STAMP 10/44
Annex

Repurposing of established medicines/active substances - STAMP Working Group activities

Background

During the 9th STAMP meeting on 8 June 2018 it was agreed that consideration of a proposal for a framework for repurposing of existing medicines should be further developed within a working group.

A working group including representatives from the following Member States and stakeholder groups was formed - Belgium, the Netherlands, Norway, Spain, Sweden, the United Kingdom, European Medicines Agency (EMA), Anticancer Fund, European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), European Federation of Pharmaceutical Industries and Associations (EFPIA), Medicines for Europe (MfE), European Organisation for Rare Diseases (EURORDIS), European Patients' Forum (EPF), European Society of Paediatric Oncology (SIOPE), International Association of Mutual Benefit Societies (AIM), supported by the European Commission.

The group was led by the UK and Spain and worked through exchange of emails and regular teleconferences.

The group considered the following 3 aspects (objectives) for a proposal for a repurposing framework:

- Complete the steps of the pathway
- Test run the pathway
- Supporting materials and communication

Sub-groups were created to consider objectives 1 and 2, objective 3 was considered by the group as a whole.

The following attached documents have been prepared by the group:

- For objective 1 - Proposal for a repurposing pathway within the current regulatory framework with outstanding comments from members of the group
- For objective 2 – Learnings and outstanding issues
- For objective 3 - Supporting materials and communication

These documents have been prepared for consideration by the STAMP to support discussions at the 10th meeting and do not represent the views of the STAMP expert group as a whole or a consensus view of a potential repurposing pathway, nor the outcome of the STAMP meeting and therefore can be subject to changes.

STAMP 10/44
Objective 1

STAMP Working Group

– Proposal for a repurposing pathway within the current regulatory framework

Members of Group:

- Member States (Belgium, The Netherlands, Norway, Spain, Sweden, United Kingdom)
- European Medicines Agency (EMA)
- Anticancer Fund
- European Society of Paediatric Oncology (SIOPE)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Medicines for Europe (MfE)
- European Patients' Forum (EPF)
- European Organisation for Rare Diseases (EURORDIS)
- European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
- Association Internationale de la Mutualité (AIM)
- European Commission representatives

November 2018

STAMP Working Group – proposal for a repurposing pathway within the current regulatory framework

For the purpose of discussions with the STAMP meeting on the 3rd of December, this paper provides some additional clarifications and changes to the proposed repurposing framework as presented by EFPIA and Medicines for Europe at the June 2018 STAMP meeting.

Information on the initial proposals can be found in the two documents below:

[1] [2]


stamp_9_40_1_en.pdf


stamp_9_40_2_en.pdf

The content below provides further elaborations following consideration by the STAMP working group, in particular describing the scope and key concepts to the repurposing of medicinal products, as well as identified outstanding issues.

Introduction and scope
In the context of the proposed STAMP pathway, the working group proposed the following definitions and scope:

- Repurposing is defined as the process of facilitating the justification of a new therapeutic use for an existing medicine outside the scope of the original indication(s), with the purpose of seeking a marketing authorisation.

- Repurposing may occur in situations where the medicine is still protected by basic patent/supplementary protection certificates (SPC) / data and market exclusivity, as well as where the medicinal product is outside of these intellectual property (IP) / regulatory protections.

- The elements discussed below cover only one possible scenario of repurposing of medicinal products, namely the one where medicines are already out of basic IP/regulatory protection.

Repurposing of medicinal products out of patent and data protection

- For this pathway, the following attributes apply to the repurposed medicinal product(s):

1 The proposed new indication should be in a condition distinct to the currently authorised indication(s) listed in section 4.1 of the relevant summary of product characteristics (SmPC) of a Member State (MS) or the European Union (EU)

2 There should be a valid marketing authorisation for the medicinal product containing the same active substance in the same formulation / dosage form, granted in a Member State or in the European Union

3 Repurposing should be encouraged in an area where significant public health benefits / Union interests are likely to be achieved

4 All authorised medicinal products containing the active substance should be out of basic patent/ SPC protection, and data & market exclusivity periods

[1] https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_9_40_1_en.pdf
[2] https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_9_40_2_en.pdf

5 The repurposing project represents a scenario that is not currently being fulfilled by a business organisation

6 There should be supporting evidence e.g. proof of concept from clinical data. It could include documentation from off label use, registry data, clinical trials or reported case studies

7 A Champion has been identified who is willing and able to take forward the roles and responsibilities required of the framework. A champion can be a person/academic unit/learned society/research fund or payer with a particular interest in repurposing a compound/product for a new indication and who has data evidence/scientific rationale to do so. Criteria to qualify as a champion include:

a. Is not a pharmaceutical company / business organisation
b. Is able to coordinate and or foster the development programme up until the point of full industry engagement
c. Is initially responsible for liaising and leading the interactions with regulatory authorities and industry / other stakeholders such as patient groups
d. Is transparent regarding interactions with relevant pharmaceutical company(s)
e. Files the request for regulatory advice on the basis of the available data

In summary, a repurposing project is defined by the aim to foster the authorisation of a new indication to an unprotected off-patent medicinal product. The new indication is not expected, at the time of proposal, to be approved or under active development by the marketing authorisation holder (MAH) or any other business organisation.

Proposed core components of the framework
The process of repurposing may be described as voluntary steps within the existing regulatory framework. Note: Some key milestones to the repurposing project are not regulatory activities, e. g. the champion finding an interested manufacturer and concluding on the necessary agreements, and ensuring that IP and exclusivity rights are not infringed.

The aim of the proposal is to provide a visible supportive framework to a stakeholder who has evidence and scientific rationale for a new indication that fits the criteria in the above definition, with an interest to bringing the indication on-label.

Rate-limiting steps

The main rate-limiting steps and disincentives for Champions may be the lack of knowledge in terms of regulatory routes and requirements, what additional data need to be generated, how to find non-published clinical and non-clinical data, how to find a manufacturer of the finished product to collaborate with etc. The administrative steps of filing a marketing authorisation application (MMA) submission and validation is also a high threshold for Champions. Champions are normally not equipped or have the resources to legally take the role as MAH when seeking approval or fulfilling post-marketing responsibilities but are understood to have conducted the data gathering and analysis from different sources or/and generated data partially or up to the full programme.

Scientific advice as entry point to regulators
Scientific Advice (SA) is the main regulatory tool that is considered important to support repurposing projects. Guidance can be provided to the Champion on the regulatory and scientific aspects of the project, e.g. data generation and the data package required to support the suggested indication. The outcomes of the SA could potentially be made more widely available in the context of encouraging engagement with MAH(s), but this will remain at the discretion of the Champion.

The future full assessment by regulators of the data in support of a new indication will follow an existing pathway for an application to the EMA or competent authority (CA) e.g. variation, extension or new marketing authorization application, whereby it could allow the granting of a new indication if successful.

Incentives – disincentives

Both legal and non-legal incentives may be important to different stake-holders. There are some incentives within the regulatory framework and other types of incentives may exist in different MS. For Champions it may be to fulfill medical needs to patients, scientific, economic (grants/funds) and reputational issues. For industry the nature of the business case will be important as well as minimising the perceived barriers.

Key components of the currently proposed framework

	Phase	Description
1	Pre-entry	Champion identifies and has an interest in a new indication. Champion to approach competent authority after cross checking the suitability of the indication against the scope criteria
2	Pre-entry	Using identified data sources and or own data, the Champion submits the proposal to enter the pathway to a regulatory authority (EMA or national competent authority) for a repurposing scientific advice meeting using the relevant template and topic check list that might include (but not limited to) the following aspects: - Compound (or product) - Proposed repurposing (prevention, treatment or diagnosis of disease) - Description of the existing supporting data for indication and proposals for future data generation - Discussions on available incentives - Approaches for accessing data - Considers industry collaboration (use Article 57 to determine list of MAH, access to list of industry contacts)
3	Repurposing SA meeting	Regulatory authority conducts meeting with the Champion and as applicable other relevant stakeholders (MAHs, patient groups, HTA, other). Discussion on the proposals.
4	Feedback	Regulators provide feedback (non-binding advice) on the current and future development programme and the clinical added value, taking into account the overall proposals and the available data. Regulators can signpost to different existing regulatory routes and incentives where appropriate
5	Post scientific meeting	Champion takes forward the recommendations and follows advice from the regulatory authority The Champion considers the timing for engaging with a potentially interested MAH, if no collaboration has previously been sought or been successful - the Champion can take forward the development programme with or without the support of a specific MAH The Champion may make the scientific advice feedback available to other

		partners to stimulate interest in the repurposing project. At the end of the development programme, the Champion confirms compliance with the advice given by the regulatory authority, e.g. additional CTs or non-clinical studies conducted, data analysis and liaises with an interested MAH.
6	Licensing route	MAH holder(s) take(s) forward the data package, constructs a regulatory dossier and submits a marking authorisation application to EMA or relevant NCA.

Summary

- A Champion puts forward a repurposing proposal for a repurposing regulatory scientific advice meeting. A Champion can be a person/academic unit/learned society/research fund/payer with a particular interest in repurposing a compound/product for a new indication and who has data evidence/scientific rationale to do so.

- A standard format/package is provided by the Champion that supports the new indication to the regulatory authorities. The repurposing scientific advice provides comments and feedback on the presented data package components, the added clinical value and the requirements of any future data generation (if required).

- On the basis of the scientific advice, the Champion conducts further development and/or consolidation of the available data.

  The Champion seeks an immediate or future partnership with MAH depending on the stage of the development.

- For the purpose of filing the data to support a new indication, the Champion and/or a MAH confirms that the available data are in compliance with the advice given by the regulatory authority.

- The MAH(s) seek(s) a marketing authorisation using the existing regulatory pathways if the data package and business case are considered robust. Marketing authorisation approval may or may not include post authorisation measures (as appropriate)

Main outstanding aspects:

1. Develop a repurposing checklist and topics to cover for the repurposing scientific advice meeting.

2. Consider ways to support the Champion, including if and how a fee waiver for a scientific advice meeting could be made for a champion (IMI interaction, other initiative), provide contact points from industry to aid communication with MAH, other support?

3. Develop further guidance that clarifies in more detail the individual identified roles and pathway milestones.

4. Determine the feasibility and practicalities of the pathway by piloting with a live asset and Champion.

STAMP repurposing working group - outstanding comments / points for discussion

Stakeholder	**Comments / topic**
EMA / SE / UK – leads from Objective 1	1. How to develop the pathway in a way that is suitable for both the EMA and NCA and what might the important differences be?
EFPIA	1. Application type should be by variation to existing MA? 2. The element of feasibility which, if fulfilled, is an incentive itself for a marketing authorisation holder - to industry the nature of the business case will be important, along with the feasibility of pursuing the regulatory variation to add the new indication to an existing MA. Relevant factors in determining feasibility include: the availability of data in the correct (eCTD) format and meeting current standards in order to build the necessary regulatory dossier for the variation application, the associated requirements for a risk management plan, requirements for further data or post marketing studies, and other pharmacovigilance and liability considerations. 3. Repurposing scientific advice (SA) meeting - there could be a standard format and standard set of questions for the EMA/NCA to answer. Suggest that the outcome should be a clear recommendation after SA that can then be communicated to MAHs: • Negative (data not fit for purpose) • Positive 'as is' (i.e. the variation to the existing MAA can be pursued) or • Positive, only after the generation of extra data – although the current framework proposal would not directly cover this, the guidance should describe what happens then 4. MAH will consider the outcome of the SA and, if positive, and the MAH considers if appropriate and feasible a variation to their MA.
Medicines for Europe	1. Objective was to look for a pragmatic solution to facilitate the update of the PILs by the MAHs when there is a scientific evidence, available data, research have been already done (or almost done) but the MAHs are not very "motivated" to collect this knowledge/ evidence by themselves and to update the PIL via existing regulatory pathway. 2. The proposal as it is described now, is built on a very close cooperation between Champion and MAH in continuity of research and in regulatory steps. In fact this pathway already exists and is used in practice when there is an interest of the MAH to invest in the project. Is the better access of Champion to the scientific advice going to increase significantly a number of common industry-researchers project in repurposing in more difficult therapeutic areas? The improvement of the quality of research thanks to scientific advice is a great value per se, however my doubts are rather related to the next step- picking up the project by the MAH and investing in next steps. 3. Using an existing knowledge (i.e. studies already finalized by Champion), the process of submitting the same data package by several MAHs and to be assessed several times by the CAs to amend the PILs is really inefficient and very resource consuming for industry and authorities. and it does not really work in practice (that's why we

	have initiated this discussion at STAMP to find a better solution). 4. The same formulation sounds to me too restrictive in view of multisource products. 5. How do we know that the indication is under development by any other MAH or any other Champion? Seems to me quite unrealistic. 6. In practice Champion (if successful) will engage with only one MAH which will amend the leaflet. I don't see the real mechanism/ benefit to reduce off label in case of several MAHs on the market (which is normally the case when molecule is out of patent). 7. The regulatory pathway part is very short and leaves quite some open questions. Also post MA obligations should be addressed.
EURORDIS	1. At the June meeting, industry explained the proposal only applies where only the label needs to be changed (not the dosage, not the administration mode, not the package etc.). Is it still the case? Or does it now include situations where more than the label need to be changed? 2. Regarding the Champion - So this can include European Reference Networks or Centres of Expertise or any academic setting, and also any patient organisation? To be clarified, as during conference calls it was expressed there could be conflicts of interest here. Which conflicts of interest this is not clear to me. Patient organisations are more and more often partnering as co-sponsor of projects or joint ventures with industry to develop new products. 3. Regarding incentives: This is too vague. Which incentives exist? "Other types of incentives may exist": examples? Where? 4. The point is not to discuss more or new incentives for MAHs who will obtain a new indication for their products. The point is to propose the incentives for champions to take all these task on board. Economic funds: which ones are available? If in all cases the champion need to perform all the work from requesting SA to generating the necessary data, for free, Eurordis expresses its greatest doubts that this proposal could be of any use. Lack of time, paper work, lack of experience, with the perception that others will benefit and the champion will "only" enjoy the sense satisfaction with the accomplished work are objective barriers which are not addressed sufficiently in this paper. 5. To add, if the new indication is for a rare disease, the champion can also submit an orphan drug designation application to benefit from incentives such as Scientific Advice fee reduction or fee waiver. 6. It is important all MAHs are involved, maybe not the originator but a generic manufacturer will be interested by the project. In any case, if only the label needs to be changed, it is in the interest of all patients that all MAHs (for multi-source products) engage into the regulatory process to add the new indication to the label. This is for all patients to receive the same information (package leaflet), and when new PASS are mandated on this new indication, all relevant MAHs become concerned by the PASS. 7. Also, the ECJ Judgment in Case C-29/17 of 21 November 2018 concluded that the reimbursement of an off-label use when an authorised product exist for the same use is compatible with EU law.

	This indicates that manufacturers may sell a product for which they did not change the label to include the new indication and the user can still be reimbursed. 8. Again, only when mandatory prescription by indication will be in place, then the company that will update its label will be incentivised to do so. 9. Even if the working group mandate is to work on a proposal with the current regulatory landscape, it should aim at recommending measures that will make this proposal work fully.
Association Internationale de la Mutualité (AIM)	1. Fees for early advice/registration could be considered part of the discussion about 'financial incentives' and could be looked at within this project.
SE	1. What steps are needed before going public with "repurposing" within the current framework to stakeholders? 2. What issues lie outside the command of regulators of MPs (NCAs) to support "repurposing"? 3. Potential impact of ECJ judgment on off-label Avastin/Lucentis with reference to national competence versus EU law.
Anticancer Fund	1. Example of cases ReDO_DB: The Repurposing Drugs in Oncology Database - Pan Pantziarka, Ciska Verbaanderd, Vidula Sukhatme, Rica Capistrano I, Sergio Crispino, Bishal Gyawali, Ilse Rooman, An M.T. Van Nuffel, Lydie Meheus, Vikas P. Sukhatme , Gauthier Bouche Abstract: Repurposing is a drug development strategy that seeks to use existing medications for new indications. In oncology there is an increased level of activity looking at the use of non-cancer drugs as possible cancer treatments. The Repurposing Drugs in Oncology (ReDO) project has used a literature-based approach to identify licensed non-cancer drugs with published evidence of anticancer activity. Data from 268 drugs have been included in a database (ReDO_DB) developed by the ReDO project. Summary results are outlined and an assessment of clinical trial activity also described. The database has been made available as an online open-access resource (http://www.redo-project.org/db/). 2. Link indicating comparable activities with a central role for the regulators in the US: https://www.focr.org/senators-hatch-and-bennet-introduce-bipartisan-solution-important-public-health-issue
ES	1. What may the STARS project offer, maybe it's not only STARS that might complement somehow the repurposing pathway but also activities related with the EU-Innovation Network and the Clinical Trials Facilitation and Coordination Group (CTFG). – interactions with other stakeholders in the pathway?

BE	1. Regarding significant public health benefits and aspect on positive financial impact, would the pathway facilitate repurposing of a cheaper alternative for which a medicine is on the market? 2. To clarify disincentives from Industry perspective. 3. Regarding SA process, do all SA procedures work in this way? 4. Scientific advice feedback on development programme is certainly important. However, it seems also important to give an appreciation on the clinical added value of proposed indication (e.g. responding to unmet medical need).

STAMP 10/44
Objective 2

STAMP Working Group

– Learnings and outstanding issues

Members of Group:

- Member States (Spain, Sweden, United Kingdom)
- Anticancer Fund
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Medicines for Europe
- European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
- International Association of Mutual Benefit Societies (AIM)
- European Commission representatives

November 2018

STAMP repurposing group Objective 2 – Learnings and outstanding issues

The goal of Objective 2 was two-fold: 1) to provide 'real life' examples of product(s) / indications that could have been put through the pathway and 2) to consider how a pilot for testing the repurposing pathway might be introduced.

Summary of the examples

Several potential examples were identified, of which two specific case studies were selected for further evaluation:

- Docetaxel in hormone sensitive metastatic prostate cancer
- Combination of 9 repurposed drugs with low-dose chemotherapy (CUSP9v3 study)

The first case was selected because docetaxel is already used off-label in metastatic hormone-sensitive prostate cancer and is therefore a good example of late entry into the pathway. The second case, CUSP9, is still in a very early development stage (Phase 1 trial completed) and highlights the importance of early entry into the pathway in order to address potential regulatory and scientific challenges in an early stage.

Learnings from the case studies

- A single entry point into the pathway, instead of an early and late entry point, would lower the threshold for champions to send in a proposal.
- Gathering data on the authorisation details of an active substance might be quite challenging for a champion. However, EMA publishes information on all authorised medicines contained in the Article 57 database in the form of an excel document on their website: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database. This database provides an up-to-date overview of all MAHs for an active substance authorised in Europe. This information could be very useful for a champion who wants to contact one or more MAHs. The link to the Article 57 database could be included in the template/check list for the champion.
- Preparing a data package for a scientific advice meeting could be difficult for a champion with limited knowledge of the regulatory process, for example*:*
  What kind of non-clinical data should be provided? Is this data already available from previous MA dossiers? What kind of clinical data are needed to support a variation or new MA? Can literature data be used? Could low-interventional trials be used for drug repurposing and how do they differ from standard trials? What about the use of real-world data from registries and retrospective studies? Could recommendations for off-label use of the active substance in clinical guidelines (e.g. ESMO guidelines for cancer) be included in the data package?
  → Additional guidance documents and a template/topic checklist should be provided.
- A lot of time and effort would be required from the champion to prepare a data package, to contact competent authorities, to liaise with MAHs, etc. Their efforts should be rewarded by removing certain disincentives, like the cost of SA.
- The champion could be a research institute (academic group, university hospital, non-profit organisation), but also a payer or other stakeholder with scientific knowledge.
- The pathway should allow combinations of repurposed drugs (e.g. CUSP9).
- The case of docetaxel showed that data from multiple phase 3 trials and real-world evidence studies might be available. If the data are mature (phase 3 clinical data), the champion should provide an exhaustive list of all available data, even if these data seem to be contradictory. This is an unexpected complexity since a MA for a new medicine is based on a single registration trial.

Suggestion for a pilot case

Adjuvant bisphosphonates for the prevention of breast cancer spreading to the bone in post-menopausal women with primary breast cancer.

→ A lot of evidence to support off-label use, off-label use is common.

Template/Topic check list

EXAMPLE X	
Available product information (in EU)	
Active substance	
Authorised indication(s) (section 4.1 SmPC)	
Authorised dosage form(s)	
Authorisation details (Article 57 database)	*MA route:* · *Centralised authorisation procedure* · *National authorisation procedures (+ MSs in which MA is valid)*
New therapeutic use	
Proposed indication	
Unmet medical need or significant public health benefit	
Potential incentives	
Regulatory incentives (e.g. ODD, PUMA)	
IP (e.g. second and further medical uses)	
Other incentives (e.g. H2020 and other grants, support from patient groups)	
Proof-of-concept	
Non-clinical data (*in vitro, in vivo*)	
Clinical trial data and case reports	
Real world data (Post-authorisation studies, registry data)	
Inclusion in clinical guidelines	

Role of key stakeholders	
Champion(s)	
MAHs	
Other stakeholders? (e.g. Regulator, HTA, payer, Patients, HCP, MS health authority)	
Remarks (main obstacles, proposed solutions, etc.)	
References	

Case 1

Docetaxel in hormone sensitive metastatic prostate cancer	
Available product information (in EU)	
Active substance	Docetaxel
Authorised indication(s) (section 4.1 SmPC)	**Breast cancer** · Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with: - operable node-positive breast cancer - operable node-negative breast cancer · For patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer (see section 5.1). · Docetaxel in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition. · Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent. · Docetaxel in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours over express HER2 and who previously have not received chemotherapy for metastatic disease. · Docetaxel in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. **Non-small cell lung cancer** · Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. · Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition. **Prostate cancer** · Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer. **Gastric adenocarcinoma**

	· Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease. **Head and neck cancer** · Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.
Authorised dosage form(s)	Concentrate and solvent for solution for infusion
Authorisation details	**Centralised authorisation procedure (EMA)** Reference product: Taxotere, Aventis Pharma S.A. Available as a generic product in Europe (Docetaxel Teva, Docetaxel Kabi, Docetaxel Accord, Docetaxel Winthrop, Taxespira)
New therapeutic use	
Proposed indication	Docetaxel in combination with androgen deprivation therapy as first-line treatment of metastatic, hormone-sensitive prostate cancer.
Unmet medical need or significant public health benefit	Prostate cancer is the most common cancer in men (approx. 450 000 new cases in Europe in 2018). Even though prostate cancer grows slowly and is often benign, up to 25% of men diagnosed with prostate cancer present with metastases and have an average 5-year survival rate of 30%. Currently, most clinicians prescribe either abiraterone acetate plus prednisone or docetaxel in combination with androgen deprivation therapy as first-line treatment of metastatic, hormone-sensitive prostate cancer. However, docetaxel is prescribed off-label in this indication, while abiraterone is authorised for the indication. So far, these treatments have not been compared directly in randomized trials (1,2). Of note, the overall treatment cost of docetaxel therapy is lower than abiraterone and docetaxel is widely available. Other aspects affecting treatment decision-making include treatment duration and side effects profile, which should be evaluated on a case-by-case basis (1,3).
Proof-of-concept	
Clinical trial data and case reports	**Completed research** Two phase III clinical trials (STAMPEDE and CHAARTED trials) support the use of docetaxel in hormone-sensitive metastatic prostate cancer (4–7). One smaller phase III trial in non-castrate [hormone-sensitive] metastatic prostate cancer (GETUG-AFU 15) obtained conflicting results and therefore, did not recommend docetaxel as part of first-line treatment (8,9). A systematic review and meta-analysis encompassing the evidence from all clinical trials concluded "the addition of docetaxel to standard of care should be considered standard care for men with M1 [metastatic] hormone-sensitive prostate cancer who are starting treatment for the first time" (10). The meta-analysis of the results from the CHAARTED, GETUG-15, STAMPEDE trials (2992 participants in total) showed that addition of docetaxel to standard of care improved survival, HR of 0.77 [95% CI = 0.68 to 0.87; p<0.0001] and reported an absolute improvement in 4-year survival of 9% [95% CI = 5% to 14%]. A recent Cochrane systematic review (Oct 2018) confirmed that the early addition of taxane-based chemotherapy to androgen deprivation therapy for hormone-sensitive prostate cancer probably prolongs overall and disease-specific survival, and delays disease progression, compared to androgen deprivation therapy alone (11).

	Ongoing research (1) A randomized phase III (PEACE-1, NCT01957436) will compare the clinical benefit of androgen deprivation therapy (+ docetaxel) with or without local radiotherapy with or without abiraterone acetate and prednisone in patient with metastatic hormone-naïve prostate cancer. Another phase III trial (ARASENS, NCT02799602) is exploring the effects of darolutamide in men receiving ADT plus docetaxel as their standard of care.
Real world data (Post-authorisation studies, registry data)	Some real-world evidence studies have indicated that the addition of docetaxel to androgen deprivation therapy might be less effective and lead to higher toxicity rate than shown in phase III clinical trials (12–14).
Inclusion in clinical guidelines	· ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Cancer of the prostate. 2015 · European Association of Urology prostate cancer guidelines. 2016 · NCCN Prostate Cancer Guidelines. 2016
Role of key stakeholders	
Champion(s)	Academic group Non-profit or Patient organisation
MAHs	Aventis Pharma S.A. Accord Healthcare Ltd Teva B.V. Fresenius Kabi Deutschland GmbH Hospira UK Limited
Other stakeholders? (e.g. Regulator, HTA/payer, Patients/HCP, MS health authority)	A lot of evidence is already available to support the use of docetaxel as first-line treatment of metastatic, hormone-sensitive prostate cancer in combination with androgen deprivation therapy. Consultation with MAHs, regulators, and HTA could help to understand why docetaxel is still used off-label for the treatment of metastatic, hormone-sensitive prostate cancer and if additional data are required to support a variation application.
Remarks (main obstacles, proposed solutions, etc.)	

- Existing scoring tables, *e.g.* table 9 of KCE report on multi-criteria decision analysis (15), might be useful to provide transparency and agreement about unmet medical needs.

Table 9 – Scoring scale and response category labels for each criterion

Criterion	Response categories and labels
Impact of the disease on life expectancy, given current treatment	0 : The disease has no impact on life expectancy 1 : The disease has some impact on life expectancy (patient loses a small proportion of his remaining life expectancy due to the disease, even if he/she gets the best available current treatment) 2 : The disease has a high impact on life expectancy (patient loses a large proportion of his remaining life expectancy due to the disease, even if he/she gets the best available current treatment) 3 : The disease has a very high impact on life expectancy (patient dies almost immediately, despite the best available current treatment or care)
Impact of disease on quality of life given current treatment	0 : The disease has no negative impact on the quality of life of patients, compared to people without the disease 1 : The disease has some negative impact on the quality of life of patients, compared to people without the disease 2 : The disease has a high negative impact on the quality of life of patients, compared to people without the disease 3 : The disease has a very high negative impact on the quality of life of patients, compared to people without the disease
Inconvenience of current treatment	0 : Current treatment is not or only slightly inconvenient to patients 1 : Current treatment is somewhat inconvenient to patients 2 : Current treatment is highly inconvenient to patients 3 : Current treatment is very highly inconvenient to patients
Frequency of disease	0 : less than 2000 people in Belgium have the condition (less than 1 per 5500) 1 : between 2000 and 10 000 people in Belgium have the condition (between 1 per 5500 and 1 per 1100) 2 : between 10 000 and 100 000 people in Belgium have the condition (between 1 per 1100 and 1 per 110) 3 : more than 100 000 people in Belgium have the condition (more than 1 per 110)
Current disease-related public expenditures per patient	0 : The disease currently has a very small impact on public expenditures per patient 1 : The disease currently has some impact on public expenditures per patient 2 : The disease currently has a high impact on public expenditures per patient 3 : The disease currently has a very high impact on public expenditures per patient

- This case study illustrates the need to provide additional guidance on how to deal with (contradictory) results from clinical trials and RWE-studies.

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Case 2

Combination of 9 repurposed drugs with low-dose chemotherapy	
Available product information (in EU)	
Active substance	Aprepitant Minocyclin Auranofin Captopril Disulfiram Itraconazole Celecoxib Sertralin Ritonavir + Temozolomide
Authorised indication(s) (section 4.1 SmPC)	**Aprepitant** Prevention of postoperative nausea and vomiting (PONV) in adults **Minocyclin** Minocycline is a broad spectrum antibiotic used for the treatment of infections caused by tetracycline-sensitive organisms. Some tetracycline-resistant strains of Staphylococci are also sensitive. (…) **Auranofin** Treatment of rheumatoid arthritis **Captopril** · Hypertension: The management of mild to moderate hypertension. In severe hypertension it should be used where standard therapy is ineffective or inappropriate. · Congestive heart failure: Captopril is indicated for the treatment of congestive heart failure. The drug should be used together with diuretics and, when appropriate, digitalis and beta-blockers. (…) · Myocardial Infarction: - Short-term (4 weeks) treatment: Captopril is indicated in any clinically stable patient within the first 24 hours of an infarction. - Long-term prevention of symptomatic heart failure: Captopril is indicated in clinically stable patients with asymptomatic left ventricular dysfunction (ejection fraction ≤ 40%) following myocardial infarction (…) · Type I Diabetic nephropathy: Captopril is indicated in insulin dependent diabetics for the treatment of macroproteinuric diabetic nephropathy (microalbuminuria greater than 30 mg/day) (see section 5.1). **Disulfiram** Treatment of chronic alcoholism **Itraconazole** · Vulvovaginal candidiasis, Oral candidiasis, Dermatophytoses caused by organisms susceptible to itraconazole, Pityriasis versicolor, Onychomycoses caused by dermatophytes and/or yeasts, Systemic candidiasis, Cryptococcal infections (including cryptococcal meningitis), Histoplasmosis, Aspergillosis, Maintenance therapy in AIDS patients to prevent relapse of underlying fungal infection who were found to be refractory or intolerant to first-line systemic anti-fungal therapy is inappropriate or has proved ineffective. **Celecoxib** Symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. **Sertralin** Treatment of major depressive episodes, prevention of recurrence of major depressive episodes, panic disorders, obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years, social anxiety disorder,

	Post traumatic stress disorder (PTSD) **Ritonavir** In combination with other antiretroviral agents for the treatment of HIV-1 infected patients
Authorisation details	**Aprepitant** Centralised procedure **Minocycline** National procedure **Auranofin** National procedure **Captopril** National procedure **Disulfiram** National procedure **Itraconazole** National procedure **Celecoxib** National procedure **Sertralin** National procedure **Ritonavir** National procedure
New therapeutic use	
Proposed indication	Glioblastoma multiforme (GBM)
Unmet medical need or significant public health benefit (including positive budgetary impact)	GBM is the most common and most aggressive type of brain tumors in humans. It is a rare cancer type, affecting 2-3 people annually per 100,000 in Europe and North America. Currently available treatment consists of surgery, radiation, and chemotherapy using temozolomide. In general, only 15-20% of patients are still alive 5 years after first treatment. Although there is a SOC for primary GBM, there is a clear unmet medical need for more and better options for recurrent patients with GBM.
Proof-of-concept	
Clinical trial data and case reports	The rationale behind the combination of nine repurposed drugs is that each drug would inhibit one or more important growth-enhancing pathways used by GBM, thus increasing the effectiveness of temozolomide (1). Similar drug combinations of the original CUSP9-protocol have been well tolerated when given on a compassionate-use basis (2). A phase I clinical trial (NCT02770378) has been completed and has shown that the CUSP9v3 protocol appears to be safe (3). However, it is not possible yet to draw any conclusions on efficacy. Additional clinical studies are required.
Inclusion in guidelines (e.g. for treatment or reimbursement)	No
Role of key stakeholders	
Champion(s)	Academic group, Anticancer Fund or patient organisation
MAHs	> 50 in total

Other stakeholders? (e.g. Regulator, HTA/payer, Patients/HCP, MS health authority)	Regulators could help to determine the most adequate regulatory pathway to bring this unique drug combination on-label in case it proves to be effective in clinical trials.

Remarks (main obstacles, proposed solutions, etc.)

- Liaising with all involved MAHs would be very complicated for the champion.
- Authorisation details are difficult to collect for all these medicines.
- Unclear what regulatory pathway should be followed to bring this combination on-label. Medicines would be administered in same dosage form as specified in original MA.

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STAMP 10/44
Objective 3

STAMP Working Group

– Supporting Materials and Communication

November 2018

STAMP Working Group – supporting materials and communication

Initial ideas for the supporting materials and communication activities were briefly discussed in a teleconference.

There is already information and guidance related to the process for the authorisation of medicines, including the research and development stage as well as the procedure to obtain a marketing authorisation. However, non-industry researchers may not be aware of these documents which include information relevant to the scientific aspects of a dossier to support an application for a new indication. A means to make these more visible and accessible could promote and support the collection of robust evidence.

As a way to support the connection of the Champion with interested marketing authorisation holder(s) it was suggested that there could be a public space where the Champion could voluntarily make available the scientific advice they had received.

The "Article 57" database of marketing authorisations was suggested as a way for Champions to identify potential marketing authorisation holders who could make an application for an extension of indication. However, it can be difficult for the Champion to identify the relevant contact in the company. Therefore, the identification of a specific contact point in a company for a Champion would facilitate this communication.

The piloting of the proposed framework would allow the identification of gaps in or aspects of the available guidance that might need to be further developed.

The discussions in STAMP have been made public through the information available on the STAMP webpage and through presentations to conferences and other events. The group considered that the activity that had been done so far could be highlighted through a commentary or article in an independent publication.

Other ideas for promoting the pilot and final repurposing framework could be through stakeholder networks, and social media.

Outstanding aspects:

1. Is there a need for the development of a specific "toolbox" for the repurposing framework?
2. How to facilitate the collaboration of the Champions and industry? Any previous experience?
3. How to reach out to the potential Champions? How the increase awareness of the marketing authorisation holders who could take forward an application to include a new indication in their product information?
4. How do we move the theoretical framework to the practical application? Who or which groups should lead on generating the supporting documents and processes?
5. What would be relevant for the EU CSA STARS (Strengthening training of academia in regulatory sciences & supporting regulatory scientific advice) to consider in their activities that would support the proposal for a repurposing framework?

STAMP stakeholders identified some additional outstanding aspects to be further discussed before concluding on repurposing within the regulatory framework.