National Institute for Health and Clinical Excellence
Medical Technologies Evaluation Programme

MT 154 – EXOGEN Ultrasound Bone Healing System for long bone fractures with non-union or delayed healing

Consultation Comments table

MTAC date: 19 October 2012

There were 32 consultation comments from 4 consultees (1 sponsor, 2 patients and 1 case manager). The comments are reproduced in full.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
1	Consultee 1, (Patient)	**1**	I was prescribed an Exogen machine in September 2009, nearly 3 years after sustaining multiple fractures of the right leg. The long term problem was a high energy fracture of the femur with bone loss. It had already been bone grafted 3 months post accident but was slow to unite. In addition to using the Exogen machine I had further surgery including leg lengthening so it is difficult to say how much of the improvement is due to Exogen but there is now clinical and radiological evidence of union and although I still have an intramedullary nail I am able to walk normally without any walking aids	Thank you for your comment.

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2	Consultee 3, Smith & Nephew (sponsor)	**1.2**	Section 1.2 states – " There is some radiological evidence of improved healing when the EXOGEN ultrasound bone healing system is used for long bone fractures with delayed healing, but there is high uncertainty about the rate at which healing progresses between 3 and 9 months after fracture and about whether or not surgery would otherwise be necessary." In its' current form, this sentence reads as though there is high uncertainty about the rate of EXOGEN healing between 3 and 9 months, whereas Smith & Nephew believes the essence of this statement refers to bone healing in general. To clarify this, we recommend a minor change to this sentence as follows: "There is some radiological evidence of improved healing when the EXOGEN ultrasound bone healing system is used for long bone fractures with delayed healing. In general, there also is high uncertainty about the rate at which bone healing progresses, without adjunctive treatment, between 3 and 9 months after fracture and about whether or not surgery would otherwise be necessary."	Thank you for your comment. The Committee decided to change section 1.2 of the guidance to further clarify the uncertainty about the rate at which bone healing progresses.
3	Consultee 3, Smith & Nephew (sponsor)	**1.2**	Smith & Nephew agrees that uncertainties in healing rates results in a range of cost consequences and propose that further	Thank you for your comment. The Committee carefully considered this comment and decided not to change the guidance because no

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			clarity should be added to guidance in the recommendation of the use of EXOGEN in the treatment of delayed unions, to help identify those scenarios where EXOGEN would be likely to be cost – saving. There are known patient groups (hereinafter "at risk population") in whom healing takes place at a slower rate than the general population. These patients are also at considerably higher risk of non-union and / or developing infection if they undergo repeat surgical intervention. Expert opinion will be the best guide to identify the "at risk population", although Taylor et al (at ISPOR 2006) identified risk factors that included diabetes, smoking and others such as steroid use, obesity, osteoporosis, older patient age and complicated fractures (Lane, et al, Journal of Ortho Trauma 1999). Moghaddam et al (Injury, doi:10.1016/j.injury.2011.05.011) conducted a prospective study of patients with tibial fractures. Their findings indicate that cigarette smoking "significantly increases the risk of impaired fracture healing, which has clinical and occupational consequences	sub-groups were specified in the scope and no specific clinical or economic evidence reporting the use of EXOGEN in at risk populations was submitted by the sponsor. The External Assessment Centre reviewed the papers cited by the Consultee and concluded that, while the studies suggest some risk factors for non union, the evidence is contradictory and it is uncertain if EXOGEN would improve healing for patients with these risk factors. Section 3.23 contains the Committee's consideration of this point.

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			for the affected patients."	
4	Consultee 1, Patient	**2**	I used an Exogen 4000+ because the manufacturer undertook to provide further machines free of charge until the fracture was healed. The machine was easy to use and I took it with me whenever I went away from home. I was very motivated to use it every day as I felt I was doing something positive.	Thank you for your comment.
5	Consultee 3, Smith & Nephew (sponsor)	**2.2**	It is an important fact that the EXOGEN EXPRESS delivers 150 treatments (approximately 5 months) as stated in 2.2, because in the delayed union cost modelling, where persistence of benefit is seen beyond 4 months, EXOGEN becomes more cost effective.(EAC report p.64 comparison of scenarios 1A with 1B, 2A with 2B) In the same model EXOGEN is shown to be cost saving in scenarios where patients heal at a slower rate than the general population and persistence of benefit is seen (EAC report p.64 scenarios 2B and 2D). As the EXOGEN EXPRESS is capable of delivering treatment that would ensure persistence beyond 4 months, the use of EXOGEN to treat patients seen to be healing slowly ("at risk population") could very plausibly be cost - saving. (please see	Thank you for your comment. The scenarios developed by the External Assessment Centre were based on the stated number of treatments delivered by the EXOGEN EXPRESS. Sections 5.22 and 5.23 of the guidance describe the Committee considerations on the most likely scenario. Please refer to comment 3 with regards to the identification of a high risk population

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			5.17)	
6	Consultee 3, Smith & Nephew (sponsor)	**2.3**	The description of the EXOGEN device is accurate and highlights the ease of adoption of the technology into routine clinical practice. It is important to note that the ultrasound signal emitted by the EXOGEN device is specific to EXOGEN due to the input frequencies and the technical specification of the transducer head.	Thank you for your comment. The Committee decided to change section 2.3 to clarify that the ultrasound signal is specific to EXOGEN.
7	Consultee 3, Smith & Nephew (sponsor)	**2.5**	In addition to the claimed benefits of using EXOGEN in the treatment of long bone fractures with impaired healing, by avoiding further surgical intervention, there is also the potential to liberate resources. Bed capacity and theatre utilisation would both be positively impacted, with approximately 30,000 bed days and 6,500 theatre sessions released.	Thank you for your comment. Section 2.5 of the guidance lists only the claimed benefits included in the scope. Section 4.2 of the guidance refers to the healthcare system benefits of the technology.

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8	Consultee 3, Smith & Nephew (sponsor)	**2.7**	The description of current management is in line with current UK practice. Expert opinion suggests that the *maximum* time that would elapse from diagnosis of a delayed union (which varies patient by patient) to the point at which further surgical intervention would be considered is approximately 3 months. In the cost models presented, this would introduce significant additional costs at an earlier point in time than is proposed in the cost modelling and make EXOGEN more cost effective.	Thank you for your comment. The Committee decided not to change the guidance because it heard from clinical experts that surgery may take place between 6 and14 months. It concluded that the best estimate of the average time lapse from the initial fracture to surgery is 9 months, and noted that this estimate was used in the economic modeling.
9	Consultee 1, Patient	**3**	I do not feel qualified to comment on the clinical evidence	Thank you for your comment.

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10	Consultee 3, Smith & Nephew (sponsor)	**3.3**	Section 3.3 makes reference to the submitted paper by Rutten which was rejected by the EAC. Although it does not include the outcomes required by the scope, it fully supports the findings of Schofer and shows significant benefit of EXOGEN in the same secondary outcome measures as those (noted and accepted by the EAC and the Committee in section 3.21) from Schofer. It also illustrates a significant progression to healing in a randomised, placebo controlled study in patients with delayed unions of the fibula (11/13 patients met the definition of delayed union in the scope). Note should also be made of the ethical and methodological constraints that make conducting comparative randomised trials in this field of medicine extremely difficult, if not impossible. This is the reason for the limited 4 month timeframe over which patients were observed in the Schofer paper (as directed by the ethics committee) and consequently leaves the question of persistence of effect, beyond 4 months, open. Please also refer to comment 2.2 and 5.17	Thank you for your comment. The Committee noted that the External Assessment Centre excluded the study by Rutten from further consideration because it did not contain any patient outcomes which were specified in the scope, and decided, therefore, not to change the guidance. Thank you for your comment. Section 3.19 contains the Committee's considerations on this important issue.
11	Consultee 3, Smith & Nephew (sponsor)	**3.6**	It is important to note the Committee's and the EAC's acceptance of the paper by Jingushi in section 3.6. Jingushi (table 5 and table 6) demonstrates the persistence of the effect of EXOGEN, as each month there is an increasing number of fractures showing radiological evidence	Thank you for your comment. Please also refer to response to comment 5. The Committee decided not to change the guidance because it was advised by the External Assessment Centre that the Jingushi study is not comparative and

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			of healing. This evidence supports the comments made in 2.2 as the EXOGEN EXPRESS not only delivers treatment beyond 4 months, but also shows persistence of clinical benefits and therefore very plausibly delivers a more cost saving outcome in the “at risk population.” Further to this data Leung (Ultrasound in Med. & Biol., Vol. 30, No. 3, pp. 389–395, 2004) published on the use of Exogen to treat complex tibial fractures. This study showed significantly better healing, as demonstrated by all assessments when compared to a placebo unit. Although the EXOGEN device was only used for 90 days, the effect was seen to increase bone mineral content at the fracture site which became significant at week 15 (3.75 months) which persisted as being significant over placebo at week 18 (3.75 months) and week 21 (5.25 months). The trend continued to be in the favour of EXOGEN up to the end of measurements at week 30. This measure of bone mineral content at the fracture site is essentially the same measurement as Schofer used in his study on delayed unions, which also showed a significant effect of EXOGEN after 16 weeks of use. Leung was not included in the sponsor’s original submission (as it concerns complex fresh fractures), but adds valuable support to the plausibility for persistence of the clinical effect beyond 4 months.	that the definition of ‘persistence’ used in the study is inconsistent with that used in the External Assessment Centre’s analyses (that is a persistence of the enhanced healing rate). The External Assessment Centre concluded that the data are unsuitable as the basis for modeling healing rates. The Committee considered that the Leung study is outside the scope of the evaluation and decided not to change the guidance. It was advised by the External Assessment Centre that it is not possible to estimate a suitable hazard ratio after cessation of treatment in delayed union patients.

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			Please also see comments 5.17	
12	Consultee 3, Smith & Nephew (sponsor)	**3.22**	Smith & Nephew agrees that the heterogeneity in healing rates and variation in time makes for greater complexity in interpreting outcomes. This adds further rationale for clearer recommendations in 1.2 regarding the “at risk population” which is consistent and homogenous in that delayed healing is expected.	Thank you for your comment. Please refer to the response to comment 3.
13	Consultee 1, Patient	**4**	I agree that the device is easy to use. Before it was prescribed I had spent almost 3 years on crutches attending Outpatient clinics and having x-rays and being told that the fracture in my femur was not uniting. I am now able to walk reasonably well and have returned to almost all the activities which I enjoyed before my accident. The improvement in quality of life is immeasurable	Thank you for your comment.
14	Consultee 3, Smith & Nephew (sponsor)	**4.1**	Although avoidance of surgery was not expressly reported, logically a healed fracture would equate to avoidance of further surgery. This is recognised by the Committee in sections 3.17 and 4.3	Thank you for your comment.
15	Consultee 3, Smith & Nephew (sponsor)	**4.2**	Smith & Nephew agrees with this statement and estimates the positive impact of adopting EXOGEN in the treatment of long bones with impaired healing to be approximately 30,000 bed days and 6,500 theatre sessions.	Thank you for your comment. The Committee’s considerations of the system impact of EXOGEN are included in section 4.2 of the guidance. No specific evidence on the overall impact of EXOGEN on bed days or theatre sessions was included in the sponsor submission.

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16	Consultee 3, Smith & Nephew (sponsor)	**4.3**	Smith & Nephew agrees with this consideration and has many other examples of patients who have undergone similar experiences and have consented to share their stories via our patient support media.	Thank you for your comment.
17	Consultee 1, Patient	**5**	Not qualified to comment	Thank you for your comment.
18	Consultee 3, Smith & Nephew (sponsor)	**5.1**	Smith & Nephew chose to use a “bottom up” approach to costs from an NHS perspective, conducted as conservatively (see 5.10) as possible. This approach was taken following expert advice that there is a flaw in the PBR grouper software which may lead to a lack of consistency in the accuracy of reference costs. For example, the reference cost for HA99Z applied by the EAC is £4,126. However, due to the software flaw, any hospital receiving the elective tariff under this code for 2012 - 2013 only receives £440.00.	Thank you for your comment. The Committee noted that the External Assessment Centre’s analysis of the sponsor’s cost model did not use tariff estimates for the cost of surgery, and decided not to change the guidance.

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19	Consultee 3, Smith & Nephew (sponsor)	**5.10**	The costs presented in the Smith & Nephew models do **not** include any of the following : • NHS costs incurred beyond one year • Costs associated with bone graft donor site complications (Friedlander reported moderate or severe pain in 80% of patients, 13 % of whom had persistent pain at 1 year) • Costs associated with managing broken implants • The removal of surgical implants • Societal costs The EAC agreed that the decision to not include societal costs removed bias in favour of EXOGEN (p.18 EAC report).	Thank you for your comment. The model inputs are described in section 5.10 of the guidance.
20	Consultee 3, Smith & Nephew (sponsor)	**5.12**	The varied rates of healing applied in the model submitted by Smith & Nephew showed a base case saving of £684 and the sensitivity analyses conducted showed a range of cost consequences, (as highlighted in comment 1.2) many of which are very plausibly cost saving when comments in 2.2, 3.6, 5.17, 5.21 and 5.23 are taken into consideration.	Thank you for your comment. As noted in the response to comment 5, the Committee accepted the External Assessment Centre's preferred scenario (scenario 1A) which showed that EXOGEN was associated with a cost increase and decided not to change the guidance. The External Assessment Centre varied the healing rate for delayed healing in a range of sensitivity analyses and EXOGEN remained more costly in all cases. This is summarised in section 5.20 of the guidance.
21	Consultee 3, Smith & Nephew (sponsor)	**5.17**	The EAC created 8 different scenarios in the case of delayed unions (EAC report table 16, p.64), and favoured the 1A	Thank you for your comment. Please refer to the responses to comments 5 and 11 respectively about the average duration of treatment

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			scenario - where there is a delay in the observation of healing, no persistence of benefit of EXOGEN beyond 4 months, and the healing rate is high (92% at 4 months for EXOGEN and a relative risk for observation of 1.69) - which led to a cost difference in favour of control of £504. Smith & Nephew agrees with the assumption that there will be delay in observation of healing, this is illustrated in Jingushi (3.6) and confirmed by expert opinion. However, Smith & Nephew respectfully disagrees with the EAC view on persistence, as the EXOGEN EXPRESS device will continue to deliver treatments for approximately 5 months, Jingushi shows a monthly increasing number of patients improving radiologically over time and Leung shows significant improvement in bone mineral density (the same measures observed by Schofer) up to 30 weeks. Scenario 1B shows that persistence of effect would reduce the cost difference to £370. Smith & Nephew also respectfully disagrees with the healing rate quoted by the EAC (92% at 4 months) as the paper referenced by Mayr shows a heal rate of 91% in all	and evidence of persistence. Please refer to the response to comment 3 about the at risk population. The Committee was advised that the baseline healing rate used in the External Assessment Centre's model is 92% over a healing time of 4.5 months. These data are specific to tibia fractures whereas the figures quoted by the consultee (91%) relate to fractures in a range of bones and 150 days is the time from fracture date to start of low intensity therapy, rather than healing time. The Committee decided not to change the guidance. The Committee considered that the External Assessment Centre's preferred scenario (scenario 1A) was the most likely as explained in sections 5.22 and 5.23 of the guidance.

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			delayed unions at 150 days (table 2, p.3). Particularly in the case of the “at risk population” the healing rate is more likely to be in the order of the lower rates quoted in the modelled scenario 2A - 2D. In scenario 2B, where there is delay in observed healing, there is persistence of clinical benefit and the healing rate is lower, then EXOGEN delivers cost saving of £390 compared to control. This supports the proposal in 2.2 that there are identifiable scenarios in which EXOGEN can be very plausibly cost-saving and guidance should include the identification of the “at risk population” for the use of EXOGEN in delayed healing.	

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22	Consultee 3, Smith & Nephew (sponsor)	**5.18**	It is understandable why the EAC assumes that EXOGEN treatment for delayed unions ceases at 4 months. This is due to the ethical limitations of the Schofer trial (referred to in comment 3.3). However, as illustrated in comment 2.2, the EXOGEN EXPRESS delivers treatment for approximately 5 months and therefore this assumption does not reflect current practice, or routine use of the device. Expert opinion says that following a diagnosis of delayed union, in general, if a patient shows radiographic evidence of healing 3 months after commencing EXOGEN treatment, then EXOGEN treatment will continue. If there is no radiographic evidence of healing at 3 months, there is a strong likelihood of further surgical intervention.	Thank you for your comment. Please refer to the responses to comments 5 and 8 respectively about the average duration of treatment and the timing of surgery.
23	Consultee 3, Smith & Nephew (sponsor)	**5.19**	Please see 5.17. Smith & Nephew respectfully disagrees with this preferred scenario, particularly in the case of the “at risk population.”	Thank you for your comment. Please refer to the response to comment 21.
24	Consultee 3, Smith & Nephew (sponsor)	**5.20**	Please see 5.17, Smith & Nephew believes that sensitivity analyses should also have been carried out on other equally plausible scenarios which would show cost saving.	Thank you for your comment. Please refer to the response to comment 21.

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25	Consultee 3, Smith & Nephew (sponsor)	**5.21 & 5.23**	Smith & Nephew agrees that the costs used by the EAC (and also by Smith & Nephew in the sponsor submission) in the models presented are underestimates. In addition to all of the potential additional costs illustrated in comment 5.10, there are no costs included for surgical implants or biologic products, identified under PBR exclusions.	Thank you for your comment.
26	Consultee 3, Smith & Nephew (sponsor)	**5.22**	Smith & Nephew agrees that the EAC approach to scenario analysis is reasonable. Several of these scenarios, especially in the “at risk population” would indicate that the use of EXOGEN is cost neutral, or very plausibly cost saving.	Thank you for your comment. Please refer to the response to comment 3.
27	Consultee 3, Smith & Nephew (sponsor)	**5.23**	Smith & Nephew respectfully disagrees with the Committee’s choice of scenario for the reasons stated in comments 2.2, 3.6 and 5.17	Thank you for your comment. Please refer to the response to comment 21.
28	Consultee 3, Smith & Nephew (sponsor)	**5.25**	The one year time horizon does not capture all costs. Smith & Nephew created conservative models (see comment 5.10 and 5.21) to illustrate the cost benefits to patients and to the NHS that would be realised within a 1 year time frame.	Thank you for your comment. This is noted in section 5.25 of the guidance.
29	Consultee 3, Smith & Nephew (sponsor)	**6.2**	Smith & Nephew respectfully disagrees with the Committee’s views about the assumptions used by the EAC in their	Thank you for your comment. Please refer to the responses to comments 3, 19, 21, 25 and 27.

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			preferred scenario for delayed union treatment. It is therefore proposed that there is sufficient evidence to show that the adoption of EXOGEN for the treatment of delayed unions in a defined “at risk population” would be at least cost neutral and very plausibly cost saving whilst delivering significant resource benefits to the NHS when the following factors are taken into consideration: • The believed underestimation of costs stated in comment 5.21 & 5.23, • The clinical data accepted in the submission (supporting persistence of effect along with the 150 treatment life of the EXOGEN EXPRESS) • There is a clearly identifiable “at risk population.” Patients at risk are susceptible to poor outcomes and increased complications. The use of EXOGEN for delayed unions in this group will offer an easy to administer, safe, clinically effective and cost effective	

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			treatment.	
30	Consultee 2, Bridge Case Management	**General**	This is my personal response regarding Exogen, as a Case Manager who has been able to purchase it privately for two of my clients, and have another who got it through the NHS. All my clients have found it very easy to use, and have had no problems with it. All have felt it was something proactive they were doing themselves to speed up the recovery process. One of the two I have purchased it for was not suffering from adversely slow healing bones, but the sheer number of injuries he had meant that speeding up the healing process post surgery (around 18 months post accident) would make a big difference to his overall rate of recovery. We therefore purchased this for the arm fracture, and it has now fully united. Of the three case they have all achieved full union in a relatively short space of time. The other two fractures were suffering from significant delayed union. The best outcome was for the client who got this through the NHS. He had been told that without Exogen it would take many	Thank you for your comment.

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			months of healing, and would probably require additional surgery. He had an external fixator on at the time when they started using Exogen. Within a few weeks he had the external fixator taken off, and after two weeks in plaster he had was told that he had achieved full union (the cast had a hole cut in so he could continue using it). He returned to work in a physical demanding role part time only a few months after having the plaster cast removed, and I believe he would have returned earlier if the weather had been better – but I discouraged him from returning to his physical outdoors job until the weather improved. I hope you find this useful, if you need more information please let me know.	
31	Consultee 3, Smith & Nephew (sponsor)	**General (Provisional Recommendations)**	Smith & Nephew broadly welcomes the recommendations by the Committee, which we believe to be both in the interests of patients with impaired bone healing and of the NHS as a whole. Smith and Nephew would welcome additional guidance in section 1.2 to direct healthcare providers to treatment scenarios in delayed unions where EXOGEN is cost saving.	Thank you for your comment. Please refer to the response to comment 3.

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32	Consultee 4, Patient	**General**	I am very pleased to write very strongly in support of this excellent device. As a retired [redacted] with an initial background in orthopaedics, I was particularly interested to try Exogen out, in view of my complete tibial non-union. I have a photographic record of my progress following my accident, and would be happy to make this available. It certainly refutes one of the treasured aphorisms of my [redacted] who once defined physiotherapy as 'damn all, multiplied by time!' I enclose a copy of [redacted] letter and will answer the five questions as best as I can. 1. Easiness of use. Extremely easy to learn to use the device. 2. In view of my near immobility extremely easy to use each day 3. Surgical interventions-two, initially the debriding of my damaged skin due to injudicious POP application, and the insertion of external fixators, and secondly the removal of the external fixator device & application of POP. 4. Non-union of my Rt Tibia diagnosed on 7 March 2011, (the accident occurred on 20 December 2011). On March 7th the right tibia was totally	Thank you for your comment.

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			mobile in its lower section. Exogen Ultrasound was commenced on 24th March, the slight delay being due to the obtaining of the device, provided financially through the great generosity of BUPA. 84 daily treatments of 20 minutes duration were applied between 24th march and the 15th June. In that time the tibia progressed from virtual complete non-union, to well advanced union by the end of June. No day was missed. 5. Active role: As someone with orthopaedic insight, I had realised from the start that delayed or non-union was a very real possibility, and when it became apparent that non-union had occurred, the tibia and fibula being in six fragments, I was delighted that I could play a part in the resolution of my problem, as indeed proved to be the case. I am extremely grateful as I have regained satisfactory mobility. With 1 and a half inches of shortening I have a built-up shoe, but can drive, and can walk a reasonable distance. I have fairly constant discomfort and, on occasion pain requiring Cocodamol, seldom more than four tablets in any one day. I have been able to fly-fish again from the bank, sadly I shall never wade again. I can also enjoy my favourite sport of game-shooting provided I am driven to my peg!	

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			I have no doubt that the Exogen device played an essential part in my recovery, and this is clearly supported by serial radiographs. I hope this account is of use to NICE.	

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