TiGenix

Living Medicines

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CAT-ESCGT ATMP Workshop

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ChondroCelect case study

- **TiGenix**
- ChondroCelect development and registration
- SANCO
- Key learnings

TiGenix : A newly created European Cell Therapy leader

- TiGenix and Cellerix joining forces early 2011
- Initial focus on damaged and arthritic joints; expansion potential into other autoimmune and inflammatory diseases
- Proven ability to develop, register, manufacture and market cell products.
- Two commercial products on the market in Europe:

  CHONDROCELECT (CC) autologous cell-based product for cartilage repair

  ChondroMimetic™ (CM) resorbable implant for small (osteo)chondral defects
- Strong development pipeline: programs in Phase III, Phase Ib/IIa and Phase I
- Proprietary validated stem cell platform

- TiGenix
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CHONDROCELECT

- **Characterized autologous** cartilage cells **expanded** *ex vivo* and expressing specific marker proteins
- **Medicinal product**
- Indication: **Repair** of single symptomatic **cartilage defects** of the femoral condyle of the knee (ICRS III or IV) in adults

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ChondroCelect development challenges

- CMC requirements
  - Consistent manufacturing - complex and autologous composition
  - Stringent product release criteria – relevant tests
- Non-clinical data
  - Animal model - rejection of the xenograft, different biology of the cells and the joint
  - Long term efficacy – problems in rehabilitation
- Clinical design
  - Randomized controlled trial
  - Relevant clinical read-outs
  - Duration of the trial
  - Safety of the product vs the procedure

Supportive evidence – Quality

- **Comprehensive cell characterization**
  - Histological assessment (stable in vivo tissue formation) at the tissue level
  - 3-dimensional culture assays (proteins and proteoglycans associated with cartilage matrix formation) at the cellular level
  - Marker analysis (marker genes important for the cartilage biology) at the molecular level

  ➔ Different assays, each measuring a different aspect of the chondrocytes and cartilage biology, all showing a strong inter-relationship

- **Relevant biological characteristics were translated into established product quality attributes**

Supportive evidence – Non-clinical

- **Relevant animal models established**
- **Mouse model: Ectopic cartilage formation assay (ECFA)**
  - Measuring biologically relevant activity, i.e. In vivo tissue formation capacity
  - Allows to discriminate cell populations that can form stable cartilage from cell populations that can't (dedifferentiated chondrocytes).
  - Outcome can be used to validate other bio-marker assays for use in process validation and comparability.

COMPARISON OF CELL POPULATIONS THAT PASS AND FAIL ECTOPIC CARTILAGE FORMATION ASSAY

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Supportive evidence – Clinical

- **Pivotal study TIGACT01**
  - Phase III RCT
  - ChondroCelect versus Microfracture (standard of care)
  - 51 CC patients – 61 MF patients
- **Multiple primary endpoints**
  - Structural superiority at 12 months
  - Clinical non-inferiority at 12-18 months
- **Secondary endpoints**
  - Clinical benefit in the long term at 36 months
  - Longitudinal analysis at 60 months and subgroups

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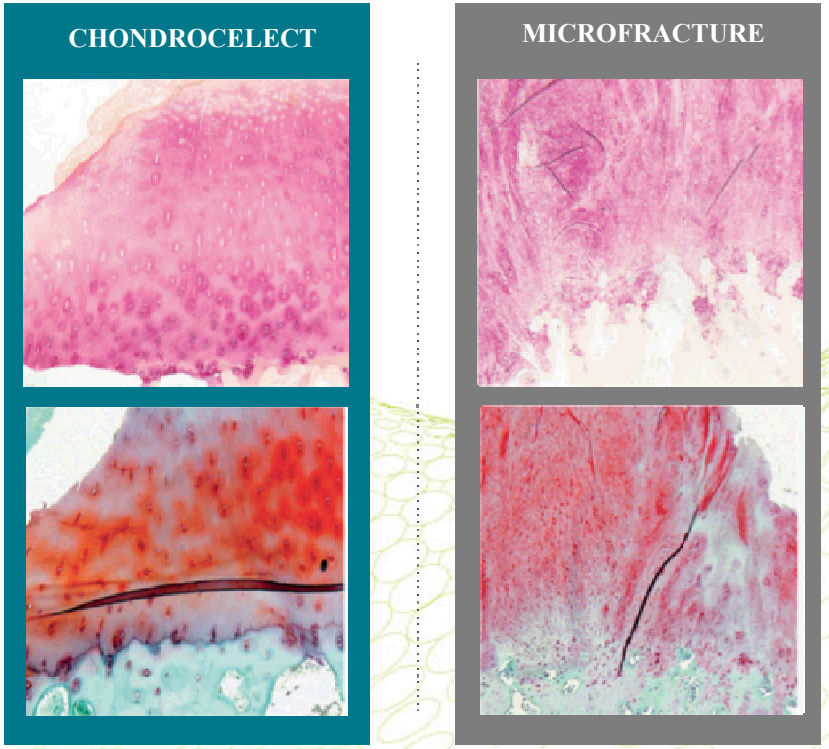
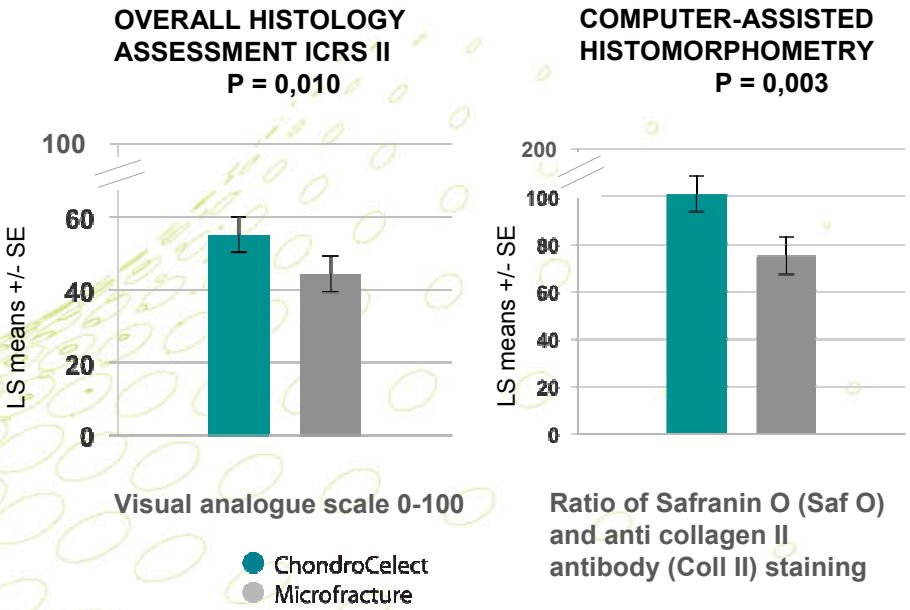
TIGACT01 - Superior structural repair at 12 months



Clear morphological superiority of tissue regeneration after ChondroCelect® implantation
(Examples of best histologies for both groups)



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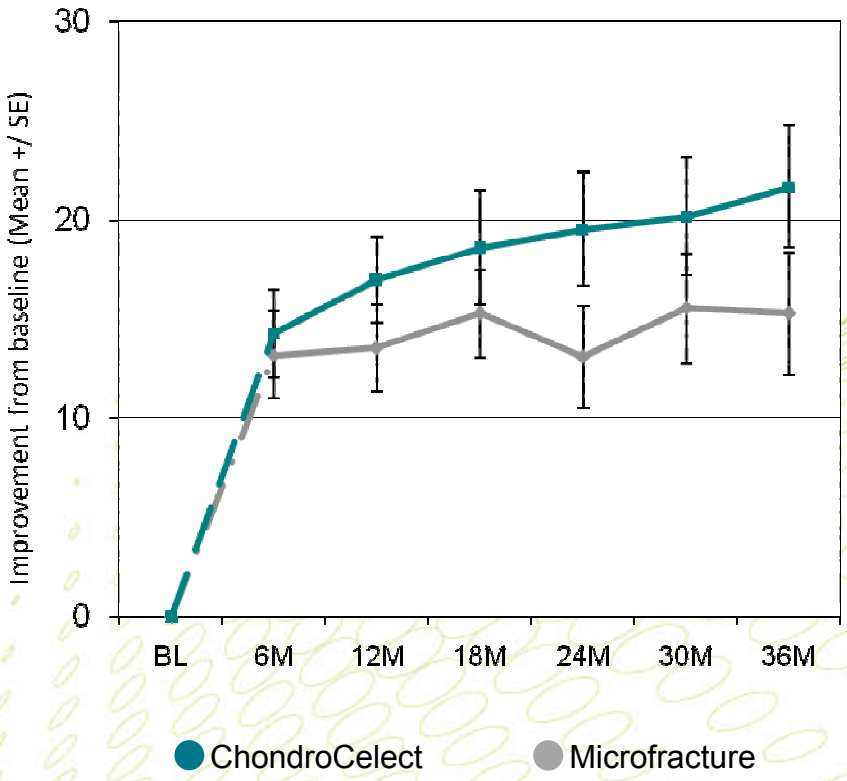
TIGACT01 - Clinical benefit over microfracture at 36 months

OVERALL KOOS - FAS[1,2]



LONGITUDINAL ANALYSIS TREATMENT EFFECT AT 36M

Mixed linear model (heterogenous compound symmetry with time as categorical variable)

KOOS	P-value[3]
Overall[1]	0.048
Pain	0.044
Symptoms	0.123
Activity (ADL)	0.064
Sports	0.123
Quality of Life	0.036

Treatment failures (reinterventions)

CC: 2 **MF: 7**

[1]Knee injury and Osteoarthritis Outcome Score - Average of all KOOS domains, except Sports
[2]Full Analysis Set excluding treatment failures and without imputation for missing data
[3]Mixed Linear Model with time as a categorical variable. Other analyses were not always statistically significant.

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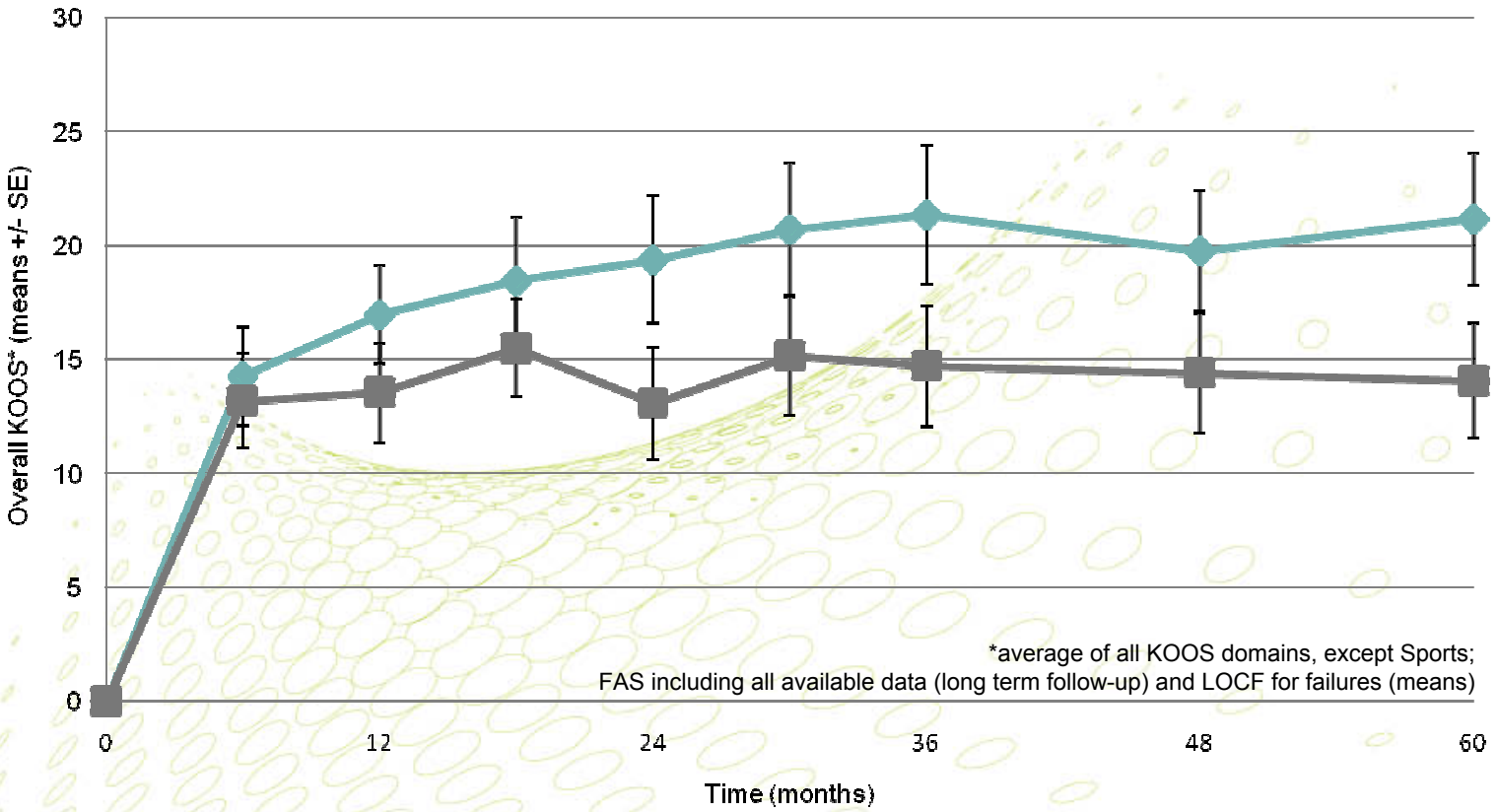
TIGACT01 - Durability of treatment effect over 60 months



N CC	51	51	51	44	45	43	42	45	43
N MF	61	59	57	51	52	51	51	49	55

Treatment failures (reinterventions)

CC: 7 **MF: 10**

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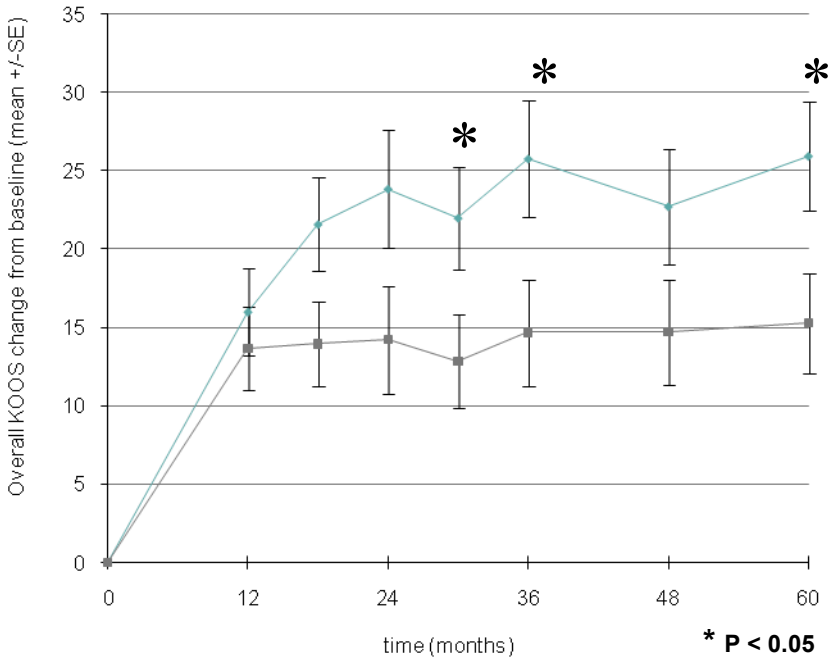
TIGACT01 - Early ChondroCelect treatment

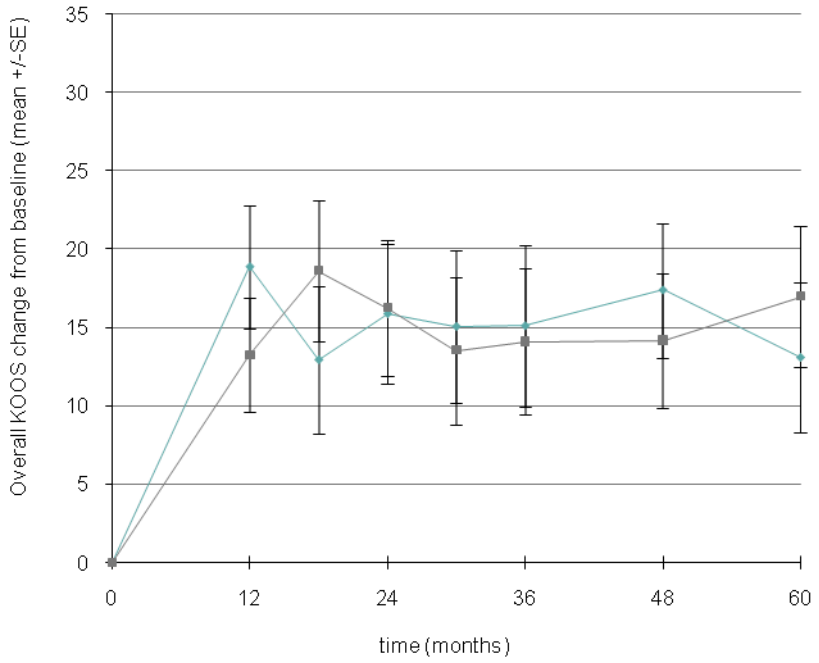
Overall KOOS
< 3 yrs since onset of symptoms

AUC 24-60M p 0.04



N CC	34	34	28	26	28	27	25	27
N MF	39	37	34	32	34	32	30	32

Overall KOOS
≥ 3 yrs since onset of symptoms



N CC	17	17	16	17	17	14	17	16
N MF	22	20	17	18	18	17	17	18

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Saris & Vanlauwe et al. AJSM 2009,;Vanlauwe and Saris, AJSM 2011

Safety profile: adverse events (AEs)

Very common AEs (≥1/10 of patients)[1]	ChondroCelect®	Microfracture
	60M (N=51)	60M (N=61)
Patients with at least one related AE (%)	82%	62%
Arthralgia	49%	41%
Joint swelling	14%	5%
Cartilage hypertrophy[2]	27%	11%
Joint crepitations	20%	3.3%
Joint effusion	12%	5%

(1) Most AEs were expected as related to the open-knee surgical procedure

(2) Compassionate Use Program (n=370): use of **a collagen membrane** instead of a periosteal flap. Incidence of cartilage hypertrophy can be reduced by using a collagen membrane to cover the lesion site instead of using a periosteal flap (Gooding et al., 2006; Niemeyer et al., 2008). **Cartilage hypertrophy was reported to be 1.8%**

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ChondroCelect : First approved ATMP in Europe

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 5.10.2009
C(2009)7726

COMMISSION DECISION

of 5.10.2009

granting marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "ChondroCelect - Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins", a medicinal product for human use

European Medicines Agency
Press office

London, 26 June 2009
Doc. Ref. EMEA/CHMP/394741/2009

PRESS RELEASE
European Medicines Agency recommends first marketing authorisation for an advanced therapy medicinal product

The European Medicines Agency has recommended the first marketing authorisation for an advanced therapy medicinal product, following a positive opinion from the Agency's Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP).

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Post-marketing phase

- Post-marketing activities
  - Regulatory requirements / expectations
  - Product related aspects
- Regulatory aspects
  - Post-marketing commitments and follow up measures
  - Risk management plan
  - Specific requirements for ATMP RMP
- Generate data on larger patient populations
  - ‘Real life’ setting
  - Further document efficacy and safety
  - Safety signal analysis

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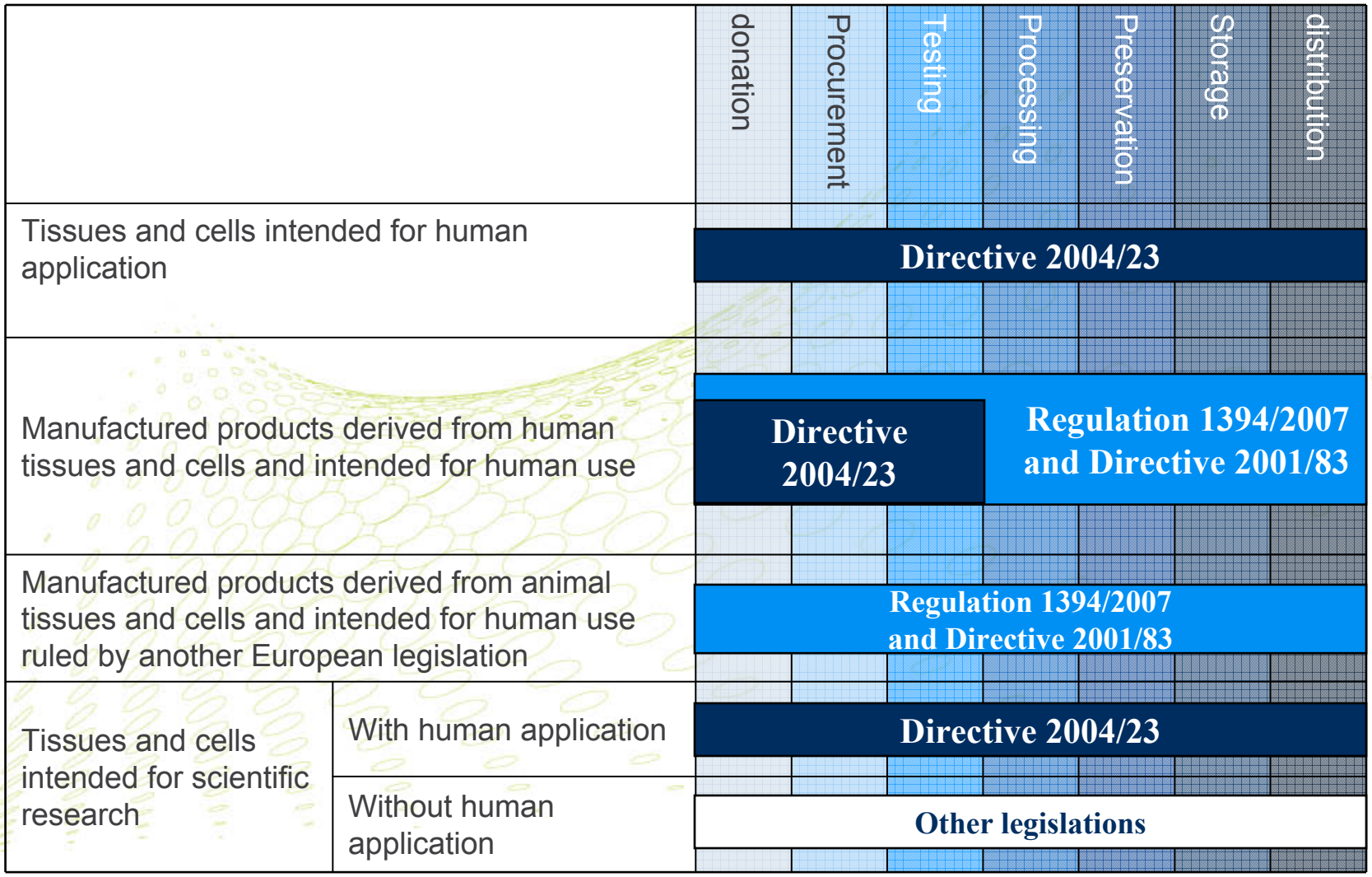
- **SANCO**
- Key learnings

SANCO vs ATMP



Source: Marc Martens, Bird&Bird

SANCO regulatory framework

- SANCO Directives compliance

- Three Sanco Cell and Tissue Directives
  - 2004/23/EC : setting **standards of quality and safety** for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
  - 2006/17/EC : certain **technical requirements** for the donation, procurement and testing of human tissues and cells
  - 2006/86/EC : **traceability requirements, notification of serious adverse reactions and events and certain technical requirements** for the coding, processing, preservation, storage and distribution of human tissues and cells

- Transposed in “27” national legislations

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SANCO regulatory framework (2)

- For ATMP, the Sanco criteria on “Donation, procurement and testing” apply

- Major requirements:
  - Informed consent
  - Documented quality systems for procurement
  - Qualified personnel
  - Traceability
  - Donor selection and testing for infectious agents
  - Responsibilities and third party contracts

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SANCO regulatory framework (3)

- Operational Sanco models
  - Germany: P and T license, full license; 16 Länder
  - The Netherlands: no P licences; Weefselinstellingen en Orgaanbank
  - UK: licenses for individual activities possible
  - Belgium:
    - P license for Productie-instelling (autologous)
    - Intermediaire structuren for allogenic ATMP
  - Spain: P and T license, full license
  - …..

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- **Key learnings**

Key learnings

- The product
  - Autologous sourcing – variability
- Product (quality) safety
  - Antibiotic free process – aseptic processing, GMP
  - FBS
- Product characteristics
  - Complex and living – wide variety of functional tests
  - Dialogue with the Regulators

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Key learnings (2)

- Manufacturing process
  - Process validation – robustness and consistency
  - Product comparability – comprehensive analysis of process and product parameters
  - GMP as driver
- Non-Clinical
  - Proof of concept (relevance of the orthotopic model)
  - Relevant safety aspects (less about tox, more about biodistribution and persistence of the cells)

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Key learnings (3)

- Clinical
  - Structural endpoint – surrogate marker?
  - Clinical relevance and benefit to the patient
  - Standardization (cfr procedures)
  - Durability of the treatment effect (ATMP)
  - Thorough understanding of the safety profile
- Regulatory
  - “It is in fact relatively simple” : Q S E
  - Know your product, don’t assume
  - Understand the rationale of the regulatory requirements
  - Dialogue
  - Risk- benefit assessment
  - Post-marketing commitments

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Putting it into a perspective

R&D Clinical (I-III) File PoMar

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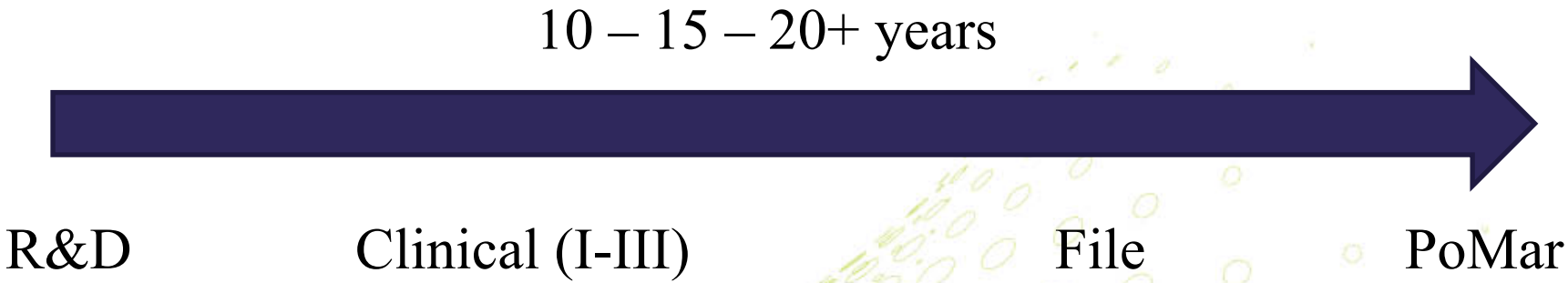
Putting it into a perspective (2)



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Putting it into a perspective (3)

Proof of Concept
Relevant safety

Severity of the disease
Treatment options

FTI Humans

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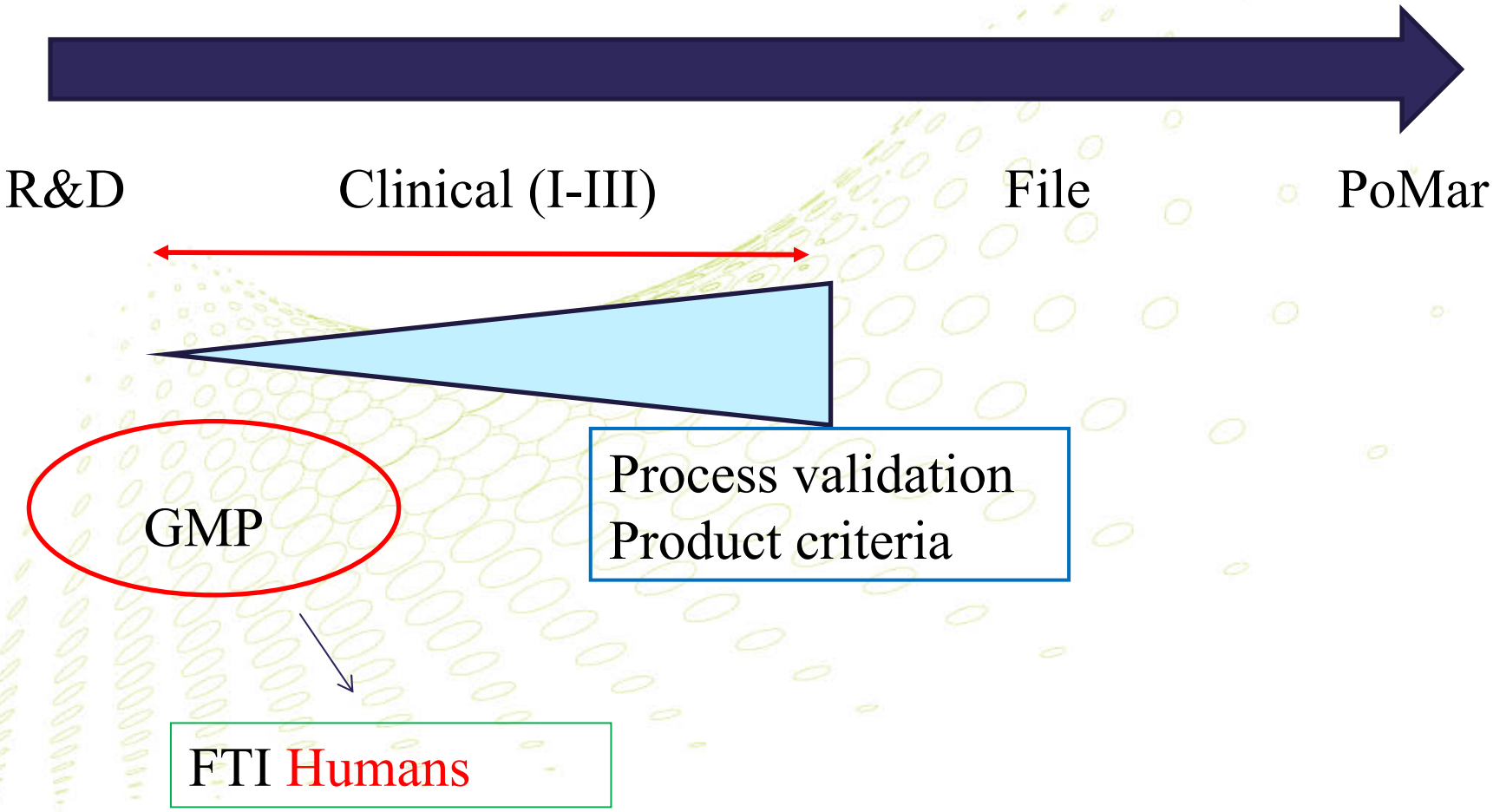
Putting it into a perspective (4)



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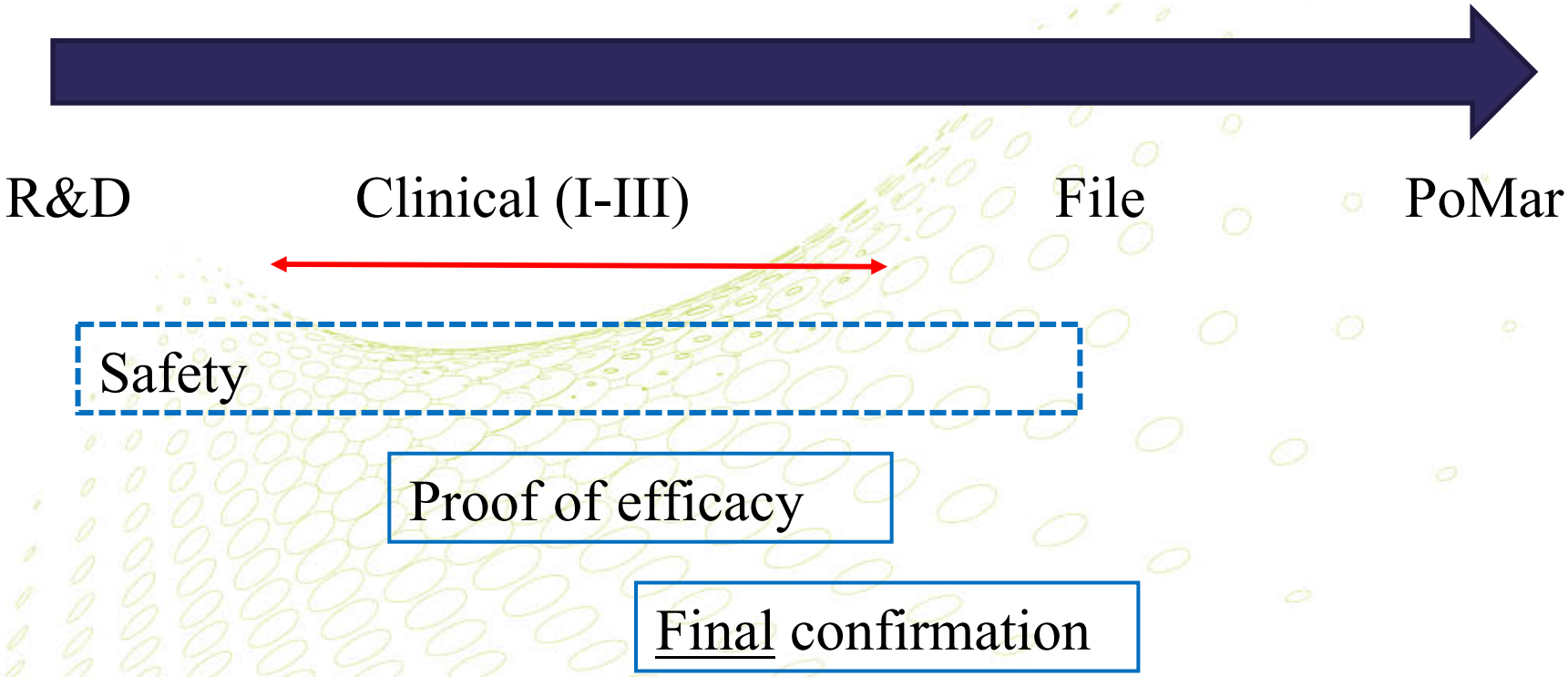
Putting it into a perspective (5)



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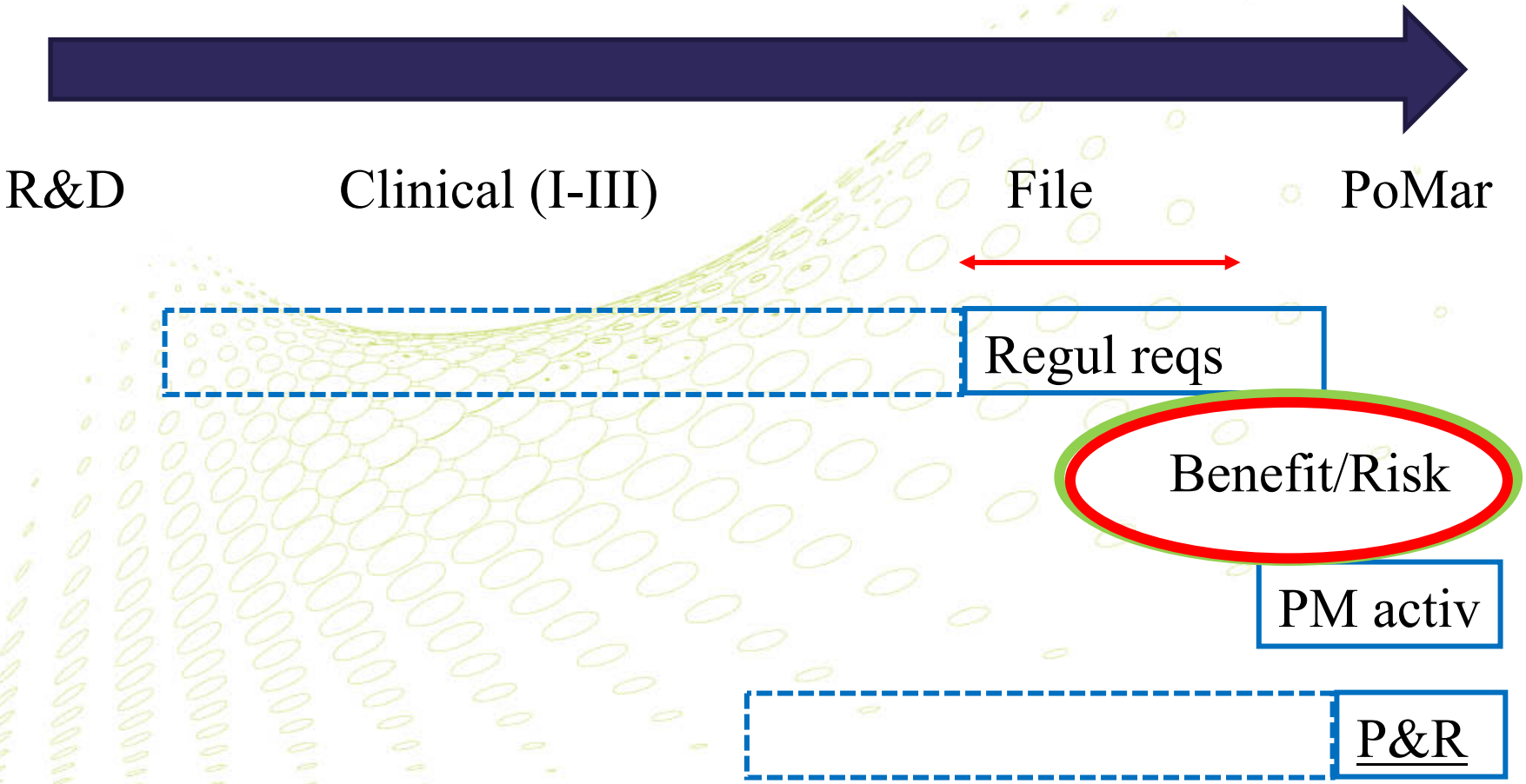
Putting it into a perspective (6)



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Putting it into a perspective (7)

R&D Clinical (I-III) File PoMar

10 – 15 – 20+ years

FOCUS on the right thing at the right time

Think carefully ahead

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Thank you for your attention

Questions?