# From Proof of Concept to Basis for Initial Marketing Authorization, HTA Appraisal and Reimbursement: Clinical Phase II in the Context of Adaptive Pathways

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KEY POINTS . . .

There are already precedents of drugs approved and reimbursed on the basis of phase II data which can be seen as evidence of an adaptive pathways approach.

For the 8 products analyzed in detail for this article, the majority was reimbursed in France and Germany but only a minority obtained HTA endorsement in the UK.

Overall, a more generalizable Adaptive Pathways approach will require a paradigm shift in the approach to the clinical phase II with inclusion of additional endpoints (e.g., quality of life and health care utilization data, harder endpoints of patient morbidity and mortality) and head-to-head comparison versus standard of care.

## Adaptive Pathways

Discussions about more flexible and iterative approaches to medicines development have been placed under the heading Adaptive Pathways (AP). On March 19, 2014, the European Medicines Agency (EMA) launched the Adaptive Licensing Pilot project (from now on referred to as Adaptive Pathways, or AP). The EMA has published an interim report of the pilot [1]. According to this report, "Adaptive Pathways is an opportunity for early brainstorming discussion among all relevant stakeholders, including regulators, companies, health technology assessment (HTA) bodies and patient representatives, to explore ways to optimize development pathways and potentially accelerate patients' access to medicines. This faster access may be achieved by shorter time to approval and/or reimbursement decision for targeted groups of patients." The EMA already has processes in place for medicines to obtain conditional marketing authorization or marketing authorization under exceptional circumstances and on the basis of less data than would be required via the standard procedure, which may enable earlier marketing authorization. On the other hand, payers and HTA bodies have clear and increasing expectations on evidence in terms of comparative data and "hard endpoints" (i.e., measures of morbidity and mortality they are willing to accept as proof of a patient-relevant benefit). A key question remains how payers and HTA bodies will assess medicines in the context of AP and potentially adjust their evidence requirements in the initial phases of a medicine's introduction before the full body of evidence is available.

## Clinical Phase II in the Context of Adaptive Pathways

Traditionally, the clinical phase II was regarded as "proof of concept" with trials focusing on surrogate endpoints and limited or no collection of quality-of-life and health care utilization data. AP may require a paradigm shift in improving and enriching phase II data generation if it is to serve as a basis for conditional marketing authorization and HTA appraisal / reimbursement. Three key questions need to be considered:

1. Should phase II trials for medicines potentially qualifying for AP tend towards including the same endpoints (at least as secondary endpoints) and breadth of data collection as phase III trials even if they may not have sufficient power to produce statistically significant results on a number of endpoints?

2. Under which circumstances will payers and HTA bodies accept statistically significant data on surrogate endpoints and trend data on harder endpoints for conditional HTA appraisal / reimbursement?

3. Under which circumstances will uncontrolled trial data be sufficient for conditional HTA appraisal / reimbursement? Under which circumstances should an active comparator be included in the phase II?

For this article, we interviewed participants in the AP pilot from the French Haute Autorité de Santé (HAS), the Gemeinsamer Bundesausschuss (G-BA), the National Institute for Health and Care Excellence (NICE) from the United Kingdom (UK), and the industry. Furthermore, the list of medicinal products under additional monitoring was accessed on the EMA website on 28th of January 2015 [2], and products approved under conditional marketing authorization were extracted. Conditional marketing authorization is closely linked to the concept of iterative development as it implies the expectation of additional evidence generation. Only products approved based on phase II data were included in the further analysis—a total of 8 products (although 1 had preliminary phase III data). HTA appraisals for France, Germany, and the UK (NICE and Scottish Medicines Consortium [SMC]) were analyzed [3-6]. A summary is provided in Table 1.

In France, 7 of the 8 products are available and reimbursed. In the 6 appraisals available, 1 ASMR II, 1 ASMR III, 2 ASMR

IVs and 2 ASMR V were given, (i.e., for 4 of the 6 products appraised, the HAS saw a therapeutic improvement). In Germany, 7 of the 8 products are available and reimbursed. All 4 products appraised were recognized to provide an added benefit. In the UK, none of the products has been recommended by NICE, and only 2 have been appraised by NICE. Three products have been recommended by the SMC. It should be noted that all were not initially recommended by the SMC, but a re-evaluation taking into account either a patient access scheme or SMC's ultra-orphan medicine process overturned the initial decision.

## Endpoints

All 8 products used surrogate parameters as primary endpoints in their trials, although some included harder endpoints as secondary endpoints. All HTA bodies have in common that evaluations will primarily be based on statistically significant results on validated endpoints. In terms of consideration of trend differences for HTA appraisal, there are significant differences across HTA bodies. The G-BA has high reservations in this regard and would only consider them as informative in the case of orphan drugs when there is a credible rationale why statistically significant results cannot be produced, (e.g., due to the difficulty of including a sufficient number of patients in a clinical trial). The HAS shares the same reservations, but would at least consider trend differences as informative as they may indicate the magnitude of effect that can be expected from further trials. This may serve to define a pre-agreed threshold against which the actual effect measured in post-launch observational data could be benchmarked. NICE will also place highest emphasis on statistically significant data, but are most open in considering the value of information of trend differences.

**Table 1: HTA appraisals of products approved under conditional marketing authorization**

| Product (EMA authori-zation) | Trial Data and control | Primary Endpoint and results | France HAS appraisal & reimbursement status | Germany G-BA appraisal & reimbursement status | UK NICE/SMC appraisal & reimbursement status | Orphan Drug |
|---|---|---|---|---|---|---|
| Arzerra (2010) | Phase II No control | • 52% overall response over 24 weeks<br>• 58% subgroup patients refractory to fludarabine and alemtuzumab | • SMR: moderate (provisional)<br>• ASMR V<br>• Hospital use only | • No G-BA appraisal [launch before AMNOG]<br>• Reimbursed | • NICE: not recommended<br>• SMC: Initially not recommended, then restricted use accepted given PAS | Yes |
| Bosulif (2013) | Phase I/II No control | Major cytogenetic response at week 24: 26,9% in chronic phase CML – previous treatment with imatinib and dasatinib or nilotinib | • SMR: substantial<br>• ASMR V<br>• Reimbursement rate 100% | • Added Benefit: Yes [as orphan drug] but not quantifiable<br>• Reimbursed | • NICE: not recommended<br>• SMC: Initially not recommended, then restricted use accepted given ultra orphan medicine process and PAS | Yes |
| Adcetris (2012) | Phase II No control | Overall response rate: 75% | • SMR: substantial<br>• ASMR III<br>• Hospital use only<br>• Nominative ATU since 01/2011 and cohort ATU since 08/2012 | • Added Benefit: Yes [as orphan drug] but not quantifiable<br>• Reimbursed | • NICE: not appraised<br>• SMC: Initially not recommended, then restricted use accepted given ultra orphan medicine process | Yes |
| Erivedge (2013) | Phase II No control | Percentage of objective response:<br>• mBCC- 30.3%<br>• laBCC-42.9% | • SMR: substantial<br>• ASMR IV<br>• Reimbursement rate 100%<br>• Nominative ATU prior to MA | • mBCC: no added benefit proven<br>• laBCC: Indication of minor added benefit<br>• Reimbursed | • NICE: not appraised<br>• SMC: not recommended [absence of submission] | No |
| Sirturo (2014) | Phase II Placebo | • Decreased time to culture conversion Sirturo vs. placebo (83 days compared to 125 days at week 24) | • 6-month pack size not validated by ANSM<br>• While awaiting 1-month pack cohort ATU | Benefit assessment stopped, reimbursement exclusion due to pack size | • NICE: not appraised<br>• SMC: not appraised | Yes |
| Deltyba (2014) | Phase II Placebo | • 53% increase sputum culture conversion after two months compared to placebo | No appraisal available | • Exempt from benefit assessment due to low budget impact<br>• Reimbursed | • NICE: not appraised<br>• SMC: not appraised | Yes |
| Trans-larna (2014) | Phase IIb Placebo | • 6 Minute Walk Test: no statistically significant difference primary analysis<br>• Post-hoc ITTc analysis suggested difference | • SMR: moderate<br>• ASMR IV<br>• Cohort ATU 7/2014<br>• 100% reimbursement via retrocession list | • Minor added benefit<br>• Reimbursed | • NICE: Proposed for highly specialised technology evaluations, no appraisal at time of writing<br>• SMC: not appraised | Yes |
| Votubia (2011) | Phase II + Prel. Phase III<br>PII: no control<br>PIII: placebo | • Response rate (phase III): 34.6% over placebo<br>• Change in SEGA volume after 6 months (phase II): 0.83 $cm^3$ | • SMR: substantial<br>• ASMR II<br>• Reimbursement rate 100% | • No G-BA appraisal<br>• Reimbursed | • NICE: not appraised<br>• SMC: not recommended [absence of submission] | Yes |

*AMNOG indicates The Arzneimittelmarkt-Neuordnungsgésetz; ANSM, Agence Nationale de Sécurité du Médicament et des Produits de Santé; ASMR, Amélioration du service medical rendu / improvement of the medical benefit; ATU, Temporary Authorisation for Use; CML, chronic myelogenous leukemia; EMA, European Medicines Agency; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; iTTc, Intent to Treat corrected; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basic cell carcinoma; NICE, National Institute for Health and Care Excellence; PAS, Patient Access Scheme; SEGA, subependymal giant cell astrocytoma; SMC, Scottish Medicines Consortium; SMR, Service Médical Rendu / medical benefit; UK, United Kingdom.*

NICE will consider trend differences as lower grade evidence, which can increase uncertainty in decision making. For the 8 products, HTA appraisals were mainly driven by the statistically significant results on the primary endpoint. However, several appraisals noted the availability of data on harder endpoints, especially when overall survival or progression-free survival data were reported.

## Comparators

Many drugs approved via conditional marketing authorization so far have confronted HTA bodies with the difficulty of evaluating a therapy when the information they value most (i.e., head-to-head data vs the appropriate comparator) is missing. None of the 8 products conducted a head-to-head trial versus an active comparator.

is limited to determine the extent of the added benefit. Seven out of the 8 drugs were orphan drugs, and for each drug where an appraisal was published, the G-BA found an added benefit (although the G-BA concluded there was not enough evidence to quantify the added benefit for 2 drugs). Erivedge is the only drug without orphan drug status in our analysis, but here the G-BA found a minor added benefit for the locally advanced basal cell carcinoma population that is not suitable for surgery or radiotherapy (i.e., a segment where no therapeutic alternative exists).

## Summary and Future Outlook

There are already precedents of drugs approved and reimbursed on the basis of phase II data which can be seen as evidence of an AP approach. However,

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The HAS representative noted that it is very important for HTA bodies to have head-to-head data, but there can be differences between countries in the choice of an appropriate comparator or even the dose considered. In the context of AP, it is important to have early discussions on this and agree upon the exceptions from the general rule of running head-to-head trials on a case-by-case basis. The advantage of AP is having those discussions ahead of time using a safe harbor approach. The HAS accepted the majority of the 8 products despite the absence of head-to-head data. However, in order to expand the scope of AP to other therapy areas and a larger number of products, head-to-head data may be required. The NICE representative noted that whether a comparator will be required will largely depend on the level of unmet need. However, providing head-to-head data will reduce uncertainty for NICE and increase the chances of a positive recommendation. Risk-sharing was mentioned as a way to mitigate uncertainty in the absence of head-to-head data. For the G-BA, head-to-head data on patient-relevant added benefit versus the relevant comparator ("Zweckmäßige Vergleichstherapie") is the main driver of the decision. For orphan drugs, an added benefit is assumed by law and the role of the Institute for Quality and Efficiency in Healthcare and G-BA the evidence of this remains anecdotal and mostly applies to orphan drugs. It remains to be seen whether the AP concept will be broadened to include additional therapy areas and a larger number of products. For the 8 products analyzed in detail for this article, the majority was reimbursed in France and Germany, but only a minority obtained HTA endorsement in the UK. While the conditional marketing authorization in itself can be seen as regulatory success for the 8 products in question, the HTA success is best described as mixed, especially when taking into account the low number of products recommended in the UK.

For phase II trials, choosing a surrogate parameter as primary endpoint will remain the best option in order to maximize the chances of statistically significant results. Early AP discussions bear the potential to reach a consensus with the EMA, payer, and HTA bodies on a mutually agreeable surrogate endpoint. In terms of secondary endpoints, there is some evidence that suggests that including harder endpoints is beneficial and can receive recognition in HTA appraisals, although the sample is too small to identify a consistent pattern. However, for a broader application of the AP concept, payers and HTA bodies are likely to require either very significant effect sizes on surrogate parameters or supportive data on harder endpoints that should be included as secondary endpoints.

For the products analyzed, the absence of an active comparator has not led to access being denied in France and Germany, but it is likely to have contributed to mixed HTA success in the UK. However, all HTA bodies have noted the absence of comparative data. For the expansion of the AP concept beyond orphan drugs, comparative data are likely to be required.

Overall, a more generalizable AP approach will require a paradigm shift in the approach to the clinical phase II trial design. This may require the pharmaceutical industry to take on greater risks , but several years of earlier market access can be the reward—and in many cases, justify a higher investment at risk. The paradigm shift applies to both big pharma and biotechs and small and medium-sized enterprises. The latter should have a particular interest in the AP approach as it may enable them to take products into the early phases of commercialization by themselves. And big pharma buyers may be more willing to consider the likelihood and preparation of an AP approach in their licensing and acquisition decisions.

### References

[1] European Medicines Agency (EMA). Adaptive pathways to patients: report on the initial experience of the pilot project. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500179560.pdf. [Accessed January 28, 2015]. [2] European Medicines Agency (EMA). List of medicines under additional monitoring. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp. [Accessed January 28, 2015]. [3] HTA appraisals sourced from: Haute Autorité de Santé (HAS). Available at: http://www.has-sante.fr/portail/. [Accessed April 20, 2015]. [4] HTA appraisals sourced from: National Institute for Health and Care Excellence (NICE). Available at: https://www.nice.org.uk/. [Accessed April 20, 2015]. [5] HTA appraisals sourced from: Gemeinsamer Bundesausschuss (G-BA). Available at: https://www.g-ba.de/. [Accessed April 20, 2015]. [6] HTA appraisals sourced from: Scottish Medicines Consortium (SMC). Available at: https://www.scottishmedicines.org.uk/Home. [July 19, 2015]. ■