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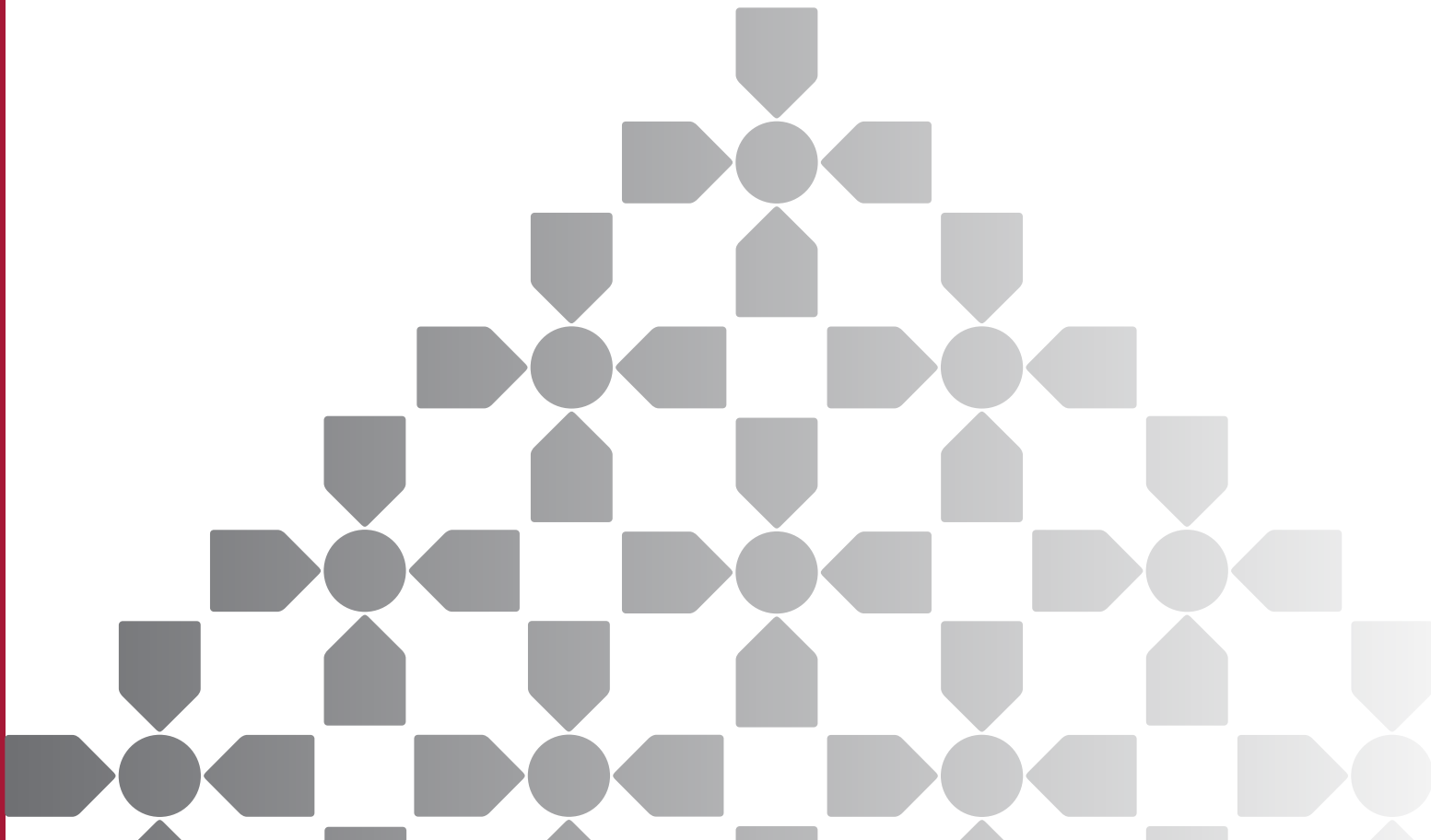

Taking the competitor's pill: when combination therapies enter pharmaceutical markets*

Kurt R. Brekke† Dag Morten Dalen‡ Odd Rune Straume§

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Abstract

We study the competitive effects of combination therapies in pharmaceutical markets, which crucially hinge on the additional therapeutic value of combinatory use of drugs and the therapeutic substitutability with the most relevant monotherapy. With large additional therapeutic value, the introduction of combination therapies leads to higher prices and, somewhat paradoxically, may reduce the health plan's surplus. Although combination therapies imply that drugs become both substitutes and complements, we show that drug prices increase if the firms are allowed to coordinate their prices. Allowing for price discrimination might increase allocational efficiency, but only at the expense of higher purchasing costs.

Keywords: Pharmaceutical markets, Combination therapies, Therapeutic competition

JEL Classification: I11; I18; L13; L65.

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1 Introduction

Advances in medicine and pharmaceutical innovations not only increase the number of drugs that can be used to treat specific diseases, they also drastically improve our ability to target and personalise treatment. This is partly achieved by combinatory use of several novel drugs within the same therapeutic class. According to Wu et al. (2015), our fast-improving understanding of biological systems is increasingly being used to identify novel therapeutic options among already available sets of drugs. Targeted combination therapies are used to enhance treatment efficacy, better prevent the development of resistance, or reduce adverse side effects.

Historically, combination therapies often consisted of a new patented drug that was used in combination with older off-patent drugs. More recently, though, it has become more common to target diseases with a combination of two or more on-patent drugs. A large-scale review of clinical trials from 2008 to 2013 showed that 25 percent of all cancer trials studied combination therapies, whereas close to 20 percent of all trials for treatment of viral and digestive diseases involved various combination therapies (Wu et al., 2015).

An improved therapy may consist of a combination of patented drugs already approved as monotherapies. In some cases, these are produced by the same pharmaceutical company, but it is also common that drugs from several companies are approved as a combination therapy. When pharmaceutical companies are launching new drugs, therefore, these are not only subjected to various degrees of therapeutic competition as monotherapies. They will also have the potential of adding therapeutic value to competitors' drugs when used in combination. In this way, biotechnology and precision medicine create pharmaceutical markets for therapies that can be both substitutes and complements for different subgroups of patients.

Although approval of combination therapies is recognised as a challenge for health technology assessment (Latimer et al., 2021, and Danko et al., 2019), the effects of combination therapies for competition and drug prices, and patients' access to these drugs, remain unexplored. In this paper we develop a theoretical model to investigate how this unique, and increasingly important, feature of pharmaceutical markets affects competition and efficiency. A better understanding of how market outcomes are affected by the introduction of combination therapies is important, both for understanding the incentives to invest in clinical trials with several drugs in the first place, and for identifying potential inefficiencies in patients' access to the different treatment options.

Although treatment of patients with diagnoses such as HIV/AIDS, hepatitis C and diabetes have long been improved by using a combination of drugs, cancer treatment is an area in which combination therapies have become particularly important (Persson and Norlin, 2018). Ten years ago, patients with diagnoses such as melanoma or lung cancer, which do not respond well to traditional methods such as chemotherapy and radiotherapy, received a grim prognosis (Torjesen, 2019). By unleashing the body's immune system to attack tumors, immunotherapy can now prolong the lives of many of these patients.

In 2014 FDA approved Keytruda, produced by Merck, which was the first immunotherapy of this class for patients with melanoma. Since then, additional drugs within the same class have been approved, including Opdivo and Yervoy, produced by Bristol-Myers Squibb. Results from clinical studies have supported the approval of a combinatory use of these drugs (Rotte, 2019). According to IQVIA (2022) there were 5761 ongoing trials testing existing and new variants of such immunotherapies, and nearly 90 percent of the clinical trials that started in 2021 were investigating their use in combination immunotherapies. According to the same report, monotherapy trials have been declining.

Another recent example of branded drugs from several companies constituting a combination therapy is found in the treatment of myeloma patients. These are patients with a type of blood cancer that can be treated, although not yet cured, with several drug options. Janssen produces the drug Darzalex and Bristol-Myers Squibb produces the drug Revlimid. Both drugs have been approved as monotherapies within the same therapeutic area, and in 2019 FDA approved a combinatory use of the two. In 2023, the same combination therapy was recommended in the UK by the National Institute for Health and Care Excellence (NICE) for a subgroup of patients.[1]

It seems well documented, therefore, that combination therapies with several novel drugs, often produced by different companies, will play an increasingly important role in pharmaceutical markets. The European Federation of Pharmaceutical Industries and Associations (EFPIA) recently identified competition and efficiency in markets for combination therapies as a key policy issue:

> "If the constituents of the combination are produced by different manufacturers, the companies may not be able to coordinate directly with each other due to concerns of infringing anti-trust regulations designed to prevent price collusion, even though

[1] https://www.nice.org.uk/guidance/gid-ta10914/documents/html-content-6 (accessed October 2023)

a mutually beneficial, and societally positive, agreement is possible that improves patient access to combination therapies."[2]

To the best of our knowledge, our model represents the first attempt to capture the presence of combination therapies when analysing competition and price setting in pharmaceutical markets. In this setup, patients face several treatment options, including combination therapies. We model a spatial competition framework with two on-patent drugs that constitute up to three treatment options, and a distribution of patients who differ with respect to their therapeutic match with each of the three options: monotherapies or a combination therapy with both drugs. In this way, we capture the importance of individual patient characteristics, as revealed by predictive biomarkers, both for selecting drugs and evaluating the efficacy and tolerance of combinations (see Brekke et al., forthcoming). Our model allows these therapies to have different maximum treatment effects (vertical differentiation) and different treatment effects for given patient characteristics (horizontal differentiation).

With two therapeutically substitutable drugs (monotherapies) in the market as a starting point, we analyse the effect of adding a combination therapy to the health plan, with particular focus on the effect on drug prices, the health plan's total purchasing costs, profits, and efficiency in the allocation of patients to the three treatment options. We show that combination therapies can have a pro-competitive effect on prices, but this depends crucially on (i) the additional therapeutic value of the combination and on (ii) the therapeutic substitutability between the combination treatment and the relevant backbone monotherapy.

We identify two countervailing effects on drug prices of approving a combination therapy: market expansion and competition on the margin. When the relevant drug reaches new groups of patients that otherwise would have used the competitor's drug as monotherapy, the market expands for a given price. All else equal, this has the anti-competitive effect of increasing the optimal price. However, the introduction of a combination therapy also makes each firm's drug demand more price responsive, since a lower price will increase the number of patients given the combination treatment. All else equal, this has a pro-competitive effect by lowering optimal drug prices. If the therapeutic value of the combination therapy is sufficiently large, the anti-competitive effect of approving the therapy dominates and, somewhat paradoxically, may lower the health plan's surplus. Furthermore, since market power prevails, with equilibrium prices

[2] www.efpia.eu/media/ue5fxxj4/access-to-oncology-combination-therapies-in-europe-todays-challenges-and-solutions.pdf (accessed October 2023).

above marginal costs of production, too few patients are shown to transition from the more relevant monotherapy to the approved combination therapy.

Since the two drugs are both substitutes and complements, there are both negative and positive externalities of unilateral price increases. In our setup, the positive externality always dominates. This has important policy implications. If the two firms illegally collude or legally negotiate a common price policy protected with a 'safe harbour' arrangement with the competition authority (Latimer et al., 2021), prices and profits will increase, with a corresponding increase in the health plan's drug purchasing costs.

We also consider the effects of so-called indication-based pricing, where the drug producers are allowed to price discriminate between different uses of the same drug; i.e., whether the drug is used as a monotherapy or as part of a combination therapy. We show that this could potentially increase patients' access to combination therapies and therefore improve allocational efficiency, but only at the expense of higher purchasing costs for the health plan.

The rest of the paper is organised as follows. In the next section we discuss the related literature. In section 3 we present the model. In Section 4 we analyse the benchmark case with monotherapies, without approved combination therapies. In Section 5 we characterise the effects on prices, drug costs, profits and efficiency of approving combination therapies. This section also includes an analysis of both price coordination and price discrimination. In Section 6 we test the robustness of the main analysis by relaxing a key simplifying assumption. Finally, in Section 7 we provide some concluding remarks.

2 Related literature

There is very little economics research concerned with combination therapies. The important contribution of the few existing papers has been the identification of challenges such therapies create for health technology assessment (HTA) bodies and health plans. Persson and Norlin (2018) present stylised examples of how a new drug used in combination may not be cost effective even at zero price. This can be the outcome if the new drug prolongs survival, with a need for continued use of the existing anchor drug. To be cost effective, the producers of drugs included in combination need to be willing to adjust their prices. This problem is claimed to be mitigated by allowing for price discrimination, but this is unusual in practice.

Danko et al. (2019) conduct a literature review to identify challenges specific to combina-

tion therapies. Their review confirms the challenge of proving cost-effectiveness of combination treatments with therapeutic value. In line with Persson and Norlin (2018), this can be partly solved by more flexible pricing schemes. Since drugs used in combination can be produced by different companies, they address the risk of violating the competition law by implementing flexible pricing. Companies could gain from coordinating prices of the drugs, while being competitors in other markets for monotherapies. Similar challenges have been discussed by other authors as well (see Latimer et al., 2021a, 2021b; Towse et al., 2021, 2022).

Although combination therapies are getting much attention from payers, HTA bodies, and the pharmaceutical industry, the literature has so far identified key policy challenges that needs to be addressed. Our paper differs substantially from these studies in that we focus on competition and the strategic interaction between producers of drugs that can be used in combination. To the best of our knowledge, the impact of combination therapies on competition strategies for pharmaceutical companies has not yet been studied in the existing literature. In addition to advancing the theoretical framework for studying competition in pharmaceutical markets, our paper provides a first step towards a more systematic analysis of the incentives to launch combination therapies and providing efficient access to these for patients.

Our framework for analysing competition in the pharmaceutical market builds on a strand of literature that uses a spatial framework. In this framework, drugs are both horizontally and vertically differentiated (see for example Brekke et al., 2007, Miraldo, 2009, Bardey et al., 2010, Bardey et al., 2016, Brekke et al., 2016, Gonzàles et al., 2016, and Brekke et al., 2022 and 2023). Among these, the general set-up in our paper relates most closely to the spatial formulation in Miraldo (2009) and Brekke et al. (2022, 2023). Like Brekke et al. (2022), we allow the health plan to decide on the market access of the drugs.

A key assumption in these models is that a given therapeutic class contains several drugs with different active ingredients. Although these drugs are not perfect substitutes, empirical research supports the assumption that treatment effects can be sufficiently overlapping to establish therapeutic competition. Danzon and Epstein (2012) found that prices of new drugs are influenced by prices of other products in the same class. Lu and Comanor (1998) analysed therapeutic competition and found that launch prices of drugs that are closer substitutes to existing brands are typically priced at comparable levels. In addition, they found that the number of branded substitutes has a substantial negative effect on launch prices.

3 Model

Consider a therapeutic market for on-patent drugs with two therapeutically differentiated drugs, denoted 1 and 2, and a unit mass of patients who differ with respect to their therapeutic benefit of drug treatment. A monopoly health plan purchases the drugs from the producers and decides which treatments are available to the patients. Suppose first that only drug treatments with either one or the other drug are available, what we henceforth refer to as *monotherapies*. Suppose further that a share λ of the patients can be successfully treated only with one of the two drugs. More specifically, we assume that a share $\lambda/2$ of the patients need one unit of drug 1, while a similar share must be treated with one unit of drug 2. Both drugs, therefore, represent a so-called *backbone therapy* for some share of the patients. For the remaining $1-\lambda$ patients, the two drugs are therapeutically substitutable and for each of these patients, the therapeutic benefit of drug 1 is given by $v-\tau x$, while the therapeutic benefit of drug 2 is given by $v-\tau\left(1-x\right)$, where the therapeutic mismatch value x is a random draw from a uniform distribution on $[0,1]$, and where (the inverse of) the parameter $\tau>0$ measures the degree of therapeutic substitutability between the two monotherapies.

Among the patients for whom the two drug treatments are therapeutically substitutable, treatment choices are made by a physician who considers both therapeutic benefits and treatment costs. More specifically, we assume that, for these patients, the utility assigned to each treatment choice by the physician is given by

$$U=\begin{cases} v-\tau x-\alpha p_1 & \text{if prescribing drug 1} \\ v-\tau\left(1-x\right)-\alpha p_2 & \text{if prescribing drug 2} \end{cases}, \tag{1}$$

where p_i is the price of drug $i=1,2$ and the parameter $\alpha\in(0,1]$ measures the price sensitivity of the physician's treatment choice. We can think of the physician as being an agent for both the patient and the health plan. In the special case of $\alpha=1$, the physician takes drug prices fully into account and acts as a perfect agent for a health plan that maximises total health benefits net of purchasing costs. However, in the more general case of $\alpha<1$, the physician is more concerned about treatment benefits than treatment costs.

Finally, we assume that each drug is produced by a different profit-maximising firm that can produce the drug at a constant marginal cost which, without further loss of generality, is set equal to zero, and which in turn implies that the total profits are equal to the total purchasing

costs of the health plan. In the following, we assume that each firm can freely set the price of its drug, and we derive the Nash equilibrium outcome of a price-setting game under different assumptions regarding the available set of treatment options in the health plan and the firms' pricing strategies.

4 Benchmark: only monotherapies available

As a benchmark for further analysis, we derive in this section the Nash equilibrium outcome of a game in which the two producers simultaneously (and non-cooperatively) set the prices of their drugs when these are only approved as monotherapies within the health plan. If drug choices are made such that (1) is maximised for all patients, the demand for drug i is given by

$$q_i = \frac{\lambda}{2} + (1-\lambda)\left(\frac{1}{2} + \frac{\alpha\,(p_j - p_i)}{2\tau}\right), \quad i,j = 1,2, \quad i \neq j. \tag{2}$$

Thus, each producer has demand from a captive segment (backbone) and a competitive segment, where drug-specific demand from the latter segment is endogenously determined by relative drug prices.

The profit of firm i is given by $\pi_i = p_i q_i$,where q_i is given by (2). The first-order condition for the optimal price set by firm i is therefore

$$\frac{\partial \pi_i}{\partial p_i} = q_i - p_i\,(1-\lambda)\,\frac{\alpha}{2\tau} = 0, \tag{3}$$

After applying symmetry we arrive at the following Nash equilibrium prices:

$$p_i^m = \frac{\tau}{(1-\lambda)\,\alpha}, \quad i = 1,2. \tag{4}$$

Intuitively, the magnitude of these prices depend negatively on the relative size of the competitive segment (measured by $1-\lambda$), on the degree of therapeutic substitutability between the drugs in this segment (inversely measured by τ), and on the price sensitivity of the physician's treatment choices (measured by α). In the symmetric equilibrium, each producer receives half of the total demand, so equilibrium profits are given by

$$\pi_i^m = \frac{\tau}{2\,(1-\lambda)\,\alpha}, \quad i = 1,2. \tag{5}$$

Notice also that treatment decisions are efficient in this equilibrium. Since total demand is exogenously fixed, the efficient treatment decisions are the ones that minimise the therapeutic mismatch costs, and these costs are minimised if, in the competitive segment, every patient with a therapeutic mismatch value of $x < (>) 1/2$ is treated with drug 1 (drug 2). This implies of course that treatment decisions are efficient in any symmetric equilibrium.

5 Combination therapies

Suppose now that a third treatment alternative is approved, namely a combination of the two. Without loss of generality we assume that the combination consists of being treated with one unit of drug 1 and one unit of drug 2, what we will henceforth refer to as a *combination therapy*.[3] We assume that the patients who have one of the drugs as the backbone therapy might also respond positively to a combination therapy. This implies that there are two viable treatment options for every patient in the market. In each of the two captive demand segments, a share $\lambda/2$ of the patients can successfully be treated either by one unit of drug i or by a combination. For each of these patients, the therapeutic benefit of the monotherapy is given by $v - ty_i$, while the therapeutic benefit of the combination therapy is given by $w - t(1 - y_i)$, where $w > v$ and where y_i is a random draw from a uniform distribution on $[0, 1]$, with $i = 1, 2$. This captures the importance of patient-specific characteristics, as revealed by predictive biomarkers, for personalisation of treatment. Patients vary in their therapeutic match or tolerance to a combination of the backbone drug and the other add-on drug.

For notational convenience, we will in the following denote the therapeutic value-added of the combination therapy by $\Delta := w - v$. Notice that, for each of the patients who might potentially benefit from the combination therapy, (the inverse of) the parameter $t > 0$ measures the degree of therapeutic substitutability between the combination therapy and the backbone therapy. The remaining share of the patients $(1 - \lambda)$ do not derive any additional therapeutic benefit from (or do not tolerate) the combination therapy and can successfully be treated by either of the two monotherapies, as before. Thus, we can think of the parameter λ as measuring the potential size of the market for combination therapies.[4]

If the purchasing price of the combination therapy is given by p_c, prescription choices for

[3] In practice, the optimal dosage of a drug will vary across patients and may also change if used in combination with another drug.

[4] In Section 5 we consider an alternative version of the model, where each patient might be prescribed any of the three treatment alternatives.

patients who potentially benefit from the combination are made to maximise the following utility function:

$$U_i^c = \begin{cases} v - ty_i - \alpha p_i & \text{if prescribing monotherapy } i \\ w - t\left(1 - y_i\right) - \alpha p_c & \text{if prescribing the combination therapy} \end{cases}. \tag{6}$$

As before, the treatment choices for patients who only benefit from the two therapeutically substitutable monotherapies are made to maximise (1). These treatment choices result in the following demand function for monotherapies with drug i:

$$q_i = \frac{\lambda}{2}\widehat{y}_i + (1 - \lambda)\,\widehat{x}, \tag{7}$$

where

$$\widehat{y}_i = \frac{1}{2} - \left(\frac{\Delta + \alpha\left(p_i - p_c\right)}{2t}\right) \tag{8}$$

and

$$\widehat{x} = \frac{1}{2} + \frac{\alpha\left(p_j - p_i\right)}{2\tau}, \tag{9}$$

with $i, j = 1, 2$ and $i \neq j$. The demand for combination therapies, denoted by Q, is then given by

$$Q = \frac{\lambda}{2}\sum_{i=1}^{2}\left(1 - \widehat{y}_i\right), \tag{10}$$

Notice that the availability of a combination therapy endogenises total demand for each drug, which now depends on the share of patients that are given a combination treatment. The total number of drug units sold is thus given by $1 + Q$.

5.1 First-best treatment choices

Before considering how the approval of the combination therapy affects the firms' pricing decisions, let us first derive the first-best treatment choices when the combination therapy is included in the health plan. For the patients who respond only to one of the two monotherapies, the optimal treatment choices are clearly such that $\widehat{x} = 1/2$, as before. Among the remaining patients, treatment choices are efficient if the combination therapy is given to all patients whose additional benefit from this treatment is higher than the difference in marginal production costs between the combination treatment and the relevant monotherapy. Since we have set marginal

costs equal to zero, efficient treatment choices are such that

$$v - ty_i = w - t\left(1 - y_i\right), \tag{11}$$

implying that all patients with a mismatch value y_i higher than $(1/2) - (\Delta/2t)$ should be prescribed the combination therapy. This implies in turn that, in the first-best solution, the share of patients given the combination therapy is

$$Q = \frac{\lambda}{2}\left(1 + \frac{\Delta}{t}\right). \tag{12}$$

5.2 Uniform pricing

Suppose that each firm is restricted to setting a uniform price for its drug, regardless of whether the drug is used in a monotherapy or in combination with the other drug. This assumption is in line with the current practice in most countries, where companies are not allowed to apply distinct prices for the same drug when used in different indications, subpopulations of the same disease, or lines of treatments, or in combinations with other treatments (Preckler, 2022).[5] This implies that, if the prices of monotherapies are given by p_1 and p_2, the price of the combination therapy is given by $p_c = p_1 + p_2$. In this case, the profit of firm i is given by

$$\pi_i = p_i\left(q_i + Q\right), \tag{13}$$

where q_i and Q are given by (7) and (10), respectively. The first-order condition for the profit-maximising price is then given by

$$\frac{\partial \pi_i}{\partial p_i} = q_i + Q - p_i\left(\left(1 - \lambda\right)\frac{\alpha}{2\tau} + \frac{\lambda}{2}\frac{\alpha}{2t}\right) = 0, \tag{14}$$

and the symmetric interior-solution Nash equilibrium under uniform pricing is given by

$$p_i^u = \frac{\left(\left(2 + \lambda\right)t + \lambda\Delta\right)\tau}{2\alpha\left(\left(1 - \lambda\right)t + \lambda\tau\right)}, \quad i = 1, 2. \tag{15}$$

This equilibrium exists if

$$\underline{\Delta} < \Delta < \overline{\Delta}, \tag{16}$$

[5] In Section 5.4 below we consider the case of indication-based pricing, where each firm can price discriminate and set different prices for its drug depending on whether it is used as a monotherapy or as part of a combination therapy.

where

$$\underline{\Delta} := \frac{((2-\lambda)\tau - 2(1-\lambda)t)t}{2(1-\lambda)t + \lambda\tau} \tag{17}$$

and

$$\overline{\Delta} := \frac{(2\tau + 3\lambda\tau + 2(1-\lambda)t)t}{2(1-\lambda)t + \lambda\tau}. \tag{18}$$

If the therapeutic value-added of the combination therapy is too low, $\Delta < \underline{\Delta}$, the Nash equilibrium is a corner solution in which no patient is given the combination treatment. On the other hand, if the additional therapeutic benefit of the combination is sufficiently large, $\Delta > \overline{\Delta}$, the Nash equilibrium is another corner solution in which all patients who potentially benefit from the combination therapy will end up receiving it. In the following, we assume that the condition in (16) holds. The equilibrium demand for monotherapies with drug i is then given by

$$q_i^u = \frac{2(1-\lambda)((2-\lambda)t - \lambda\Delta)t + \lambda((6-\lambda)t - \lambda\Delta)\tau}{8t((1-\lambda)t + \lambda\tau)}, \quad i = 1, 2, \tag{19}$$

whereas the equilibrium demand for combination therapies is given by

$$Q^u = \lambda\frac{(2(1-\lambda)t + \lambda\tau)(\Delta + t) - 2\tau t}{4t((1-\lambda)t + \lambda\tau)}. \tag{20}$$

The resulting profits for each firm (which correspond to the total purchasing costs of each drug) are then given by

$$\pi_i^u = p_i^u(q_i^u + Q^u) = \frac{((2+\lambda)t + \lambda\Delta)^2(2(1-\lambda)t + \lambda\tau)\tau}{16\alpha((1-\lambda)t + \lambda\tau)^2 t}, \quad i = 1, 2. \tag{21}$$

5.2.1 The effect of combination therapies on drug prices

What is the competitive effect of approving a combination therapy in the health plan? Is price competition softened or intensified? A comparison of (4) and (15) allows us to reach the following conclusion:

Proposition 1 *(i) Approval of a combination therapy in the health plan leads to lower drug prices if either Δ or t is sufficiently small, while it leads to higher drug prices if both Δ and t are sufficiently large. (ii) The scope for an anti-competitive effect of introducing the combination therapy is larger if either τ or λ is smaller.*

Thus, whether the inclusion of the combination therapy has a pro-competitive or an anti-competitive effect on drug prices depends crucially on the therapeutic value-added of the combination (measured by Δ) and the therapeutic substitutability between the combination therapy and the relevant backbone drug (inversely measured by t). The intuition behind the results stated in Proposition 1 can be pinpointed by comparing the two first-order conditions in (3) and (14), which show that the inclusion of a combination therapy adds the following two terms to firm i's profit gain of a (unilateral) marginal price increase:

$$\frac{\partial \pi_i^u}{\partial p_i} - \frac{\partial \pi_i^m}{\partial p_i} = \frac{\lambda}{2}\left(1 - \widehat{y}_j\right) - p_i\left(\frac{\lambda\alpha}{4t}\right). \tag{22}$$

These two terms capture the two counteracting effects on price setting resulting from the inclusion of a combination therapy in the health plan. For given prices, such an inclusion yields a positive demand effect for firm i in firm j's captive patient segment, since some of the patients who were previously prescribed monotherapy j is now being given the combination treatment with both drugs. This effect, which is captured by the first term in (22), makes firm i's demand less price elastic and contributes to a higher profit-maximising drug price, all else equal. However, the introduction of a combination therapy also makes each firm's drug demand more price responsive, since a lower (higher) price will increase (reduce) the number of patients given the combination treatment. This effect is captured by the second term in (22) and contributes, all else equal, to a lower optimal drug price.

Notice that the relative magnitudes of the two above-described effects depend crucially on the parameters Δ and t. Since the demand effect of the combination therapy depends on its therapeutic value-added, the magnitude of the first effect is monotonically increasing in Δ, and it turns out that the first effect is always dominated by the second effect, implying that introducing the combination therapy is pro-competitive, if Δ is sufficiently close to the lower bound $\underline{\Delta}$. Furthermore, since the effect of the combination therapy on the price responsiveness of demand depends on the degree of therapeutic substitutability between the combination therapy and the relevant monotherapy, the magnitude of the second effect is monotonically decreasing in t. It turns out that, if t is sufficiently low, the second effect dominates the first effect, implying that the presence of combination therapies are pro-competitive, for all values of $\Delta \in \left(\underline{\Delta}, \overline{\Delta}\right)$. On the other hand, if t is sufficiently high, the second effect is always dominated by the first effect, implying that combination therapies are anti-competitive, if in addition Δ is sufficiently

close to the upper bound $\overline{\Delta}$.

In order to understand the intuition behind the second part of Proposition 1, notice that the equilibrium prices in the absence of a combination therapy are monotonically increasing in τ and λ, as can be seen from (4). This implies that the scope for an anti-competitive effect of combination treatments is larger if the drug prices in the absence of such treatments are lower. The reason is that lower drug prices reduce the cost difference between monotherapies and the combination therapy, which in turn increases the positive demand effect of including the latter type of treatment in the health plan. All else equal, this increases the scope for a drug price increase following the introduction of a combination treatment option.

5.2.2 The effects of combination therapies on drug costs and health benefits

Since the inclusion of the combination therapy always leads to higher total demand, total profits (and thus total drug costs) clearly increase if such inclusion is anti-competitive. A more interesting question is whether a pro-competitive effect of combination treatments can be strong enough to outweigh the demand increase, implying lower profits for the firms and thus lower drug expenditures for the health plan? The answer to this question is 'yes', and the next proposition confirms that, in qualitative terms, the parameter conditions ensuring a pro-competitive effect of combination therapies are sufficient to ensure a negative effect on total drug expenditures:

Proposition 2 *Inclusion of a combination therapy in the health plan leads to lower profits and thus lower drug expenditures for the health plan if either* Δ *or* t *is sufficiently small.*

If the inclusion of a combination treatment leads to lower drug costs for the health plan, the benefit of including this treatment alternative is unambiguously positive, since such an inclusion also leads to higher health benefits for the patients. On the other hand, if drug costs increase, the net benefit of including the combination therapy depends on whether or not this cost increase outweighs the increase in health benefits. The latter benefits consist of the additional health gains for the patients who switch from a monotherapy to a combination therapy and are given

by[6]

$$\begin{aligned} H &= \lambda \int_{\widehat{y}}^{1} (\Delta - t(1-s) + ts)\, ds \\ &= \frac{\lambda \left((t+\Delta)\left(2(1-\lambda)t + \lambda\tau\right) - 2t\tau\right)\left((t+\Delta)\left(2(1-\lambda)t + 3\lambda\tau\right) + 2t\tau\right)}{16t\left((1-\lambda)t + \lambda\tau\right)^2}, \end{aligned} \tag{23}$$

where $\widehat{y}$ is given by (8) for $p_i^u = p_j^u$. Defining the health plan's surplus as the total health benefits minus total purchasing costs, we are able to derive an analytically unambiguous result for the special case of $\alpha = 1$:

Proposition 3 *Suppose that the prescribing physician acts as a perfect agent for the health plan (i.e., $\alpha = 1$). In this case, the inclusion of a combination therapy always increases the health plan's surplus.*

Thus, even if the introduction of a combination treatment is anti-competitive, leading to higher drug prices in the market, these cost increases are always outweighed by higher health benefits as long as physicians act as perfect agents for the health plan. By continuity, this result also holds if α is sufficiently close to one. For lower values of α, it is possible that the inclusion of a combination therapy might reduce the health plan's surplus. Numerical simulations suggest that this might happen within a relatively restricted parameter set. An illustrative example is given in Figure 1 which is drawn in (Δ, τ)-space, and where the remaining parameters are set to $\lambda = \alpha = 1/2$ and $t = 2$. For these parameter values, the equilibrium in (15) exists for values of Δ between the upper and lower curves in the figure.

[Figure 1 here]

For the case depicted in Figure 1, the inclusion of a combination treatment leads to a reduction in the health plan's surplus for the parameter set given by the shaded area. This area is characterised by a relatively high degree of therapeutic substitutability between the two monotherapies (i.e., low τ) and a relatively high therapeutic value-added of the combination treatment (i.e., high Δ). We already know from Proposition 1 that, in qualitative terms, these are parameter combinations that increase the scope for the combination treatment to have an anti-competitive effect on drug prices.

[6] Notice that the expression in (23) is not the total health benefits in the equilibrium where the combination therapy is available, but instead the *additional health benefits* obtained by including the combination therapy in the health plan.

Somewhat paradoxically, the health plan's surplus is reduced only if the therapeutic value-added of the combination therapy is sufficiently large. However, notice that the increased health benefits only accrue to a subset of the patients (those who switch from monotherapy to combination therapy) while the cost increase applies to all drug treatments in the market, as long as the producers set uniform prices for drugs used in monotherapies and combination therapies, respectively. This explains why a higher value of Δ might increase purchasing costs more than it increases health benefits, thus leading to an overall reduction in the health plan's surplus.

5.2.3 Treatment allocation efficiency

Finally, we are interested in establishing the efficiency properties of the treatment decisions in the equilibrium where the combination therapy is included in the health plan. A comparison of the equilibrium treatment choices with the first-best solution yields the following result:

Proposition 4 *Compared with the first-best solution, the equilibrium treatment decisions are such that too few patients are given the combination therapy.*

The intuition behind the underprovision of combination treatments is relatively straightforward. The efficient provision of combination therapies is such that the therapeutic value-added for the marginal patient is equal to the difference in marginal production costs between the combination treatment and the relevant backbone therapy. The equilibrium treatment choices, on the other hand, are such that the therapeutic value-added for the marginal patient is equal to the difference in drug costs (as perceived by the prescribing physician), which is given by

$$\alpha p_i^u = \frac{\left((2+\lambda)\,t + \lambda\Delta\right)\tau}{2\left((1-\lambda)\,t + \lambda\tau\right)} \tag{24}$$

and is strictly higher than marginal production costs (which in our model are normalised to zero). Thus, as long as the drug producers have some market power, resulting in drug prices higher than marginal production costs, too few patients are given the combination treatment compared to what is socially optimal.

5.3 Price coordination

Since the cost of combination therapies often are determined by the prices set by several producers, the producers of drug 1 and drug 2 in our model, there is a direct externality between the

two producers that comes in addition to the strategic interaction in the market for substitutable monotherapies. The question is then how this affects the gains from price coordination for the producers. As explained in the Introduction, this externality is held to pose potential problems for health technology assessments, especially if producers are not allowed to coordinate the drug costs of a new combination therapy. In this section, we therefore analyse the effect of price coordination on prices and patients' access to treatments. As in the main analysis, we assume that $p_c = p_1 + p_2$, implying that the profits of firm i are given by (13).

If the two producers coordinate their price setting and choose drug prices that maximise their joint profits, all externalities will be internalised. These externalities can be identified by comparing the first-order conditions under coordinated and non-cooperative pricing:

$$\frac{\partial \left(\pi_i + \pi_j\right)}{\partial p_i} - \frac{\partial \pi_i}{\partial p_i} = p_j \left(\frac{\partial q_j}{\partial p_i} + \frac{\partial Q}{\partial p_i}\right). \tag{25}$$

Using (7) and (10), we find that

$$\frac{\partial Q}{\partial p_i} = -\frac{\lambda \alpha}{4t} < 0 \tag{26}$$

and

$$\frac{\partial q_j}{\partial p_i} = \frac{(1-\lambda)\,\alpha}{2\tau} + \frac{\lambda \alpha}{4t} > 0. \tag{27}$$

Thus, there are two different externalities; one positive and one negative. The negative externality, represented by (26), arises from the existence of combination therapies. If one of the producers increases the price of its drug, this will make the combination therapy more expensive and will therefore reduce the sales of drugs used in such treatments. All else equal, this sales reduction also affects the competing producer and therefore constitutes a negative externality. When seen in isolation, the internalisation of this externality through price coordination therefore contributes to a lower drug price.

However, there is also a positive externality, represented by (27), which arises from the fact that a unilateral price increase makes the monotherapies based on the competing producer's drug relatively cheaper and therefore shifts demand in the direction of such therapies. All else equal, the internalisation of this externality through price coordination therefore contributes to a higher price. Notice, however, that the increased demand for the competing producer's monotherapy comes from two different sources. If producer i increases the price of its drug, some patients switch from monotherapy i to monotherapy j, whereas some other patients switch

from the combination therapy to monotherapy j. The latter effect is given by the second term in (27) and is of the exact same magnitude (in absolute terms) as the negative externality given by (26). In other words, if drug i becomes more expensive, the reduction in demand for combination therapies is exactly offset by an increase in the demand for monotherapy j. In addition, however, there is a demand increase for monotherapy j that is caused by the patients who switch from monotherapy i to monotherapy j when the former therapy becomes more expensive, and the magnitude of this demand increase is given by the first term in (27).

The sum of the two counteracting externalities described above is therefore positive. More generally, the sum of these two externalities will always be positive as long as the reduction in the demand for combination therapy is offset by a corresponding increase in the demand for competing producers' monotherapies. In this case, price coordination will lead to higher prices and therefore make combination therapies *more* expensive. The profit-maximising price under price coordination is easily found by maximising the joint profits of the two producers and is given by

$$p_i^c = \frac{(2+\lambda)t + \lambda\Delta}{2\alpha\lambda}, \quad i = 1, 2. \tag{28}$$

This price has been derived under the assumption that the market segment in which patients choose between the two monotherapies is fully covered. This is the outcome of profit-maximising price coordination if the following parameter condition holds:

$$\Delta \leq \Delta^c := 2v - \tau - \left(\frac{2+\lambda}{\lambda}\right) t. \tag{29}$$

This condition always holds if the willingness to pay for monotherapies (v) is sufficiently high. Notice that the equilibrium existence condition given by (16) does not depend on v. Thus, by assuming a sufficiently large value of v, the equilibrium implies fully covered markets both with and without price coordination and therefore facilitates a meaningful comparison.

A comparison of the equilibrium price with and without price coordination allows us to state the following results:

Proposition 5 *Price coordination between producers of drugs that can be used both as monotherapies (therapeutic substitutes) and in combination (therapeutic complements) always increases the prices and reduces patients' access to combination therapies. The price increase is larger if (i) the value-added of the combination therapy (Δ) is higher, (ii) the therapeutic substitutability*

between the two monotherapies (the inverse of τ) is higher, and (iii) the share of patients that can be treated with the combination therapy (λ) is smaller.

Overall, our analysis in this section shows that allowing for price coordination between producers of drugs used in combination therapies is not necessarily a good idea. On the contrary, if these producers also compete with substitutable monotherapies in the same market, a demand loss for combination therapies is likely to be offset by demand increases for monotherapies in a way that creates an overall positive externality in pricing, implying that price coordination is likely to result in higher rather than lower prices and thus reduce patients' access to combination therapies.

5.4 Price discrimination

In this final subsection of our main analysis we analyse the effects of price discrimination where producers can set different prices of their drug depending on whether it is used as a monotherapy of as part of a combination therapy This form for price discrimination is often referred to as *indication-based pricing*, which usually is not allowed by regulators in most countries, as discussed in the Introduction. However, we know from the economics literature that uniform prices across heterogenous patient groups can lead to a suboptimal treatment allocation. Indeed, this was confirmed in our above analysis of uniform pricing, where we found that the consumption of the combination therapy was too low compared to the first-best allocation of treatments (cf. Proposition 4).

To investigate whether price discrimination can improve the access to the combination therapy, let p_i and P_i be the prices of drug i when used as a monotherapy and as part of a combination therapy, respectively, where $i = 1, 2$. Thus, the price of the combination therapy is now $p_c = P_1 + P_2$, and can in principle be higher or lower than the sum of the prices of drugs when used as monotherapies, in contrast to the case of uniform pricing. Firm i's profits under price discrimination is thus given by

$$\pi_i = p_i q_i + P_i Q, \tag{30}$$

where q_i and Q are given by (7) and (10), respectively, with $p_c = P_1 + P_2$.

Maximisation of (30) with respect to p_i and P_i yields the following first-order conditions

$$\begin{aligned} \frac{\partial \pi_i}{\partial p_i} &= q_i + p_i \frac{\partial q_i}{\partial p_i} + P_i \frac{\partial Q}{\partial p_i} \\ &= q_i - p_i \frac{\alpha \left(2t\left(1-\lambda\right)+\lambda\tau\right)}{4t\tau} + P_i \frac{\alpha\lambda}{4t} = 0, \end{aligned} \tag{31}$$

$$\begin{aligned} \frac{\partial \pi_i}{\partial P_i} &= Q + P_i \frac{\partial Q}{\partial P_i} + p_i \frac{\partial q_i}{\partial P_i} \\ &= Q - P_i \frac{\alpha\lambda}{2t} + p_i \frac{\alpha\lambda}{4t} = 0. \end{aligned} \tag{32}$$

The first two terms in (31) and (32) are the standard effects of a marginal price increase on profits (revenues) extracted from inframarginal and marginal patients, respectively. The last term, on the other hand, is an indirect effect due to the induced demand substitution between the monotherapy and the combination therapy among the patients who has drug i as their backbone therapy. If drug i becomes more expensive when used as a monotherapy, part of the demand loss for such therapies will be recaptured because some of the patients switch to using the same drug in a combination therapy instead, and *vice versa* in the case of a price increase for drug i when used as part of a combination therapy. This last term is therefore positive and contributes to higher prices of drug i both as a monotherapy and as part of a combination therapy, all else equal. Furthermore, since the value of the demand that is shifted from monotherapies to combination therapies depends positively on P_i, and the value of the demand that is shifted in the other direction depends positively on p_i, this creates an additional strategic complementarity between the two prices, and the strength of this complementarity is increasing in the size of the potential market for combination therapies, given by λ.

Solving the set of first-order conditions given by (31)-(32), the symmetric price equilibrium under price discrimination is given by

$$p_i^d = \frac{4t\tau}{\alpha\left(4t\left(1-\lambda\right)+\lambda\tau\right)}, \tag{33}$$

$$P_i^d = \frac{\left(t+\Delta\right)\left(4t\left(1-\lambda\right)+\lambda\tau\right)+6t\tau}{3\alpha\left(4t\left(1-\lambda\right)+\lambda\tau\right)}. \tag{34}$$

The resulting demand for drug i as a monotherapy and as part of a combination therapy is given by, respectively,

$$q_i^d = \frac{6t-\lambda\left(t+\Delta\right)}{12t} \tag{35}$$

and

$$Q^d = \frac{\lambda}{6t}(t + \Delta), \tag{36}$$

and the equilibrium profits are

$$\pi_i^d = \frac{\lambda(t+\Delta)^2(4(1-\lambda)t + \lambda\tau) + 36\tau t^2}{18t\alpha(4t(1-\lambda) + \lambda\tau)}. \tag{37}$$

This equilibrium exists if

$$\Delta < \overline{\Delta}^d := 5t.$$

In order to facilitate a meaningful comparison between the cases of uniform pricing and price discrimination, for the remainder of the analysis in this section we assume that $\tau < 4t$. In words, this assumption means that the degree of therapeutic substitutability is not very much lower between the two monotherapies than between each monotherapy and the combination therapy. It is easily shown that $\overline{\Delta}^d > \overline{\Delta}$ if $\tau < 4t$, implying that the equilibrium given by (33)-(34) exists for the entire parameter set in which the interior-solution uniform pricing equilibrium exists.

The next proposition provides a complete characterisation of the equilibrium prices under price discrimination:

Proposition 6 *Let* $\widehat{\Delta} \in \left(\underline{\Delta}, \overline{\Delta}\right)$ *and* $\widehat{\lambda} \in (0,1)$ *be two threshold values of* Δ *and* λ*, respectively. (i) Compared with uniform pricing, price discrimination leads to more (less) expensive monotherapies if* $\Delta < (>)\,\widehat{\Delta}$*, it leads to less expensive combination therapies if* $\Delta < \widehat{\Delta}$ *and* $\lambda < \widehat{\lambda}$ *or if* $\Delta > \widehat{\Delta}$ *and* $\lambda > \widehat{\lambda}$*, and it leads to more expensive combination therapies if* $\Delta < \widehat{\Delta}$ *and* $\lambda > \widehat{\lambda}$ *or if* $\Delta > \widehat{\Delta}$ *and* $\lambda < \widehat{\lambda}$*. (ii) Under price discrimination, each drug is always more (less) expensive when used as a monotherapy than when used as part of a combination therapy if* $\Delta < (>)\,\widehat{\Delta}$*.*

Perhaps the most basic insight from Proposition 6 is that, if the producers are allowed to price discriminate between different uses of their drugs, it is not obvious whether a drug will be priced higher or lower when used in a combination therapy than when being used as a monotherapy. This depends crucially on the therapeutic value-added of the combination therapy, Δ. Notice that price discrimination allows the producers to create a market for the combination therapy even if $\Delta = 0$. By setting a lower price for drug i when used in a combination therapy, firm i can capture some demand in firm j's captive segment without losing revenues on inframarginal patients in its own captive segment, and without losing demand for

monotherapies in the non-captive segment. Thus, as long as Δ is sufficiently low, the optimal price-discrimination strategy for each firm is to set a lower price for its drug when used in a combination therapy.[7] However, a higher value of Δ leads to more, and thus less price elastic, demand for combination therapies, all else equal, which in turn gives each producer an incentive to increase the price for drugs used in such therapies. Consequently, if Δ is sufficiently large, $\Delta > \widehat{\Delta}$, the optimal price-discrimination strategy is to set a higher price for a drug when it is used in combination therapies rather than as a monotherapy.

When compared with the case of uniform pricing, we see that price discrimination always leads to more (less) expensive monotherapies when the equilibrium price-discrimination strategies are such that drugs are price higher (lower) when used as a monotherapy rather than being used in a combination therapy, i.e., when $\Delta < (>) \widehat{\Delta}$. Combination therapies, on the other hand, can be more or less expensive under price discrimination regardless of whether Δ is below or above the threshold level $\widehat{\Delta}$. This depends on the parameter λ, which measures the potential size of the market for combination therapies. Notice that a higher value of λ increases the magnitude of the price complementarity effect between p_i and P_i, as previously explained, which all else equal contributes to the two prices moving in the same direction. Thus, if λ is sufficiently high, $\lambda > \widehat{\lambda}$, a switch from uniform pricing to price discrimination makes both treatments more (less) expensive when $\Delta < (>) \widehat{\Delta}$.

The next proposition summarises the effects of price discrimination on treatment efficiency and purchasing costs:

Proposition 7 *(i) Compared with uniform pricing, price discrimination reduces (increases) the inefficiency in treatment allocations if $\Delta < (>) \widehat{\Delta}$. (ii) If price discrimination makes the treatment allocation more efficient, the purchasing costs of the health plan always increase.*

We know from Proposition 4 that the access to combination therapies under uniform pricing is too low, compared with the first-best solution. Such an inefficiency always exists as long as combination therapies are offered at prices above marginal cost. However, price discrimination might increase or reduce this inefficiency, depending on whether the equilibrium access to combination therapies decreases or increases. This depends not only on whether combination

[7] Notice, however, that the total price of a combination therapy is always higher than the price of a monotherapy, since

$$2P_i^d - p_i^d = \frac{2}{3\alpha}(t + \Delta) > 0.$$

therapies become more or less expensive, but it also depends on whether price discrimination makes the backbone therapy more or less expensive. The first part of Proposition 7 confirms that what matters for treatment allocation efficiency is the price change of combination therapies *relative* to the backbone therapy. As long as combination therapies become relatively less expensive, which happens if $\Delta < \widehat{\Delta}$, price discrimination leads to increased access to combination therapies, and thus a more efficient treatment allocation, even if the absolute price of combination therapies also goes up. Conversely, price discrimination makes the treatment allocation less efficient if $\Delta > \widehat{\Delta}$, even if both treatments become cheaper.

Although price discrimination (or indication-based pricing) has the potential to improve access to combination therapies and thereby reduce the inefficiencies in treatment allocations, the second part of Proposition 7 shows that such an efficiency gain always comes at the cost of higher purchasing costs for the health plan. The reason is simply that increased access to combination therapies requires that such therapies become relatively cheaper, and this happens only if monotherapies become more expensive. Even if combination therapies become cheaper in absolute terms (which happens if $\lambda < \widehat{\lambda}$), this is more than outweighed by the price increase for monotherapies, thus leading to an overall increase in drug purchasing costs.

6 Robustness: allowing for more than two treatment options

In the main analysis we have made the simplifying assumption that each patient has only two treatment options, which implies that the combination therapy is not an option for a share of the patients. These patients will only tolerate monotherapies, or are expected to experience no positive effect of a combination therapy. In the main analysis, therefore, these will treated with either of the two monotherapies. In order to test the robustness of our main results, we now extend the analysis to consider a scenario in which each patient might be given any of three different treatments: monotherapy with drug 1, monotherapy with drug 2, or the combination treatment with both drugs.[8] Suppose that each patient is characterised by a pair (x, z), where x and z are independent draws from a uniform distribution on $[0, 1]$. The utility of the monotherapy are given by (1), whereas the utility of the combination treatment is given by $w - tz - \alpha p_c$, as before.

[8] The technical correspondence to our main model is that we now set $\lambda = 0$ and introduce the combination therapy as a third option for all patients in the competitive segment (which now constitutes all patients in the market). We could alternatively have kept the captive segments (i.e., $\lambda > 0$), but this would just complicate the model without offering much additional insights.

In order to derive the demand for each drug, notice that the physician is indifferent between the two monotherapies for patients characterised by

$$x = \xi := \frac{1}{2} + \frac{\alpha (p_2 - p_1)}{2\tau}. \tag{38}$$

A patient with $x \leq \xi$ will be given the combination therapy if

$$z < \frac{\Delta - \alpha (p_c - p_1) + \tau x}{t}, \tag{39}$$

and a patient with $x > \xi$ will be given the combination therapy if

$$z < \frac{\Delta - \alpha (p_c - p_2) + \tau (1 - x)}{t}. \tag{40}$$

We restrict attention to the parameter set that is such that, for every $x \in [0, 1]$, some patients will be given a monotherapy and some patients will be given a combination therapy. In this case, demand for monotherapies with drug 1 is given by

$$q_1 = \int_0^{\xi} \left(1 - \left(\frac{\Delta - \alpha (p_c - p_1) + \tau x}{t}\right)\right) dx, \tag{41}$$

demand for monotherapies with drug 2 is given by

$$q_2 = \int_{\xi}^{1} \left(1 - \left(\frac{\Delta - \alpha (p_c - p_2) + \tau (1 - x)}{t}\right)\right) dx, \tag{42}$$

and demand for the combination therapy is given by

$$Q = 1 - \int_0^{\xi} \left(1 - \left(\frac{\Delta - \alpha (p_c - p_1) + \tau x}{t}\right)\right) dx - \int_{\xi}^{1} \left(1 - \left(\frac{\Delta - \alpha (p_c - p_2) + \tau (1 - x)}{t}\right)\right) dx. \tag{43}$$

This yields the following total demand for drug i:

$$q_i + Q = \frac{\tau \left(4 \left(t + \Delta - \alpha p_c\right) + \tau + 2\alpha \left(p_i + p_j\right)\right) + \alpha \left(p_i - p_j\right) \left(\alpha \left(p_i + 3p_j\right) - 4 \left(t - \Delta + \alpha p_c\right)\right)}{8t\tau}, \tag{44}$$

where $i, j = 1, 2$ and $i \neq j$.

6.1 Benchmark and first-best treatment allocations

Let us once more use as a benchmark the case in which the combination therapy is not included in the health plan. In this case, the model corresponds to the one in Section 3 when setting $\lambda = 0$, where drug demand is given by (2) and the Nash equilibrium drug prices are given by (4). Thus,

$$p_i^m = \frac{\tau}{\alpha}, \quad i, j = 1, 2. \tag{45}$$

In order to assess the efficiency properties of the Nash equilibrium we derive below, it is also useful to derive the first-best treatment allocation when the combination therapy is available. As in the previous version of the model, the optimal treatment choices clearly imply $\xi = 1/2$. Furthermore, a patient with $x \leq \xi$ should optimally be given the combination therapy if $z < (\Delta + \tau x)/t$, while a patient with $x > \xi$ should optimally be given the combination treatment if $z < (\Delta + \tau(1 - x))/t$. In the first-best solution, the number of patients given the combination therapy is therefore given by

$$Q^{fb} = 1 - \int_0^{\frac{1}{2}} \left(1 - \left(\frac{\Delta + \tau x}{t}\right)\right) dx - \int_{\frac{1}{2}}^1 \left(1 - \left(\frac{\Delta + \tau(1 - x)}{t}\right)\right) dx = \frac{1}{t}\left(\Delta + \frac{\tau}{4}\right). \tag{46}$$

6.2 Combination therapy with uniform pricing

Suppose now that the combination treatment is included in the health plan, and that each firm is restricted to setting a uniform price for its drug, regardless of whether the drug is used as a monotherapy or included in the combination therapy, which implies that $p_c = p_1 + p_2$. In this case, drug prices in the symmetric Nash equilibrium are found to be given by

$$p_i^u = \frac{1}{4\alpha}\left(2(\Delta - t) - 3\tau + \sqrt{4(t - \Delta)^2 + \tau(4(\Delta + 7t) + 13\tau)}\right), \quad i = 1, 2. \tag{47}$$

In this equilibrium, for every value of x, a share of patients (strictly between 0 and 1) is given the combination therapy. This share is largest for $x = 1/2$ and decreases monotonically as x goes towards each of the endpoints (0 or 1). An illustration of the equilibrium treatment allocation is provided in Figure 2. The equilibrium exists for a parameter set characterised by

$$0 < \frac{\Delta - \alpha p_i^u}{t} < \frac{\Delta - \alpha p_i^u + \frac{\tau}{2}}{t} < 1, \tag{48}$$

which implicitly defines a lower and an upper bound on Δ, as in the main model.

[Figure 2 here]

The effect of including the combination therapy on equilibrium drug prices, and the efficiency properties of the equilibrium, are summarised as follows:

Proposition 8 *Suppose that each patient in the market might be given any of the three different therapies, and that the drug producers are restricted to uniform pricing across different treatment alternatives. In this case, inclusion of the combination therapy in the health plan leads to lower (higher) prices for both drugs if* $\Delta < (>) \frac{9}{8}\tau$. *In either case, a suboptimally low number of patients is given the combination therapy, compared with the first-best solution.*

As in the main model, the introduction of a combination treatment can have either a pro-competitive or an anti-competitive effect, depending on parameter values. The effect is pro-competitive if the therapeutic value-added of the combination treatment (Δ) is sufficiently low. This is qualitatively in line with the results in Proposition 1 for the main model, and the intuition is also similar. As in the main analysis, the introduction of a combination therapy has two counteracting effects on drug pricing incentives. On the one hand, it leads to a positive shift in demand which makes demand less price elastic, all else equal. On the other hand, it also makes demand more sensitive to price changes, since a unilateral price reduction not only shifts demand from one monotherapy to the other, but also induces a larger number of the competitor's patients to choose the combination therapy. This effect contributes to a more price-elastic demand and therefore pulls in the opposite direction. As in the main analysis, the latter (former) effect dominates when the positive demand shift from introducing a combination treatment is sufficiently small (large), which in turn depends on the magnitude of Δ.

The threshold value of Δ given in the above proposition also implies that the scope for an anti-competitive effect of combination treatments is larger when τ is smaller, i.e. when the two drugs are closer therapeutic substitutes when used as monotherapies. Once more, this is qualitatively in line with the results in Proposition 1 and the intuition is similar. Higher substitutability between the monotherapies leads to lower drug prices, which reduces the additional cost of a combination treatment and therefore increases the positive demand shift of introducing such a treatment in the health plan. Consequently, a lower value of τ enlarges the scope for drug demand to become less price elastic after the introduction of a combination therapy, because of a larger increase in the demand for each drug.

The Nash equilibrium in this alternative model is also characterised by too few patients being prescribed the combination therapy, and the intuition for this is exactly the same as in the main model, namely a distortion caused by drug prices above marginal cost.

6.3 Price coordination

Finally, it is also relatively straightforward to show that the effects of price coordination between the two producers would be qualitatively similar to the one analysed in Section 5.3. When evaluated at the equilibrium prices, the externalities identified by (26) and (27) are now given by, respectively,

$$\left.\frac{\partial Q}{\partial p_i}\right|_{p_i=p_j=p^u} = -\frac{\alpha}{2t} < 0 \tag{49}$$

and

$$\left.\frac{\partial q_j}{\partial p_i}\right|_{p_i=p_j=p^u} = \frac{\alpha}{4t\tau}\left(2\left(t+\alpha p^u-\Delta\right)+\tau\right) > 0, \tag{50}$$

while the sum of the two externalities is given by

$$\left.\frac{\partial q_j}{\partial p_i}+\frac{\partial Q}{\partial p_i}\right|_{p_i=p_j=p^u} = \frac{\alpha}{4t\tau}\left(2\left(t+\alpha p^u-\Delta\right)-\tau\right) > 0, \tag{51}$$

where the positive signs of (50) and (51) are established by invoking the equilibrium existence condition in (48). As in the main analysis, non-cooperative pricing is characterised by two externalities, one negative and one positive, but the sum of the two externalities is positive, which implies the following:

Proposition 9 *Suppose that each patient in the market might be given any of the three different therapies, and that the drug producers are restricted to uniform pricing across different treatment alternatives. In this case, price coordination always leads to higher drug prices and thus more expensive combination therapies.*

7 Concluding remarks

The introduction of combination therapies is a game changer in pharmaceutical markets. Firms selling competing drugs as monotherapies are now suddenly selling complementary products that jointly increase the therapeutic benefit to (some groups of) patients. The fact that competing firms' drugs are not just substitutes but also complements (when used as combination therapies)

changes the strategic interaction in the market and the firms' pricing incentives.

Despite the growing importance of combination therapies, our paper is a first study of the competitive effects of including such therapies in the health plan. Using a stylised duopoly model with a captive patient segment (trading off a monotherapy against the combination therapy) and a non-captive patient segment (trading off the two monotherapies), we consider market outcomes, health expenditures, and welfare effects under three different pricing regimes; i.e., uniform pricing, price discrimination, and price coordination.

Based on this set up, we report several novel and non-trivial results. First, we show that the competitive effects of the inclusion of combination therapies are generally ambiguous and depend on two countervailing effects: market expansion versus competition on the margin. If the therapeutic value-added is large, the introduction of combination therapies may, somewhat paradoxically, reduce the health plans' surplus, which is due higher drug prices and in turn also higher expenditures. Second, although combination therapies imply that drugs become both substitutes and complements, we show that price coordination between the firms (or collusion) always yields higher prices and profits to the firms at the expense of a lower surplus to the health plan and lower allocative efficiency due to fewer patients receiving the combination therapy. Third, allowing for price discrimination (indication-based pricing) can increase allocational efficiency, but only at the expense of higher purchasing costs. Thus, the choice of pricing regime from a policy perspective depends crucially on the competitive effects of combination therapies.

By way of conclusion, we should mention that our study has not taken into account the innovation stage. Firms have strong incentives to innovate as long as they appropriate the profits from the new drug development. This is potentially different for combination therapies where competing firms also have profits from their monotherapies and thus risk to cannibalise on their existing treatment. And perhaps more importantly, the profits associated with combination therapies is to be shared between competing firms. Thus, the optimal innovation policy scheme for development of combination therapies is far from obvious. While this is an important issue, it is beyond the scope of our study and thus left for future research.

Appendix

Proof of Proposition 1

A comparison of (4) and (15) yields

$$p_i^u - p_i^m = \lambda\tau \frac{(1-\lambda)(\Delta + t) - 2\tau}{2\alpha(1-\lambda)((1-\lambda)t + \lambda\tau)} > (<)\, 0 \quad if \quad \Delta > (<)\, \widetilde{\Delta}, \tag{A1}$$

where

$$\widetilde{\Delta} := \frac{2\tau}{1-\lambda} - t. \tag{A2}$$

Using (17) and (18), we derive

$$\widetilde{\Delta} - \underline{\Delta} = \frac{2\tau((1-\lambda)t + \lambda\tau)}{(1-\lambda)(2(1-\lambda)t + \lambda\tau)} > 0 \tag{A3}$$

and

$$\overline{\Delta} - \widetilde{\Delta} = \frac{2(t(1-\lambda) + \lambda\tau)(2(1-\lambda)t - \tau)}{(1-\lambda)(2(1-\lambda)t + \lambda\tau)} > 0 \quad if \quad t > \frac{\tau}{2(1-\lambda)}. \tag{A4}$$

Thus, $p_i^u < p_i^m$ if Δ is sufficiently close to $\underline{\Delta}$ or if t is sufficiently low so that $\widetilde{\Delta} > \overline{\Delta}$, while $p_i^u > p_i^m$ if Δ is sufficiently close to $\overline{\Delta}$ and t is sufficiently high so that $\widetilde{\Delta} < \overline{\Delta}$.

(ii) The second part of Proposition 1 follows directly from the condition in (A1) and the definition of the threshold $\widetilde{\Delta}$ in (A2).

Proof of Proposition 2

A comparison of (5) and (21) yields

$$\pi_i^u - \pi_i^m = \frac{\lambda\tau\Psi}{16t\alpha(1-\lambda)((1-\lambda)t + \lambda\tau)^2}, \tag{A5}$$

where

$$\begin{aligned} \Psi \;:\; &= 2t^3(4+\lambda)(1-\lambda)^2 + \Delta(1-\lambda)(2(1-\lambda)t + \lambda\tau)(4t + 2t\lambda + \Delta\lambda) \\ &\quad - ((6+\lambda)(1-\lambda)(2-\lambda)t + 8\lambda\tau)t\tau. \end{aligned} \tag{A6}$$

The sign of (A5) depends on the sign of Ψ, which is monotonically increasing in Δ, since

$$\frac{\partial\Psi}{\partial\Delta} = 2(1-\lambda)((2+\lambda)t + \lambda\Delta)(2t(1-\lambda) + \lambda\tau) > 0. \tag{A7}$$

Evaluating Ψ at the lower and upper bounds of Δ yields

$$\lim_{\Delta \to \underline{\Delta}} \Psi = -\frac{8t\tau \left((1-\lambda)\, t + \lambda\tau\right)^2}{2\,(1-\lambda)\, t + \lambda\tau} < 0 \tag{A8}$$

and

$$\lim_{\Delta \to \overline{\Delta}} \Psi = \frac{8t\,(2t\,(2+\lambda)\,(1-\lambda) - \tau)\,((1-\lambda)\, t + \lambda\tau)^2}{2\,(1-\lambda)\, t + \lambda\tau} < 0 \quad if \quad t < \frac{\tau}{2\,(2+\lambda)\,(1-\lambda)}. \tag{A9}$$

Thus, $\pi_i^u < \pi_i^m$ if Δ is sufficiently close to $\underline{\Delta}$ or if t is sufficiently low.

Proof of Proposition 3

The change in the health plan's surplus when including the combination therapy is given by

$$S := H - 2\,(\pi_i^u - \pi_i^m)\,, \tag{A10}$$

where H is given by (23), π_i^m is given by (5) and π_i^u is given by (21). From (A10) we derive

$$\left.\frac{\partial^2 S}{\partial \Delta^2}\right|_{\alpha=1} = \frac{\lambda\,(2\,(1-\lambda)\, t + \lambda\tau)^2}{8t\,((1-\lambda)\, t + \lambda\tau)^2} > 0. \tag{A11}$$

Thus, for $\alpha = 1$, S is a globally strictly convex function of Δ, which implies that it has a unique minimum, implicitly given by

$$\left.\frac{\partial S}{\partial \Delta}\right|_{\alpha=1} = 0, \tag{A12}$$

and explicitly given by

$$\Delta^* = \frac{\left(4t\,(1-\lambda)\,((2-\lambda)\,\tau - (1-\lambda)\, t) + \lambda\,(6-\lambda)\,\tau^2\right) t}{(2\,(1-\lambda)\, t + \lambda\tau)^2}. \tag{A13}$$

Evaluating S at its minimum yields

$$S|_{\alpha=1,\Delta=\Delta^*} = \frac{\lambda\,((1-\lambda)\, t + \lambda\tau)\,\tau^2}{(1-\lambda)\,(-2t + 2t\lambda - \lambda\tau)^2} > 0, \tag{A14}$$

which implies that $S|_{\alpha=1}$ is strictly positive for all Δ, including the entire parameter set for which the equilibrium exists, given by $\Delta \in \left(\underline{\Delta}, \overline{\Delta}\right)$.

Proof of Proposition 4

A comparison of (20) and (12) yields

$$Q^u - Q^{fb} = -\lambda\tau \frac{(2+\lambda)\,t + \lambda\Delta}{4t\,((1-\lambda)\,t + \lambda\tau)} < 0. \tag{A15}$$

Proof of Proposition 5

A comparison of (15) and (28) yields

$$p_i^c - p_i^u = \frac{(1-\lambda)\,((2+\lambda)\,t + \lambda\Delta)\,t}{2\alpha\lambda\,((1-\lambda)\,t + \lambda\tau)} > 0. \tag{A16}$$

It follows directly from (A16) that this price difference is increasing in Δ and decreasing in τ. It can also be verified that the price difference is decreasing in λ, since

$$\frac{\partial\,(p_i^c - p_i^u)}{\partial\lambda} = -\frac{t}{2}\frac{2t^2\,(1-\lambda)^2 + \lambda\tau\,((4-\lambda)\,t + \Delta\lambda)}{\alpha\lambda^2\,((1-\lambda)\,t + \lambda\tau)^2} < 0. \tag{A17}$$

Proof of Proposition 6

(i) A comparison of (15) and (33) yields

$$p_i^d - p_i^u = \frac{\lambda\tau\,[6t\tau - (4\,(1-\lambda)\,t + \lambda\tau)\,(t+\Delta)]}{2\alpha\,(4t\,(1-\lambda) + \lambda\tau)\,(t\,(1-\lambda) + \lambda\tau)} > (<)\,0 \text{ if } \Delta < (>)\,\widehat{\Delta}, \tag{A18}$$

where

$$\widehat{\Delta} := \frac{6\tau - (4\,(1-\lambda)\,t + \lambda\tau)}{4\,(1-\lambda)\,t + \lambda\tau}t. \tag{A19}$$

Furthermore, a comparison of (15) and (34) yields

$$P_i^d - p_i^u = \frac{[2t\,(1-\lambda) - \lambda\tau]\,[(4t\,(1-\lambda) + \lambda\tau)\,(t+\Delta) - 6t\tau]}{6\alpha\,(4\,(1-\lambda)\,t + \lambda\tau)\,((1-\lambda)\,t + \lambda\tau)}. \tag{A20}$$

The sign of this expression is determined by the sign of the numerator, which is the product of two factors (the two bracketed parentheses) that each have an *a priori* indeterminate sign. The sign of the first factor is positive (negative) if $\tau < (>)\,\widehat{\lambda}$, where

$$\widehat{\lambda} := \frac{2t}{2t+\tau}, \tag{A21}$$

whereas the sign of the second factor is positive (negative) if $\Delta > (<) \widehat{\Delta}$, where $\widehat{\Delta}$ is given by (A19). It is immediately obvious that $\tau < (>) \widehat{\tau}$ if λ is sufficiently low (high). Thus, the sign of the first factor is positive (negative) if τ or λ is sufficiently low (high). From (A21) it is immediately obvious that $\widehat{\lambda} \in (0,1)$. The proof of the first part of the proposition is completed by establishing that $\widehat{\Delta} \in \left(\underline{\Delta}, \overline{\Delta}\right)$, which is true since

$$\overline{\Delta} - \widehat{\Delta} = \frac{4t\left(1-\lambda\right)\left(4t-\tau\right)\left(\left(1-\lambda\right)t+\lambda\tau\right)}{\left(4t\left(1-\lambda\right)+\lambda\tau\right)\left(2\left(1-\lambda\right)t+\lambda\tau\right)} > 0 \text{ if } \tau < 4t \tag{A22}$$

and

$$\widehat{\Delta} - \underline{\Delta} = \frac{4t\tau\left(\left(1-\lambda\right)t+\lambda\tau\right)}{\left(4t\left(1-\lambda\right)+\lambda\tau\right)\left(2\left(1-\lambda\right)t+\lambda\tau\right)} > 0. \tag{A23}$$

(ii) A comparison of (33) and (34) yields

$$P_i^D - p_i^D = \frac{\left(4\left(1-\lambda\right)t+\lambda\tau\right)\left(t+\Delta\right)-6t\tau}{3\alpha\left(4\left(1-\lambda\right)t+\lambda\tau\right)} > (<)\, 0 \text{ if } \Delta > (<)\, \widehat{\Delta}, \tag{A24}$$

where $\widehat{\Delta}$ is given by (A19).

Proof of Proposition 7

(i) A comparison of (20) and (36) yields

$$Q^d - Q^u = \lambda \frac{6t\tau - \left(4\left(1-\lambda\right)t+\lambda\tau\right)\left(t+\Delta\right)}{12t\left(\left(1-\lambda\right)t+\lambda\tau\right)} > 0 \text{ if } \Delta < \widehat{\Delta}, \tag{A25}$$

where $\widehat{\Delta}$ is given by (A19).

(ii) When production costs have been set to zero, the purchasing costs of the health plan are given by the profits of the drug producers. A comparison of (21) and (37) yields

$$\pi_i^d - \pi_i^u = \frac{\lambda\left[\left(4t\left(1-\lambda\right)+\lambda\tau\right)\left(t+\Delta\right)-6t\tau\right]\Omega}{144t\alpha\left(4t\left(1-\lambda\right)+\lambda\tau\right)\left(\left(1-\lambda\right)t+\lambda\tau\right)^2}, \tag{A26}$$

where

$$\Omega := \left(8t^2\left(1-\lambda\right)^2+\lambda^2\tau\left(2t-\tau\right)\right)\left(t+\Delta\right)+2\left(\lambda\left(29t-21\tau\right)-\left(30t+\lambda\Delta\right)\right)t\tau. \tag{A27}$$

From the first part of the proposition we know that the inefficiency in treatment allocations is reduced if $\Delta < \widehat{\Delta}$, which implies that the sign of the expression in square brackets in (A26) is

negative, which in turn implies that $\pi_i^d - \pi_i^u$ has the opposite sign of Ω. From (A27) we derive

$$\frac{\partial \Omega}{\partial \Delta} = (4(1-\lambda)t + \lambda\tau)(2(1-\lambda)t - \lambda\tau) > (<) 0 \text{ if } \lambda < (>) \widehat{\lambda}, \tag{A28}$$

where $\widehat{\lambda}$ is given by (A21). Evaluating Ω at the lower and upper bounds of the relevant range of Δ, given by $\Delta \in \left(\underline{\Delta}, \widehat{\Delta}\right)$, yields

$$\lim_{\Delta \to \underline{\Delta}} \Omega = -\frac{4t\tau((1-\lambda)t + \lambda\tau)(26(1-\lambda)t + 11\lambda\tau)}{(2(1-\lambda)t + \lambda\tau)} < 0 \tag{A29}$$

and

$$\lim_{\Delta \to \widehat{\Delta}} \Omega = -48t\tau((1-\lambda)t + \lambda\tau) < 0. \tag{A30}$$

Since $\Omega < 0$ at both the lower and upper bounds of Δ, the monotonicity of Ω in Δ implies that $\Omega < 0$, and thus $\pi_i^d - \pi_i^u$, for all $\Delta \in \left(\underline{\Delta}, \widehat{\Delta}\right)$, regardless of whether Ω is increasing or decreasing in Δ.

Proof of Proposition 8

(i) Using (45) and (47), the introduction of a combination therapy leads to lower (higher) drug prices if

$$\frac{1}{4\alpha}\left(2(\Delta - t) - 3\tau + \sqrt{4(t-\Delta)^2 + \tau(4(\Delta + 7t) + 13\tau)}\right) < (>) \frac{\tau}{\alpha}, \tag{A31}$$

which is equivalent to

$$\sqrt{4(t-\Delta)^2 + \tau(4(\Delta + 7t) + 13\tau)} < (>) 7\tau + 2(t - \Delta), \tag{A32}$$

which is equivalent to

$$4(t-\Delta)^2 + \tau(4(\Delta + 7t) + 13\tau) - (7\tau + 2(t-\Delta))^2 < (>) 0, \tag{A33}$$

which reduces to

$$4\tau(8\Delta - 9\tau) < (>) 0, \tag{A34}$$

or

$$\Delta < (>) \frac{9}{8}\tau. \tag{A35}$$

What remains to be shown is that the threshold value of Δ is contained in the parameter set for which the equilibrium exists. Equilibrium existence requires that the condition in (48) holds. Using (47) and setting $\Delta = (9/8)\,\tau$, this condition reduces to

$$0 < \frac{\tau}{8t} < \frac{5\tau}{8t} < 1, \tag{A36}$$

which holds for all $\tau < 8t/5$.

(ii) Setting $p_c = p_i + p_j$ in (43), the number of patients receiving the combination therapy, as a function of drug prices, is given by

$$Q = \frac{1}{t}\left(\Delta + \frac{\tau}{4}\right) - \frac{2\tau\alpha\,(p_i + p_j) + \alpha^2\,(p_i - p_j)^2}{4t\tau}. \tag{A37}$$

Comparing with (46), it is straightforward to see that $Q < Q^{fb}$ for any pair of positive prices (p_i, p_j), including the equilibrium ones.

Proof of Proposition 9

The result stated in the Proposition follows directly from (25) and (51).

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