Betrokkenheid van de patient in nationale aanvragen voor Scientific-Technical Advice betreffende klinische proeven: FAGG Pilootproject

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Christophe Lahorte

famhp
federal agency for medicines and health products

.be

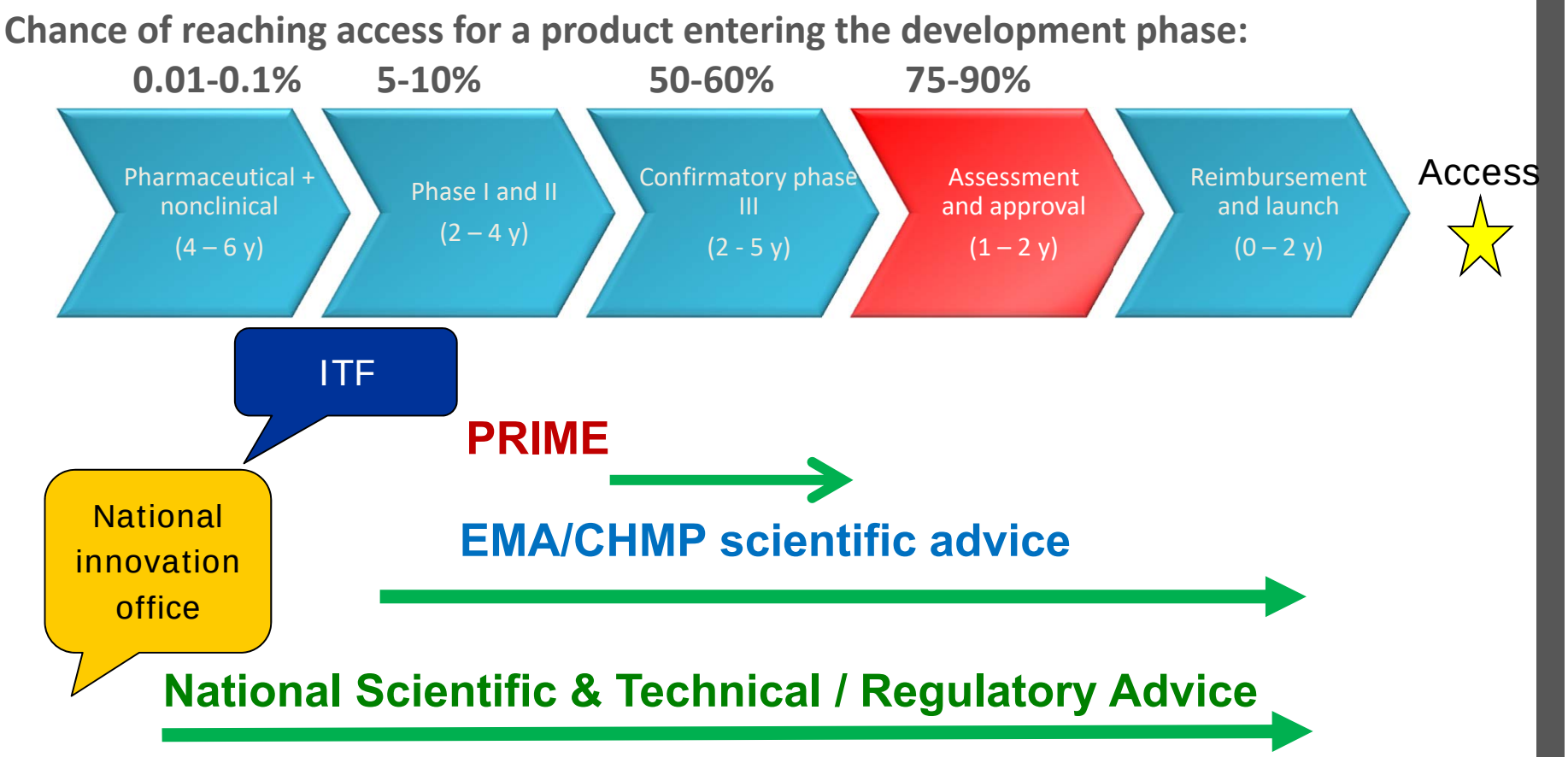
1. Introduction to national STA: procedural aspects

- voluntary procedure
- specific questions (eg. 70 % CTA related)
- expert responses are prepared & discussed internally
- outcome :
  - written advice: max. 30 days (Type I STA)
  - scientific advice meeting & written advice report
    max. 70 days + 14 days (Type II & IIIa, IIIb STA)
- Non-legally binding opinion
- No pre-assessment / pre-approval of the dossier
- Focus on “one-stop-shop” approach: eg.
  - Joint advice with Sciensano (GMO’s, vaccines)
  - Joint STA-HTA advice with RIZIV-INAMI
- Coordination: FAMHP’s innovation office
- Throughout development life cycle

STA = Valuable tool for facilitating drug development & early patient access to highly innovative drug products

1. National Innovation Offices as starting point

The typical long route of medicines to patients



1. Introduction to national STA: Type of questions

- **Scientific:**
  - Quality, non-clinical, clinical (incl./excl. criteria, endpoints, target population, PRO's, statistical aspects …)
  - Study design
  - Clinical development plan
  - Benefit /Risk balance
  - Unmet medical need
  - Swith Rx to OTC status
  - Pharmacovig issues (RMP's, PAES/PASS, Referrrals)

- **Technical - regulatory:**
  - GMP, GCP, GLP, …
  - Regulatory statute of borderline products
  - Guidelines
  - Regulatory filing strategy (eg. CTA, SAWP, PIP, MAA, CHMP re-examination, WHO pre-qualification,…)

STA = Valuable tool for increased success rate of clinical development plans & tailoring to patient needs

2. Involvement of patient organizations / experts in national STA: summary of pilot project

Initial goal:

Involve disease-specific patient organizations in national STA requests related to CTA applications

National STA:

- Pilot project (phase 1: Q3-Q4 2018): retrospective setting
- Project evaluation: Q1 2019
- Pilot project (phase 2: Q2-Q4 2019): real-life setting

CTA:

Pilot project: start up based on the learnings from the STA pilot project phase 1 & 2

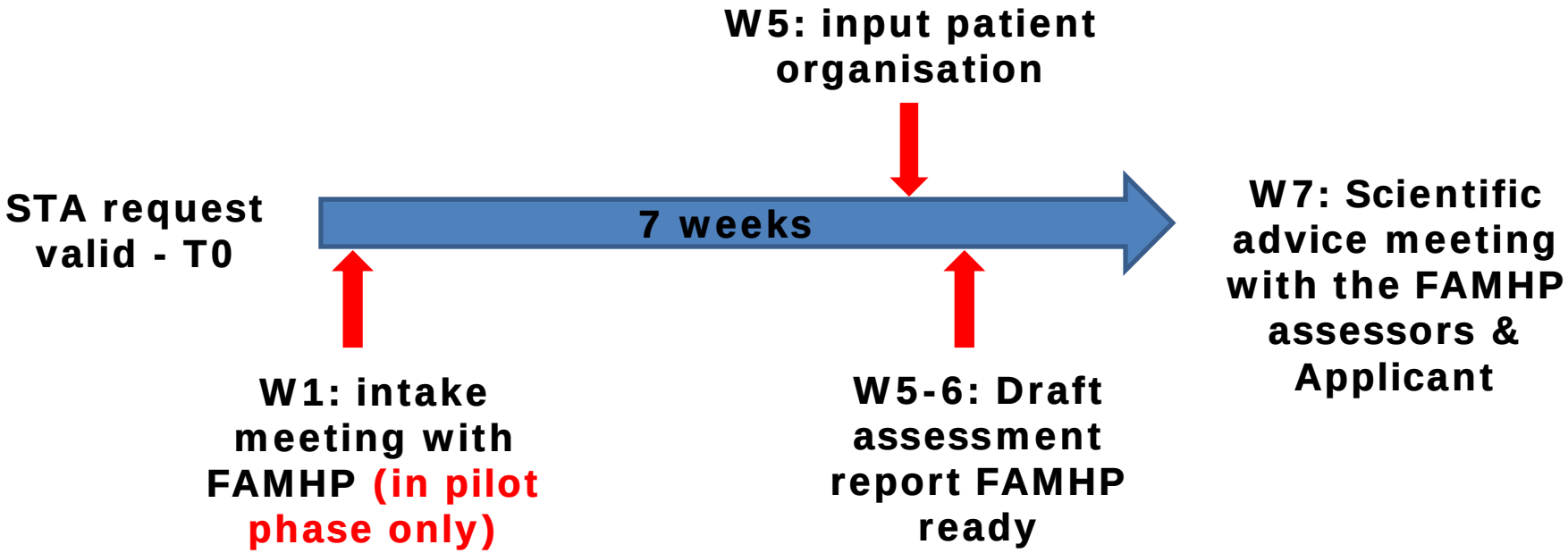
2. Setup for the collaboration with disease-specific organizations

Pilot STA project (Phase 1): general features:

- 5 post-hoc STA procedures
- STA with clinical (non-clinical) questions related to a planned CTA
- 1 dossier per month
- Simulation according to standard procedural timelines of procedure
- Tandem between disease-specific organizations and umbrella organisation
- Consultative advice only
- 2 interaction moments: Intake meeting + scientific discussion meeting

2. Practical aspects

Real-life setting to be mimicked as much as possible:



2. Practical aspects

Written advice

- Not all questions had to be assessed
- Focus on questions demanded by applicant
- **But:** other/more general comments were also welcome
- Advice needed to represent the view of the patient population and **not** of 1 specific patient

2. Practical aspects

Other CONSIDERATIONS

- The STA dossiers needed to be treated confidentially
- **declaration of interest** and confidentiality agreement prior to receipt of the STA dossier
- Timelines should be respected to mimic the real life procedure
- No training foreseen, support by umbrella organisation

Criteria for the selection

Pilot dossiers were selected based on:

- **Match** between interested disease-specific patient organisations and recent scientific advice requests given between 2015-2018 (post-hoc approach)

- Minimal (scientific and/or EU) **expertise** present at the level of the patient organisation

- **Topic** included:
  - clinical trials in patients
  - FIH studies in healthy volunteers only were excluded

- **Sufficient information** available in the briefing package

List of Disease-specific patient organizations

Following organisations showed interest:

- HTAP voor pulmonaire hypertensie België
- BOKS: metabolic diseases
- Muco vereniging
- NET&MEN kanker
- Werkgroep hersentumoren
- 22q13 (Phelan McDermid Syndroom)
- Bindweefsel
- Crohn en colitis ulcerosa vereniging
- Hodgkin non-Hodgkin
- LGD alliance (lymphangiomatosis & gorham's disease)
- Ligue Huntington
- Lymfklierkankervereniging Vlaanderen
- MS-liga
- RA liga (via reumanet)

List of Disease-specific patient organizations

Following organisations showed interest:

- Vlaamse Parkinson Liga
- Diabetes Liga
- GIRTAC: anticoagulants
- HAE: heredic angiodemia
- Association Lupus Erythématuex
- GESED: Ehlers-Danlos syndrome

Projects selected

General remark:

Disease area (interested patient organisations)

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the disease area of potential STA dossiers

STA Patient pilots selected (retrospective pilots)

Product	type	Disease area	Organisations
Defymed	Medical device (extraperitoneal insulin administration)	Diabetes type 1	Diabetes liga/VPP
ELX02	translational read-through inducing drug (TRID)	cystic fibrosis (nonsense mutations)	Mucovereniging/RaD iOrg / LUSS as observer
Genmab – GEN 3013	antibody	patients with relapsed, progressive or refractory mature B-cell malignancies	LVV, Hodgkin non-Hodgkin vzw, Erik Briers (patient expert CAT/EMA)/VPP
VE202	Biotherapeutic Product	treatment of ulcerative colitis	Crohn en colitis ulcerosa vereniging/VPP
CFZ533	antibody	Diabetes type 1 paediatric patients)	Diabetes liga/VPP

Summary

Different methodologies used in different pilots

Patients
(questionnaire + summary of STA dossier in lay language)

+ : bigger group of patients reached

- : essential information got lost, non-relevant comments received as well, scientific training needed, no regulatory awareness of « average » patient

patient "experts"
(full STA dossier)

+ : scientific and relevant comments, regulatory awareness

- : point of view of one/two person – not always representative for the whole patient population?

Feedback from patient organisations

- Positive about the possibility to be heard/implicated = incentive

- Positive on interaction with FAMHP assessors, STA unit & exploring ways for future collaboration = learning curve

- Input provided about clinical trials & providing added value on different aspects: eg.
  - Perceived benefits/risks for patient
  - patient-relevant clinical endpoints
  - Feasibility of trial design
  - Admin. schedules & medical interventions (type & frequency)
  - Technical info on admin. devices (DDCP's)
  - Treatment compliance
  - Patient follow-up: hospital setting vs remote follow-up
  - Burden for patient on daily life (cave: patient drop-out rate)

= valuable input for increasing trial outcome, patient enrolment & retainment, treatments fitting better to patient's needs & preferences

Feedback from patient organisations

- Willingness to provide additional, more general patient input: eg. further drug development,
  - Questions for additional info towards Applicant (cfr. validation phase of STA / STA meeting)
  - Positioning the Drug Product versus existing treatments,
  - other potential indications,
  - Access to Drug Product
  - Patient information (cfr. ICF related)

- Somme patients/laymen are rather reluctant about FIH trials in patients, especially in young children – training needed (also for parents) !

- Info on patient profile and previous treaments is very informative to interpret patient input !

- Input from specific type of HCP's (eg. Nurses) can be very informative

Feedback from patient organisations

Hurdles / concerns

- Time consuming work
- Administrative burden (DOI, CA) = often hurdle to participate
- Briefing package too difficult to understand (eg. laymen, patients)
- Blinding of data + patient-friendly summary = work intensive & time consuming (= rate-limiting step to respect STA timeline)
- Questions not always relevant for patients or too technical
- Reformulation of patient questions often needed = extra workload & time consuming
- Language barrier (English)
- Too strict deadlines
- Too high / wrong expectations about STA involvement or the advice report

Suggestions

Suggestions from patient organisations

1. **Patient friendly package**
   = Lay language, summarizing the dossier in 1 to 2 pages

2. **Relevant questions**
   Standard list of patient-oriented/relevant questions

3. Continue with **feedback** from FAMHP after the meeting with the Applicant needed = incentive for long-term collaboration with patients

4. **Training** about basic principles of pharmaceutical development, STA and CTA evalution principles

5. Patient organisations: willing to create **subgroup of « dedicated patients »**
   = key facilitator for collaboration on future STA, CTA procedures

Proposal for future collaboration

Patient expert

Technical dossier

Focus on questions of applicant

Patient representative

Patient information = lay language, Dutch or French

Standard list of questions

Role umbrella organisations:

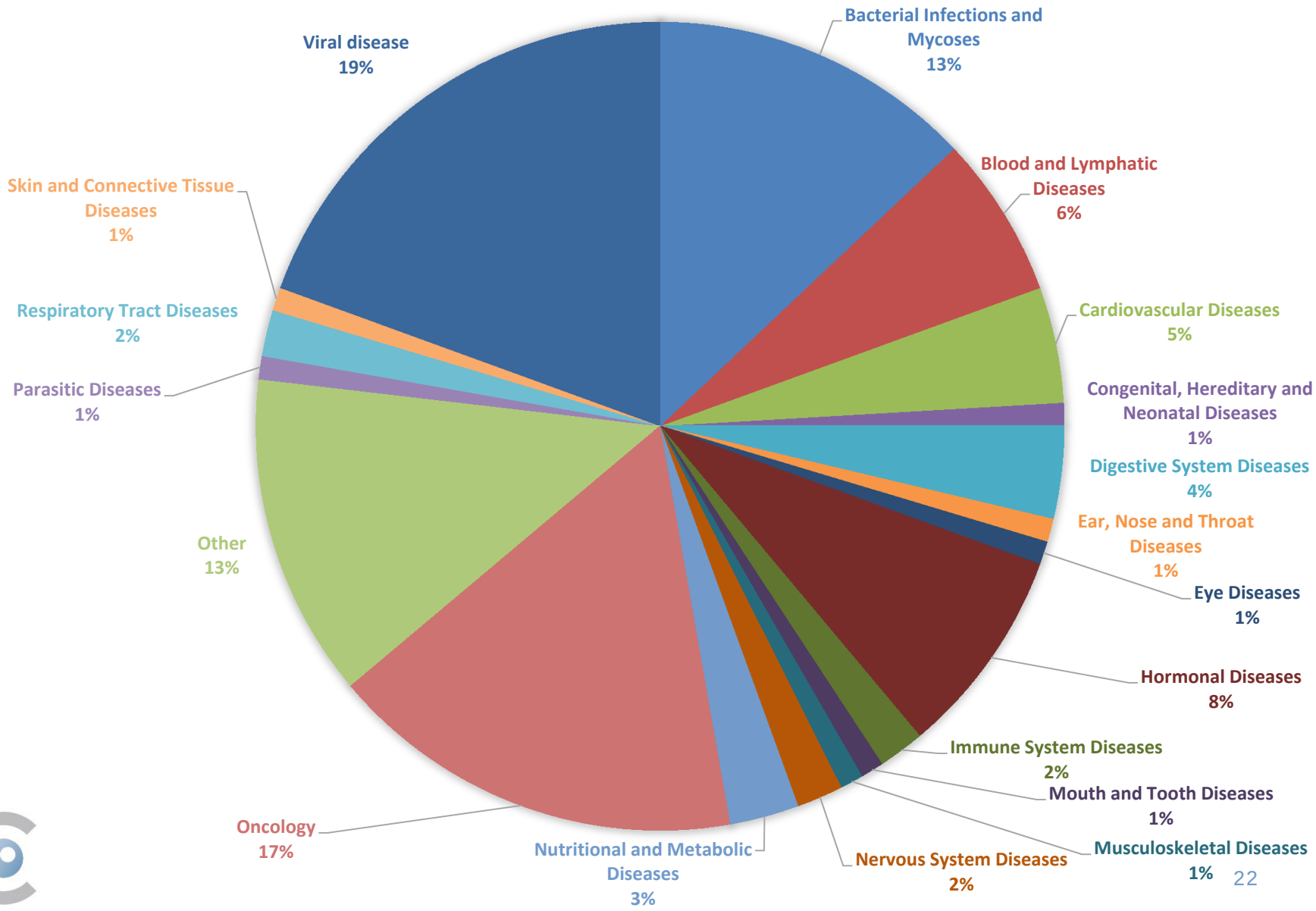
- Network, identification of patient « experts » and organisations interested in collaboration, DOI & CA policy, sensibilisation & communication
- Identifying training needs

3. Stepwise continuation of patient involvement in STA

STA procedures (Pilot Phase 2): general approach

- 5 STA procedures in real-life setting: Q2-Q4 2019
- 1 Patient expert (broad sense) / STA dossier
- Consultative role (internal advice meeting with FAMHP assessors)
- On Ad-hoc basis:
  Selection criteria for patient expert involvement TBD depending on: eg.
  - available expertise, capacity & interest
  - creating max. added value towards patients
  - max. match with Therap. Areas covered in STA
- following real-life procedural timelines: assessment time = 5 – 6 weeks
- Data package = STA briefing package (+ executive summary if needed)
- Focus on:
  - list of Applicant's questions (other patient-oriented comments also welcome)
  - specific FAMHP assessor questions

Domains for possible collaboration: STA



Stepwise continuation of patient involvement in STA

Pilot STA project (Phase 2): procedural aspects

- No intake meeting at start of procedure: unless considered needed
- Patient expert selection & DOI check: during validation phase or before: eg. in case of intent to submit + draft list of questions is received prior to formal STA
- internal advice/discussion meeting with FAMHP assessors (week 6)
- timing STA internal AR exchange: patient expert is asked to deliver his/her AR first in order to avoid bias – before the preparatory meeting, AR's are exchanged so that all opinions are known
- Final STA report (after Company meeting): includes patient expert identity
- Feedback to Patient expert: final FAMHP scientific advice is sent, for information to the patient expert

1st Interim Evaluation: end 2019

STA Patient pilots selected since Q2 2019:

Product	type	Disease area	Patient Expert/Organisations
Faecalibacterium Prausnitzii CNCM I-4573 (ELX1)	Bio(techno)logical	Crohn's Disease	Lynn Debrun (Crohn Colitis Ulcerosa Vereniging vzw)
STA551	Bio(techno)logical	locally advanced or metastatic solid tumours	E. Briers (European Cancer Patient Coalition (ECPC), CAT/EMA patient expert)
UCB6114	Bio(techno)logical	Advanced solid tumours	E. Briers (European Cancer Patient Coalition (ECPC), CAT/EMA patient expert)
Upcoming: Vafidemstat	Chemical	Borderline Personality Disorder	TBD
Upcoming: triheptanoin (UX007)	Chemical	long-chain fatty acid oxidation disorders (LC-FAOD)	BOKS vzw (Belgische Organisatie voor Kinderen en volwassenen met een Stofwisselingsziekte)
Upcoming: New oncology product	Not known yet	Oncology	TBD

- 3 STA pilots successfully completed
- 3 STA pilot upcoming
- Predominantly: oncology related (3/6 STA pilots)

First results from real-life STA pilots:

PRO's: involvement of patient experts:

- **One common, streamlined methodology**
- **Providing added value to:**
  - Discussion with FAMHP assessors
  - scientific STA meeting preparation (incl. identification of critical questions/issues towards Applicant)
  - final STA opinions
- **Procedural timelines can be maintained**
- **Limited additional workload**
- **Limited training needs**
- **Positively received by Applicants, Patient experts & FAMHP experts**
- **Patient experts can provide: eg.**
  - scientific and relevant patient oriented comments
  - regulatory awareness
  - possibility of intergrating the patient expert advice into the FAMHP assessment report, to align opinions & provide "stronger" recommendations to Applicant
  - often complementary input to FAMHP expert views

First results from real-life STA pilots:

CON's: involvement of patient experts:

- point of view of one/two person(s) – may not always be fully representative for the whole patient population?
- Patient expert input: often technical, may leave « blind spots » i.e. input from patients with the specific disease may provide addditional value
- Difficulties to find patient experts in different therap. areas in Belgium
- Strict COI rules to be followed (may prevent FAMHP from consulting patient experts previously consulted by Pharma sector)

Opportunity:

Added value could be further increased by active involvement of patient experts in formal STA meeting with Applicant (eg. possibly in future pilot phase)

Next steps & Opportunities

1. **Interim evaluation** of real-life STA Pilots: end 2019
2. **Preparing next steps for 2020:**
   - Continuation of patient STA pilots: building up experience in multiple therap. areas
   - Expanding patient « expert » network & collaboration with eg. patient organisations, HCP's, health authorities, other stakeholders
   - Identifying potential synergies with new initiatives: eg. PEC initiative
   - Defining potential objectives for next STA pilot phase
   - Link with future CTA pilots with patient involvement
3. **Follow up of evolutions to advance patient focused drug development at national & international level (EMA, ICH, …)**
4. **Preparing for the future challenges:** eg. RWD, digitalisation, medical technologies used in clinical research, decentralized trials,...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Contact

Federal Agency for Medicines and Health Products – FAMHP

Place Victor Horta 40/40
1060 BRUXELLES

e-mail: innovationoffice@fagg-afmps.be

http://www.afmps.be
http://www.fagg-afmps.be/en/innovationoffice

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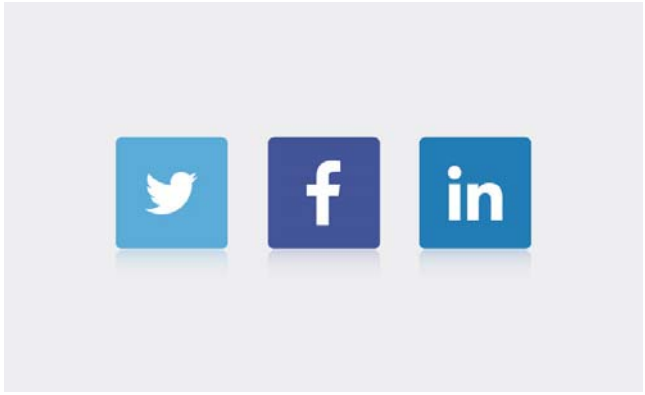

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