Background
One of the major determinants of medicine prices in the EU markets is the external reference pricing (ERP) system, used to mitigate the public health-care expenditure.

Studies show that aggressive ERP rules and consequently low price levels may indirectly affect the availability of medicines in several ways. To protect global revenue, marketing authorisation holders may delay, sequence or withhold launch of a medicine in countries with such conditions.[2]

Objectives
Our work aimed to analyze the consequences of ERP rules for both companies and the national authorities through optimal market access timing. The following analyses were done over a 5-year time horizon:

- The impact of various launch sequence strategies on projected earnings
- The evolution of the average price for each strategy
- Total price erosion per country at the end of the simulation

Methods
An ERP sequence simulation was developed to determine the country-level price evolution over time. ERP rules and baskets (as of March 2016) for individual countries were implemented. Revenues were estimated on the basis of additional country data (willingness to pay, population size, frequency of price revisions, currency volatility).

Initial conditions
- A fictional medicine was present on the market in the following countries:
  - Finland
  - Germany
  - Luxembourg
  - United Kingdom
  - An initial price of the medicine was 1.005 USD in all countries
  - The medicine was launched to 25 EEA countries
  - The whole launch sequence consisted of 60 rounds, each round simulating a month, together 5 years
  - During the first 25 rounds, the medicine was consequently launched in individual markets
  - External price referencing was implemented from the first round until the end of the simulation. Each country could reference according to their ERP rules, referencing to the previous prices of their basket countries
  - Willingness to pay of a country was considered
  - Currency volatility affected the prices
  - Expected revenues were calculated based on the evolution of the medicine’s price, country population and disease prevalence (equal in all countries)
  - The initial country order in the launch sequence was chosen based on four launch sequence strategies (Table 1)
  - GDP strategy: by order of GDP per capita in PPP Int$ (largest to smallest)
  - POP strategy: by order of population size (largest to smallest)
  - CHE strategy: by order of health expenditure (largest to smallest)
  - RAN strategy: random sequence (for comparison)

Genetical Algorithm
A genetical algorithm was developed to search for a launch sequence which would maximise the revenues. The most successful sequences obtained during the search were then evaluated as a separate strategy called “best genetical sequence” (BGS).

A genetical algorithm is a search heuristic that is inspired by the theory of natural evolution. This algorithm reflects the process of natural selection where the fittest individuals (sequences) are selected and then combined to produce new (potentially superior) sequences.[2]

Results
Performance of the initially defined strategies
Four initial strategies were tested to obtain prices and projected revenues, calculated based on the evolving prices, determined by the ERP strategy (Figure 1).

Subsequently, the products remained on market in all countries until the 56th year mark (86th round) It can be seen that they differed in their revenue per round mainly in the launch portion of the simulation. After that, they had similar revenue per round, since they already had the product in the same set of countries.

Search for the best strategy
A new strategy was defined as the best sequence found by the genetical algorithm search (best genetical sequence - BGS). The algorithm was designed to maximise the total revenue of a sequence. The resulting sequence BGS is shown in Figure 4. Although we see it originally produced a better result than the RAN, CHE and GDP strategy, it didn’t manage to achieve a superior revenue to the population strategy (POP).

A detailed comparison of final revenues is found in the Figure 5. The POP strategy succeeded the BGS strategy by 7.5% (245 million $). The GDP strategy had the lowest total revenue, lagging behind POP strategy by 91.5% (2.3 billion $).

Price evolution of the selected strategies
Price evolution for the selected strategies is shown in the Figure 4. The average price of the medicine across countries for tested strategies is shown in the Figure 5. The BGS strategy had the lowest average price, followed by the CHE strategy.

Total price erosion in countries with ERP system
The best performing strategy (POP) in terms of total revenues was used in the analysis of total price erosion across countries using the ERP same environment. Figure 5 shows the final percent reduction of the first established price in a country: Poland (-25%), and Romania (-25%) experienced the most aggressive erosion. On the other side, Ireland (-7%) and Denmark (-6.9%) experienced the mildest price erosion. The average price erosion was -17%. We see that with a few exceptions, countries which are referenced most frequently generally encounter more extensive price erosions.

Conclusions
Our analysis provides a notion of how the companies consider the launch of an innovative product on the EU market. We defined four baseline strategies, which served as a benchmark for maximising revenues. In contrast, the strategy of launching to countries with the highest population first (POP strategy) was the winning one, prevailing over the least successful strategy by 9%. The search for optimised sequence by the genetic algorithm improved the performance from baseline strategies, but lagged in total revenues behind the winning strategy by 7%.

We found that different strategies did not have a strong impact on the evolution of the average price, it staying roughly within 1% range across all strategies. The analysis of price erosion found substantial differences across countries, with a span from -7% to -23% of the initial prices.

The apparent consequence of launch sequencing can be delays in the availability of innovative medicines, negatively affecting predominantly countries with smaller markets and aggressive ERP rules. Countries with higher population size, small ERP basket and value-based pricing can reasonably prioritise market entry. In addition, companies may occasionally avoid disclosing the "real" price of the medicine by setting up contractual agreements with health insurance funds or single national fund (44-46).

The suggestion for national policies on how to keep prices of pharmaceuticals low while ensuring their good availability could be setting weaker ERP rules (e.g. overviews rather than minimum price / fewer basket countries and take advantage of confidential price discounts, which reduces the risk of further price erosion in other markets and increases the appeal of such markets for companies.

References