

## 4.1 Introduction to Pharmacology Studies

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This submission focuses on the use of OP-1<sup>®</sup> Putty as a device for treatment of patients requiring posterolateral lumbar spinal fusion. The goal of spinal fusion is to attain solid arthrodesis. Nonunion remains a significant challenge and may lead to added morbidity and requirements for additional surgeries. Data from numerous preclinical studies that support the development of OP-1<sup>®</sup> Putty for spinal fusion are summarized in Table 2-1 (Refer to P060021/A011 Appendix 1a-32, page 14), and include the following:

- Binding of OP-1 to OP-1 receptors with affinity that is similar in humans, rats and rabbits (Refer to P060021/A011 Appendix 1a-32, Section 2.3.2, page 17).
- Dose response in baboon and rabbit models of posterolateral fusion (see Section 4.2.1).
- Evidence of efficacy in uninstrumented models of spinal fusion in dogs that demonstrated OP-1 is superior to other treatments including bone autograft for spinal fusion of the thoracic and lumbar vertebrae (see Section 4.2.1).
- Efficacy of OP-1<sup>®</sup> Putty in a multilevel spinal fusion study in sheep. OP-1<sup>®</sup> Putty was at least as effective as bone autograft alone (see Section 4.2.1).
- Improved efficacy of OP-1<sup>®</sup> Putty compared with Grafton<sup>®</sup> Putty in a rat spinal fusion model (see Section 4.2.1).
- Activity of OP-1<sup>®</sup> Putty in a rabbit pseudoarthrosis model and the capacity to overcome inhibitory effects of nicotine (see Section 4.2.1).
- Effectiveness of OP-1<sup>®</sup> Putty in instrumented versus uninstrumented lumbar fusion in sheep and primates. In sheep, instrumentation did not improve OP-1 efficacy when compared to the uninstrumented treatment group (see Section 4.2.1).
- Efficacy of OP-1<sup>®</sup> Putty in a canine laminectomy and posterolateral spinal fusion model with laminectomy (for dural access) in adult male dogs. OP-1<sup>®</sup> Putty was an effective adjunct to autograft and superior to autograft alone. Also, no adverse effects were noted in the spinal cord (see Section 4.2.1).

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- Osteoinductive effects of OP-1 used in models of long bone healing, craniomaxillofacial surgery and other fusion studies using OP-1 in solution or in combinations with other carriers (Refer to P060021/A011 Appendix 1a-32, Section 2.5, page 30).
- Osteoconductive effects of Type I collagen in a sheep tibial defect model (Refer to P060021/A011 Appendix 1a-32, Section 2.4, page 24).

Taken together, these studies provide ample evidence that the OP-1 is effective in a variety of models and species and more specifically, OP-1<sup>®</sup> Putty device promotes spinal fusion in multiple species. These results support the clinical development of OP-1<sup>®</sup> Putty for spinal fusion.