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Clinical evaluation of medicinal products for acceleration of fracture healing in patients with osteoporosis ☆

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ABSTRACT

Pre-clinical studies indicate that pharmacologic agents can augment fracture union. If these pharmacologic approaches could be translated into clinical benefit and offered to patients with osteoporosis or patients with other risks for impaired fracture union (e.g. in subjects with large defects or open fractures with high complication rate), they could provide an important adjunct to the treatment of fractures. However, widely accepted guidelines are important to encourage the conduct of studies to evaluate bioactive substances, drugs, and new agents that may promote fracture union and subsequent return to normal function.

A consensus process was initiated to provide recommendations for the clinical evaluation of potential therapies to augment fracture repair in patients with meta- and diaphyseal fractures.

Based on the characteristics of fracture healing and fixation, the following study objectives of a clinical study may be appropriate: a) acceleration of fracture union, b) acceleration of return to normal function and c) reduction of fracture healing complications. The intended goal(s) should determine subsequent study methodology. While an acceleration of return to normal function or a reduction of fracture healing complications in and of themselves may be sufficient primary study endpoints for a phase 3 pivotal study, acceleration of fracture union alone is not. Radiographic evaluation may either occur at multiple time points during the healing process with the aim of measuring the time taken to reach a defined status

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(e.g. cortical bridging of three cortices or disappearance of fracture lines), or could be obtained at a single pre-determined timepoint, were patients are expected to reach a common clinical milestone (i.e. pain free full weight-bearing in weight-bearing fracture cases). Validated Patient Reported Outcomes (PRO's) measures will need to support the return to normal function co-primary endpoints. If reduction of complication rate (e.g. non-union) is the primary objective, the anticipated complications must be defined in the study protocol, along with their possible associations with the specified fracture type and fixation device.

The study design should be randomized, parallel, double-blind, and placebo-controlled, and all fracture subjects should receive a standardized method of fracture fixation, defined as Standard of Care.

Introduction

Fracture healing results in regeneration of the fracture site into bone that has similar biomechanical competence as before the injury [1]. This type of regeneration involves stages of tissue differentiation resembling aspects of embryological skeletal development [2]. The fracture repair process is triggered by both the response of local tissue to the injury and the rupture of bony continuity. Specifically, the initial injury provokes an inflammatory response, followed by periosteal response and (with the exception of e.g. compression fractures) endochondral bone formation. Cartilage resorption and woven bone formation are the next steps in fracture repair, followed by secondary bone formation via remodeling.

The duration of each of the healing phases can vary significantly, depending on the location and characteristics of the fracture, patient-related factors, and the chosen treatment [3]. While most fractures heal with conventional therapy, there is potential for permanent deficits and complications with this method, particularly among patients at risk for poor healing. Such complications have direct consequences for the patient and can have a significant socioeconomic impact. Prolongation of the rehabilitation process, delay in return to work, salvage procedures, and/or permanent need for care— all require additional resources.

Likewise, osteoporosis and advanced age may contribute to delayed or impaired fracture union. Indeed, in animal models, fracture union takes longer in older and/or ovariectomized animals[4–6]. In addition, biomechanical testing has shown that implant anchorage or screw purchase is impaired in osteoporotic cadaveric bones. Clinical reports have detailed similar problems during surgical fracture fixation in patients with osteoporosis. A recent literature review evaluated complication rates in patients treated for proximal femur fractures and found a pattern of increased cut-out, re-fracture, or fixation failure in patients with suspected osteoporosis [7]. Pre-clinical studies support that pharmacologic agents can augment fracture union [8]. If these pharmacologic approaches could be translated into clinical benefit and offered to patients with osteoporosis or patients with other risks for impaired fracture union (e.g. in subjects with large defects or open fractures with high complication rate), they could provide an important adjunct to the treatment of fractures [9]. However, for this to occur, widely accepted guidelines are important to encourage the conduct of studies to evaluate bioactive substances, drugs, and new agents that may promote fracture union and subsequent return to normal function.

Given the growing amount of expertise in the area of fracture healing, a consensus process was initiated among experts in the areas of fracture healing, bone biology, and clinical trial design. During the first meeting, appropriate endpoints were defined for studies of medicinal products for improving fracture union (and subsequent return to normal function) in patients with osteoporosis [10]. A second meeting convened to provide further recommendations for the clinical evaluation of potential therapies to augment fracture repair in patients with meta- and diaphyseal fractures. The following recommendations do not cover delayed and/or non-union fracture repair but only pertain to acute fractures and do not cover devices as current guidelines exist.

Aim of treatment

The goals of fracture treatment are twofold: to restore the biomechanical properties of the fractured bone and to facilitate the return to normal physiological function of the affected limb or region. Based on the characteristics of fracture healing and fixation, the following study objectives of a clinical study may be appropriate:

a) Acceleration of fracture union.
b) Acceleration of return to normal function.
c) Reduction of fracture healing complications.

The intended goal(s) should determine subsequent study methodology. While an acceleration of return to normal function or a reduction of fracture healing complications in and of themselves may be sufficient primary study endpoints for a phase 3 pivotal study, acceleration of fracture union alone is not. A clinical important difference in the time of fracture healing should be accompanied by faster return of function and/or more reliable healing, which corresponds to less healing complications.

Pre-clinical evaluations

In accordance with International Conference on Harmonization guidance, the purpose of the non-clinical safety evaluation includes characterization of the toxic effects with respect to the target organs, dose dependence, relationship to exposure, and potential reversibility. It should be emphasized that the non-clinical safety studies should be adequate to characterize potential toxic effects under the conditions of the supported clinical trial (ICH M3(R2) [11].

Valid techniques for non-invasive, *in vivo* assessment of bone architecture and bone strength in humans are currently not available. Hence, for medicinal products intended to enhance fracture healing, documentation of drug-induced effects on these variables in animals displays an important component of the assessment. However, equally critical is the choice of an appropriate model in which to study the fracture healing under osteoporotic circumstances [12]. Whereas each animal model is best suited to answer a particular question no direct extrapolations can be made to human size, weight, or doses according to an extensive review by O´Loughlin et al. [13]. Therefore, in addition to incorporating generally accepted scientific principles, the following specific study design issues should also be taken into consideration:

- Skeletally mature animals should be studied.
- The model should be representative of the proposed indications for use, including the range of anatomical sites proposed for use.
- Radiography, including quantitative computed tomography (QCT), histology, and histomorphometry, could be used to assess the fracture site at various relevant time points over the course of healing.
- Biomechanical testing of the healed fracture should be performed and compared to that of normal bone.
- The studies should be of adequate study duration to demonstrate bone healing and long-term effects on bone remodelling.

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Clinical trials

General considerations

Fracture healing is a complex process that is greatly affected by biological and mechanical conditions. Both diaphyseal and metaphyseal fracture healing can show substantial biomechanical, histologic and radiographic differences between individual patients that pose a challenge to the clinical investigator [14]. Therefore clinical studies should be designed to be sufficiently detailed and robust to clearly demonstrate the effect of the medicinal product.

Population to be studied

Inclusion criteria

The intended patient population depends on the study objectives. The most important inclusion criterion is fracture type, the target of the medicinal product. The following specifications must be provided: fracture classification, open or closed, accompanying soft tissue damage, concurrent fractures or injuries, and method of fixation. In principle, preferably, subjects with isolated fractures due to a monotrauma should be chosen for inclusion to avoid interaction with other fractures or injuries. It is understood that concurrent fractures that do not affect the assessment of functional outcomes may also be accepted, as would additional minor injuries not affecting fracture union or return to normal function.

Aside from fracture type, inclusion criteria should also be specified with respect to co-morbidities or age groups such as patients with osteoporosis. Both genders should be studied, and as menopausal status may affect fracture healing, both pre- and post-menopausal women should be included.

Exclusion criteria

Patients unable to sign an IRB/IEC-approved informed consent, and/or are incapable of completing a clinical trial should not be enrolled. Patients unable to participate in regular rehabilitation, and/or have planned surgical procedures prior to random treatment allocation that could potentially affect study endpoint(s), should be also excluded.

Confounding variables

A number of variables are known to influence fracture healing. These variables must be recorded to assess baseline characteristics and to provide possible explanations for unexpected treatment effects by randomization. Specifically, the following details should be noted: specific fracture and injury characteristics method of fracture fixation; detailed soft tissue conditions; patient characteristics (e.g. age, sex, smoking status, co-morbidities, surgical intervention, pain treatment, including NSAID use, rehabilitation, and concomitant medications, including use of other bone active drugs), and the responsible surgeon's experience. Patients who have a fracture should be evaluated for osteoporosis if their status is unknown. Management of the patient should include both the immediate treatment of the fracture and a long-term approach to reducing their risk for future fracture. Studies of fracture healing should incorporate both of these clinical principles. Because potential treatments for fracture healing could include a one-time administration, could enhance fracture healing and treat osteoporosis at the same time, or could potentially interact with osteoporosis treatments the impact on study design and entry criteria will depend on the specifics of the agents to be tested and the fracture studied.

Criteria of efficacy and their assessment

Acceleration of fracture union

To assess time to fracture union, repeated radiographic evaluations are necessary, particularly around the expected mean time to union. This assessment is remarkably complex, since validated methods for quantitatively monitoring fracture union are not fully established. Staging of fracture healing and subsequent function at defined points of healing, combined with precise definitions of expected complications (e.g. loss of fracture reduction, revision of fracture fixation construct, bone grafting), is necessary to assess a reduction in complication rate. Radiographic evaluation of fracture union incorporates several parameters, including assessment of the disappearance of fracture lines, the presence of cortical bridging, and assessment of the diameter and shape of the callus [15]. Radiographic scoring of fracture union has largely relied on investigator assessment, and currently there are no *in vivo* techniques for quantifying union in mechanical terms for fractures involving mainly trabecular bone. Further validation of radiographic scoring should be undertaken and semi-automated methods are required. Radiographic evaluation may either occur at multiple time points during the healing process with the aim of measuring the time taken to reach a defined status (e.g. cortical bridging of three cortices or disappearance of fracture lines), or could be obtained at a single pre-determined timepoint, were patients are expected to reach a common clinical milestone (i.e. pain free full weight-bearing in weight-bearing fracture cases). Blinded rating of fracture repair at this time point may have a higher statistical power, and is equally relevant as time to full radiographic repair with complete disappearance of fracture lines, which often occurs a long time after clinical fracture healing. Imaging techniques such as computed tomography (CT) may enhance the ability to assess fracture union. Roentgen stereometric analysis (RSA) was introduced to measure increase in stiffness during fracture healing and has the potential to monitor fracture displacement *in vivo*, if loss of fracture reduction is an endpoint [16]. However, RSA is not yet feasible for use in large clinical trials. Time to fracture union should be calculated from the time of injury rather than the commencement of fracture repair therapy. If time to fracture union and/or an analysis of outcomes at a pre-defined time point is a pivotal phase 3 study variable, then an independent review committee, masked to therapy assignment, is required.

Acceleration of return to normal function

Parallel to objective outcome parameters, validated instruments intended to demonstrate return to normal function should also be incorporated in clinical studies of fracture healing [17]. These could potentially include patient-reported outcomes and functional tests. Functional improvement does not necessarily follow the same time course as fracture union but shows recovery as a consequence of fracture union. Patient-reported functional outcome and quality of life help to quantify relevant therapeutic effects for individuals, as well as for groups of patients. It also corresponds to the holistic International Classification of Functioning, Disability and Health (ICF) approach of the World Health Organization (WHO), looking at different levels of impact the healing process has on patients (e.g. in distal radius fractures). Based on the assumption that return of function parallels fracture union to a certain extent, self-assessment should be utilized by patients for repeated measures without (radiological) adverse effects. Important functional endpoints also include time to full weight-bearing, pain during weight-bearing (in case of fractures in weight-bearing bones), and time to return to work. Clear rules regarding validity and reliability exist that should help with selection of the most appropriate patient self-assessment score. Only validated functional instruments pertaining to the affected limb should be used. The EMEA provided guidance on Patient Reported Outcomes in July 2005 [18], and the FDA did the same in February 2006 [19]. These Guidances indicate that efficacy and health-related quality of life (HRQoL) can be co-primary endpoints. Whereas site specific tests are most responsive to the testing intervention, generic instruments may add information about the consequences for activities of daily life and

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health-related quality of life and help to compare different indications and patient groups as shown for the shoulder [20]. Alternatively, the hierarchical testing of endpoints may be applied.

Therefore, for clinical evaluation of treatments for fracture healing, functional outcomes, and complication rates should be supplemented by radiographic scoring of the fracture union process.

Reduction of fracture healing complications

If reduction of complication rate (e.g. non-union) is the primary objective, the anticipated complications must be defined in the study protocol, along with their possible associations with the specified fracture type and fixation device. Obviously, only complications associated with a certain fracture type and/or treatment modality can be addressed with a new pharmaceutical intervention. A typical example is the reduction of the frequency of secondary interventions and the overall invasiveness of these procedures, when rhBMP-2 is used in open tibial fractures requiring additional intervention [21]. Other complications that can be used as study endpoints, especially in patients with osteoporosis, include implant cut-out/cut-through in metaphyseal bone, delayed healing, or secondary fracture dislocation. Clear definitions of the anticipated complications will minimize bias in the assessment of this outcome. A central evaluation of the fracture healing complications by an independent committee at study completion is recommended.

Criteria of safety and their assessment

Adverse event (AE) assessments should be comprehensive and compliant with Good Clinical Practice (GCP) guidelines. AEs must be separated into device (implant)- and drug-related events. Whereas device-related AEs correspond to an orthopedic complication and might be an outcome variable of the trial (see former paragraph), drug-related events must also be addressed according to ICH guidelines of drug development.

Human pharmacology

Studies involving the first administration of fracture repair agents may not differ from the first administration of medicinal products in general. A distinction should be made between systemically administered and locally administered fracture repair agents. The applicant should provide data to support that the obtained pharmacology results could be extrapolated from effects on the target bone to the rest of the skeleton or to lack of effect on the skeleton in the case of a locally administered fracture repair agent. If the fracture repair agent is to be administered locally at the fracture site, dose escalating phase 1 studies should be performed in male subjects who have sustained an isolated fracture at a location of the intended indication, rather than arbitrarily in healthy volunteers.

Extensive pre-clinical pharmacology studies, including both *in vitro* and with various animal species, such as non-human primates, are required prior to first human dose. With regard to a locally administered fracture repair agent, the effects of the proposed carrier on the human pharmacology should be clearly understood. The initial studies should therefore determine the general safety of the compound and should concurrently provide an indication of potential clinically relevant doses.

The pharmacokinetic information required for a clinical trial is stated in detail in the CHMP guideline on the "Pharmacokinetic Studies in Man" [22]. However, pharmacokinetic information should also be obtained in subjects who have sustained a fracture, as the associated trauma may alter the agent's pharmacokinetics. Antibody formation may need to be assessed depending on the nature of the fracture repair agent. For locally administered agents, release kinetics may need to be assessed. Depending on the distribution and clearance of the agent, clinical studies may also need to be conducted with elderly fracture patients (age 65 and older) and the very elderly fracture patients (age 75 and older), as well as in patients with varying degrees of renal and hepatic dysfunction. With an older target population, the guidelines on the investigation of drug interactions (CPMP/EWP/560/95) should be observed closely [22].

General considerations for dose–response studies

Studies should be designed to allow robust evaluation of dose–response. The type of fracture studied should be representative of the indication that is ultimately sought; (i.e. diaphyseal or metaphyseal fractures), and should clearly define whether conservative or surgical fracture fixation is acceptable within the given protocol. The study duration should extend well beyond the average time to fracture healing, so as to allow for safety assessments of the drug under study and potential healing complications. The duration of subject participation should be clearly justified within the study protocol and the primary analyses associated with this endpoint. Depending on the nature of the fracture repair agent, dose–response studies may be parallel or serial in design. Evaluation of at least three dosages is recommended. If conclusive data are not obtained, at least two doses should be studied in Phase 3 studies to determine levels of efficacy.

Clinical trials of this nature should preferably be double-blind and placebo-controlled in design, and all fracture subjects should receive a standardized method of fracture fixation defined within the protocol as Standard of Care (SOC). Placebo control may be less feasible for locally administered fracture repair agents, as buffer alone or a buffer/carrier combination may have different safety profiles, including different resorption profiles, from the fracture repair agent or fracture repair agent/carrier combination. For locally administered fracture repair agents, the study should contain an SOC-only arm to allow for the assessment of the effect of the carrier alone in the placebo-controlled arm of the study and thus to facilitate safety, efficacy, and feasibility comparisons of the test article administration procedure. The primary analysis should include fracture union. Return to normal function, whether by means of patient-reported outcomes or by functional tests, will still need to be examined at this stage of development, irrespective of whether the fracture in the limb under study is weight-bearing or not. A functional endpoint such as absence of pain at the fracture site during ambulation without a weight-bearing assistive device (pain free full weight-bearing) may be included. The clinical investigator can conduct the weight-bearing assessments. However, for studies containing an SOC-only arm, a qualified assessor, masked to therapy randomization, should be assigned to minimize bias.

Conversely, for systemically administered fracture repair agents, it is recommended to use variables such as bone mineral density (BMD) measured at the spine and/or the hip, along with appropriate biochemical markers of bone turnover, so as to monitor possible systemic effects on the skeleton. Overall, dose–response studies should be of sufficient size to allow for appropriate assessment of the safety of the fracture repair agent, as well as the feasibility of administration, particularly in case locally administered agents.

General considerations for main therapeutic studies

One difficulty encountered recruiting trauma patients into clinical trials is the environment in which they are treated. In the emergency room, acute patient care has priority over clinical research, and thus, clinical investigators must first appropriately prioritize subject well-being before presenting them with an opportunity to take part in research activities. On the patient level, given the significant changes on the prospects of life that may often follow a traumatic experience, research participation may fall short of consideration. Additionally, many of these patients suffer from impaired awareness either due to

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the trauma itself or as a result of narcotic or alcohol abuse. Obtaining informed consent for research activities is crucial, but may be difficult to obtain under the aforementioned circumstances. As a consequence, sponsors may be confronted with low enrolment rates per site. Due to the inherent recruitment difficulties, phase 2 studies might be expanded into phase 3 studies, upon meeting pre-defined interim analysis criteria. However, any suggested changes to the protocol analysis should be pre-specified and justified. In case of extension of a phase 2 study into phase 3, the primary endpoint(s) of the study must not change or otherwise a new phase 3 study should commence. Similar to the dose–response studies, the type of fracture and its method of fixation studied identified for the main therapeutic studies should be representative of the indication that is being sought. The method of fracture fixation and fracture reduction should be standardized. In case of locally administered fracture repair agents, the integration of the investigational treatment into standard surgical care should be thoroughly described.

In the case that the dose-finding studies are inconclusive, at least two doses should be examined in phase 3 clinical trials. The trials should be designed to allow robust evaluation of efficacy and safety. Time to fracture union and time to return to normal function of the limb under study should be co-primary endpoints of the phase 3 protocol. Treatment initiation in subjects with acute fractures can be as early as the time of fracture fixation or within a pre-defined time window thereafter.

As the treatment duration required for evaluating significant effects may vary depending on the fracture repair agent, the study duration and subject surveillance should be clearly justified in the protocol, along with the primary analysis to be performed at this endpoint. As the normal remodeling phase of fracture healing is at least a year, subjects should be followed for a minimum of 12 months.

The study design should be randomized, parallel, double-blind, and placebo-controlled, and all fracture subjects should receive a standardized method of fracture fixation, defined as Standard of Care (SOC). Placebo control will also be required for locally administered fracture repair agents, as buffer alone or a buffer/carrier combination may have a different safety profile, including a different resorption profile, from the fracture repair agent or fracture repair agent/carrier combination. For locally administered fracture repair agents, the study should also contain an SOC-only control arm, so as to be able to assess the effect of the carrier alone in the placebo-controlled arm of the study, as well as to be able to compare safety and feasibility of the administration procedure.

The primary analysis should include the co-primary endpoints of fracture union, defined as bridging callus or disappearance of the fracture line on three out of four cortices, plus return to normal function of the affected limb, defined as absence of pain at the fracture site during ambulation without weight-bearing assistive device (pain free full weight-bearing in case of lower extremity fractures). Validated Patient Reported Outcomes (PRO's) measures will need to support the return to normal function co-primary endpoints. In order to minimize the potential for bias, an independent central evaluations committee should assess fracture union. This evaluation committee must be masked to therapy assignment and should be comprised of board-certified radiologists or orthopedists with experience in evaluating fracture radiographs [23].

The study investigator can assess pain (during weight-bearing), but in order to minimize the potential for bias, he/she could assign a qualified assessor, masked to therapy assignment for studies containing an SOC-only arm. The subject will report on PROs that support the return to normal function endpoint. For systemically administered fracture repair agents, it is recommended to use variables including BMD measured at the spine and/or the hip and appropriate biochemical markers of bone turnover. Feasibility of the procedure to administer the locally administered fracture repair agent should be assessed and confirmed.

In addition to safety monitoring by the sponsor, an independent data monitoring committee (DMC), unblinded to therapy assignment, will oversee subject safety. The DMC may recommend changes in the study design pertaining to sample-size, based on observed efficacy, as well as a discontinuation of study arms, based on safety or futility.

Conclusion

There is need for new pharmacologic therapies that accelerate fracture healing in patients with osteoporosis. Trials of potential new therapies should be designed to provide clear information on the effect of treatment with relationship to fracture union, complications, and patients' return to normal function. The development of widely accepted guidelines is important to ensure that the conduct of studies consistently meets these objectives.

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