5±11.7
Acute gain (mm)	NA		NA	NA	NA
In-scaffold		1.25±0.35			
In-segment		0.96±0.40			
Late lumen loss (mm)	NA	NA			
In-scaffold			0.43±0.36	0.39±0.27	0.54±0.38
In-segment			0.26±0.36	0.24±0.22	0.43±0.40
Paired data (6-12-36 months)	**N=25**	**N=25**	**N=25**	**N=25**	**N=25**
RVD (mm)	2.74±0.34				
In-scaffold		2.82±0.35	2.63±0.31	2.63±0.37	2.59±0.39
In-segment		2.79±0.36	2.60±0.37	2.59±0.40	2.57±0.40
MLD (mm)	1.09±0.31				
In-scaffold		2.51±0.34	2.12±0.36	2.08±0.36	1.95±0.43
In-segment		2.32±0.37	1.99±0.35	1.98±0.37	1.87±0.43
Diameter stenosis (%)	59.9±11.0				
In-scaffold		11.0±7.2	19.7±9.2	20.7±9.8	24.9±12.0
In-segment		16.8±8.4	23.2±9.9	23.7±8.8	27.5±12.0
Acute gain (mm)	NA		NA	NA	NA
In-scaffold		1.37±0.40			
In-segment		1.18±0.47			

	Baseline	Post-procedure	6 months	12 months	36 months
Late lumen loss (mm)	NA	NA			
In-scaffold			0.36±0.27	0.42±0.30	0.55±0.31
In-segment			0.17±0.20	0.35±0.23	0.46±0.25
Paired analysis (12-36 months)	**N=25**	**N=25**	**N=25**	**N=25**	**N=25**
RVD (mm)	2.74±0.34		-		
In-scaffold		2.82±0.35		2.63±0.37	2.59±0.39
In-segment		2.79±0.36		2.59±0.40	2.57±0.40
MLD (mm)	1.09±0.31		-		
In-scaffold		2.51±0.34		2.08±0.36	1.95±0.43
In-segment		2.32±0.37		1.98±0.37	1.87±0.43
Diameter stenosis (%)	59.9±11.0		-		
In-scaffold		11.0±7.2		20.7±9.8	24.9±12.0
In-segment		16.8±8.4		23.7±8.8	27.5±12.0
Acute gain (mm)	NA		-	NA	NA
In-scaffold		1.37±0.40			
In-segment		1.18±0.47			
Late lumen loss (mm)	NA	NA	-		
In-scaffold				0.42±0.30	0.55±0.31
In-segment				0.35±0.23	0.46±0.25
Paired analysis (6-36 months)					
	Baseline N=47	**Post-procedure N=47**	**6 months N=47**	**12 months N=47**	**36 months N=47**
RVD (mm)	2.7±0.40			-	
In-scaffold		2.83±0.39	2.66±0.43		2.60±0.49
In-segment		2.79±0.40	2.62±0.43		2.58±0.49
MLD (mm)	1.13±0.30			-	
In-scaffold		2.47±0.37	2.11±0.41		1.92±0.51
In-segment		2.28±0.44	1.99±0.40		1.85±0.49
Diameter stenosis (%)	57.8±10.6			-	
In-scaffold		12.8±7.4	20.2±10.2		26.6±12.1

	Baseline	Post-procedure	6 months	12 months	36 months
In-segment		18.6±9.2	23.6±10.5		28.5±11.7
Acute gain (mm)	NA		NA	-	NA
In-scaffold		1.27±0.42			
In-segment		1.09±0.50			
Late lumen loss (mm)	NA	NA		-	
In-scaffold			0.36±0.26		0.54±0.38
In-segment			0.17±0.25		0.43±0.41

Core laboratory analysis. Data are displayed as mean±SD.

MLD: minimum lumen diameter; NA: not applicable; RVD: reference vessel diameter

Supplementary Table 4. Serial intravascular ultrasound (IVUS) and optical coherence tomography (OCT) analysis up to 3 years in patients who had both assessments (n=6).

	Post-procedure	12 months	36 months	Δ 12 months vs post-proc.	Δ 36 vs 12 months	*p*-value 12 months vs post-proc.	*p*-value 36 vs 12 months
Mean lumen area (mm²) OCT	7.29 (7.08–7.84)	5.48 (5.00–6.64)	5.01 (3.91–5.75)	-1.81 (-2.12– -1.39)	-0.57 (-0.89–0.41)	<0.001	0.292
Minimal lumen area (mm²) OCT	5.86 (5.43–6.56)	3.81 (3.60–4.75)	3.37 (3.13–3.65)	-1.90 (-2.30– -1.48)	-0.37 (-1.10– -0.14)	0.003	0.031
Mean lumen area (mm²) IVUS	6.53 (5.80–7.00)	5.64 (5.32–6.60)	5.55 (5.24–5.89)	-0.81 (-1.21– -0.24)	0.07 (-0.65–0.22)	0.027	0.885
Minimal lumen area (mm²) IVUS	5.33 (5.00–5.81)	4.33 (3.82–4.89)	4.14 (3.28–4.81)	-1.05 (-1.25– -0.91)	-0.20 (-0.33– -0.08)	<0.001	0.213

Data are shown as median and interquartile range (Q1-Q3) or n (%).

IVUS: intravascular ultrasound; NA: not applicable; OCT: optical coherence tomography