Patient-Centred Research and Regulatory Decision Making in Rare Diseases

A Case Study in Acromegaly

David Schwicker, November 2016

Patient-Centered Evidence in Rare Diseases

- EMA COMP * defines a significant benefit of a product for orphan designation in three equal categories
  - an assumption of improved efficacy
  - an assumption of improved safety
  - an assumption of a major contribution to patient care, defined as:
    - ✓ more convenient modes of administration and/or
    - ✓ improving patient compliance and/or
    - ✓ improved availability of the product and/or
    - ✓ improved quality of life of the patients
  - Expected that most of the data to demonstrate significant benefit will be generated during the clinical development and available prior to market authorization
- Patient-relevant outcomes measures (PROMs) and HRQoL are, therefore, an integral and crucial component of the development and appraisal of medicines in rare diseases

* Committee for Orphan Medicinal Products (COMP), Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation, EMA, 2012

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Background – Acromegaly

- A rare debilitating endocrine disease characterised by hypersecretion of growth hormone as a result of a benign pituitary adenoma
- Associated with increased morbidity and mortality, due to cardio-, cerebrovascular and respiratory diseases and decreased quality of life
- Parenteral somatostatin analogues/receptor ligands (SRLs) are used as first-line medical treatment for patients with inadequate response to surgery or radiotherapy, or when these treatments are not indicated
- SRLs are depot formulations administered as monthly intramuscular or deep subcutaneous injection, treatment is lifelong
- The sponsor's proprietary technology enables an oral formulation of a somatostatin analogue, which is being developed with the expectation of equal efficacy and safety as compared to the current gold standard parenteral treatment

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COMPs Initial Appraisal

- While orphan designation was granted by the FDA, EMA's COMP was initially not convinced that the oral formulation provided a possible significant benefit based on a major contribution to patient care
- COMP invited the sponsor to provide further real-world evidence:
  - "without documenting the currently hypothetical problems with the current formulation, significant benefit is difficult to consider."
- Literature on PROs and HRQoL in acromegaly was scarce, there was no study or instrument available addressing the specific impact of chronic parenteral injections
- Information on the patient-relevant issues with the injections was only available from anecdotal sources, mainly patient interviews
- The timeline was crucial → 9 months till the next COMP meeting
- The sponsor approached Phase IV with the challenge to provide comprehensive and systematic patient-reported evidence on SRL injections in time for the COMP meeting

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Rapid Response To COMP

- A observational real-world survey in 195 patients with acromegaly treated with parenteral SRLs used a specifically developed non-validated questionnaire, and received approval by Ethics Committees in 9 acromegaly centres in Germany, UK and The Netherlands
- The survey documented that injections of SRLs have significant burden on the functioning, well-being and daily lives of acromegaly patients and that alternatives to injections represent an unmet medical need
- A further key finding was that variation of symptom control throughout the monthly parenteral treatment interval ("breakthrough symptoms") is not a negligible issue that had not yet been addressed in studies
- A white paper format interim analysis based on the first 65 patients was completed in time for the COMP meeting and contributed to achieving EMA orphan drug designation for the product
- The final study report with 195 patients was re-submitted to COMP as further evidence and included in the US NDA

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Long Term Patient-Centered Research

- Extensive additional post-hoc exploratory and statistical analyses were conducted with the unique pseudonymised survey data and published in a leading endocrinology journal:
  - Strasburger CJ et al., Patient-reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly, Eur J Endocrinol March 1, 2016 http://www.eje-online.org/content/174/3/355
- While the initial survey had to rely on a non-validated tool due to the timeline constraints, the learning was that further investment in the development of a validated PRO was justified
- A study including 79 patients at 15 US and European sites to develop and validate the parenteral injection-specific Acromegaly Treatment Satisfaction Questionnaire (Acro-TSQ) was recently completed
  - Disclaimer: Phase IV supported the study but did not lead the PRO validation
- The validated Acro-TSQ is currently being used in the Phase III development of the sponsor's oral technology

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Takeaway Points

1. The rising influence of patients and patient organisations in the European regulatory bodies will lead to an emphasis on accelerated access to transformative medicines and the inclusion of patient views in benefit-risk and value judgements
2. Patient-relevant outcomes, unmet medical need and significant contributions to patient care will increasingly guide development decisions
3. Patient-centred research is a crucial element of product development and should be fully integrated early in the process (Phase II)
   - Validated generic and disease-specific PROMs and HRQoL tools
   - Further methods to elicit and measure patient-centred preference and benefit-risk assessment (e.g. CA, DCE, MDCE)
4. The increasing opportunities for early scientific advice in Europe (EMA/HTA) should be explored and include patient representatives

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Phase IV Programs – www.p4pro.eu

- Specialized independent HTA consultancy focused on real-world and patient-centered research in rare diseases and orphan products
- Founded in 1998 (Start-up company of the year 2000)
- Headquartered in Basel, Switzerland
- EU Office based in Austria (near Munich, Germany)
- Pan-European Registries and programs including over 10’000 sites / physicians and more than 200´000 patients
- Knowledge and experience in many therapeutic areas
- Broad coverage of outcomes, including clinical, economic, HRQoL and PROMs
- Proven scientific track record and peer-reviewed publications
- Longstanding established network of professionals and strategic collaborations across the major markets

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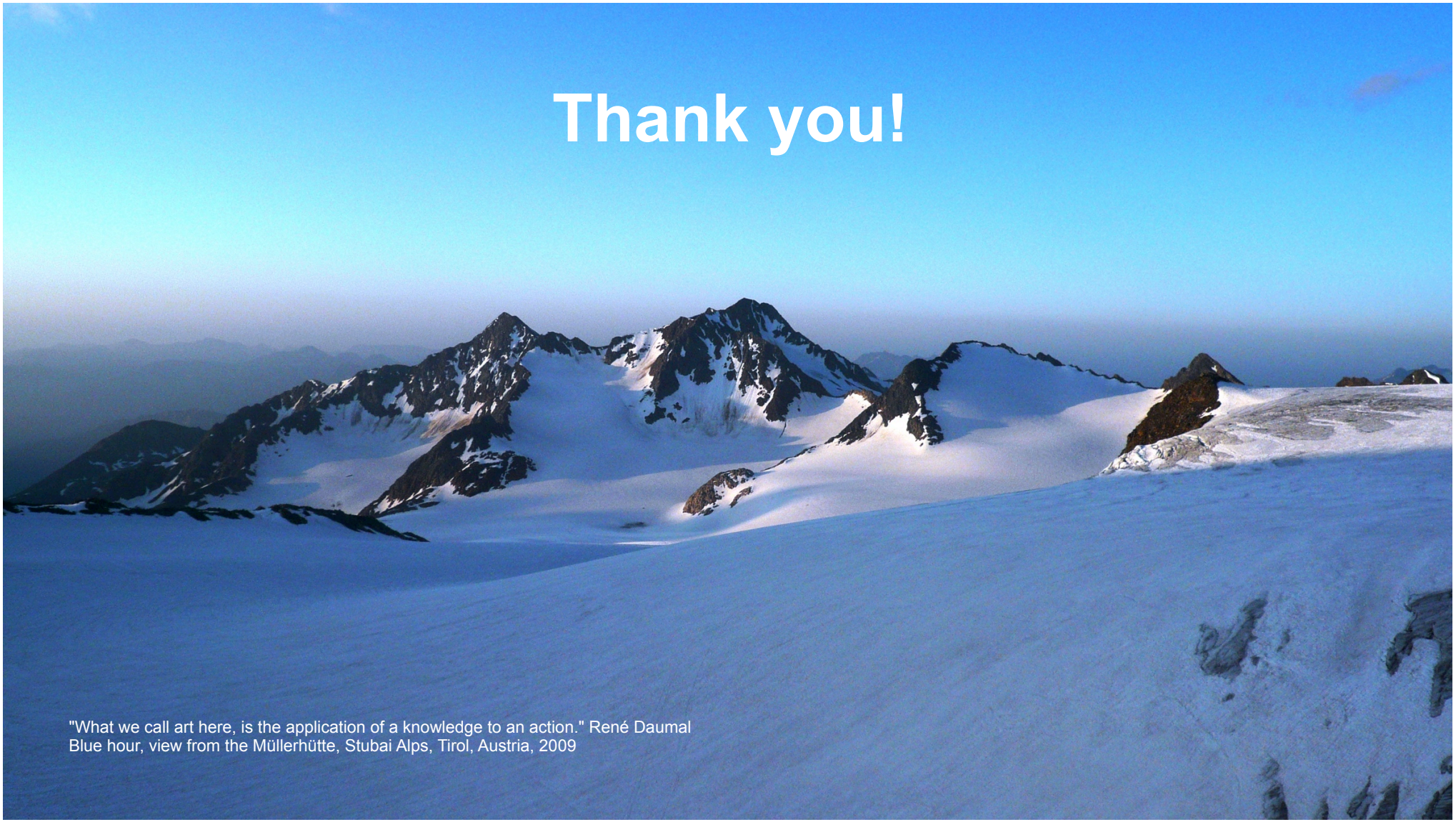
Thank you!



"What we call art here, is the application of a knowledge to an action." René Daumal
Blue hour, view from the Müllerhütte, Stubai Alps, Tirol, Austria, 2009

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