A cost-effectiveness analysis comparing the originator follitropin alfa to its biosimilars in patients undergoing a medically assisted reproduction program from a French perspective

M Grynberg, C Murphy, C Dore, L Fresneau, S Paillet, N Petrica, F Maurel, H Ravonimbola

A cost-effectiveness analysis comparing the originator follitropin alfa to its biosimilars in patients undergoing a medically assisted reproduction program from a French perspective

Michaël Grynberg[1], Claire Murphy[2], Carole Doré[2], Laurence Fresneau[2], Ségolène Paillet[2], Nicoleta Petrica[3], Frédérique Maurel[3], Harinala Ravonimbola[3]

[1] Hôpital Antoine Béclère, 157, Rue de la Porte de Trivaux, 92140 Clamart, France
[2] Merck Santé S.A.S., affiliate of Merck KGaA, Darmstadt, Germany 34 Rue Saint-Mathieu, 69008 Lyon, France
[3] IQVia, 17 bis Place des Reflets, 92319 La Défense, France

Correspondence: Michaël Grynberg, Chef de service - Service de Médecine de la Reproduction & Préservation de la Fertilité, Hôpital Antoine Béclère, 157, Rue de la Porte de Trivaux, 92140 Clamart; email: michael.grynberg@aphp.fr

Transparency

Declaration of funding

This study has been funded by Merck Santé S.A.S, which is developing products related to research described in this publication.

Declaration of financial/other interests

The authors declare no financial/other interests. Peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no other relevant financial relationships to disclose.

Author Contributions

All authors contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

Acknowledgments

No assistance in the preparation of this article is to be declared.

Previous presentations

The subject of this article was presented during the 2017 ISPOR conference.

Abstract

Objective: To assess the cost-effectiveness (CE) of the originator follitropin-α (Gonal-F) in patients undergoing a medically assisted reproduction (MAR) program in comparison to its biosimilars Bemfola and Ovaleap in a French context.

Methods: A CE model was developed for France with a National Health Service (NHS) perspective. Clinical, safety, and dosage data were derived from pivotal clinical trials that compared Gonal-F to Ovaleap and Bemfola. Costs pertaining to drugs, hospitalizations, specialist visits, and examinations were retrieved from the French Programme de Médicalisation des Systèmes d'Information (PMSI) hospital database, literature review, and French clinical experts using 2017 Euro tariffs. In order to test the robustness of results, deterministic one-way sensitivity analyses were carried out on the main variables to assess the impact of treatment cost, probability of birth, ovarian hyperstimulation syndrome (OHSS) rates, and dosage.

Results: The average incremental cost per live birth with OHSS and without OHSS was €259.56 and €278.39, respectively for Gonal-F compared to the pooled biosimilars (i.e., Ovaleap and Bemfola). GONAL-F had an incremental efficacy of 0.06 over the pooled biosimilars. The incremental cost-effectiveness ratio for Gonal-F with OHSS ranged from €3,274.80 to €4,877.76 compared to the pooled biosimilars, owing to the additional live births reported with Gonal-F. Sensitivity analyses also supported results from the base case analyses, with Gonal-F being cost-effective or the dominant strategy in most cases.

Conclusion: Gonal-F seems to be a cost-effective strategy compared to its biosimilars Ovaleap and Bemfola, irrespective of the incidence of OHSS events, but further data are needed to confirm these results.

Keywords: follitropin alfa; cost-effectiveness; infertility; Gonal-F; gonadotropin

JEL codes: I10; I19

Introduction

Infertility is a medical condition which is recognized as a global public health issue by the World Health Organization (WHO)[1]. Infertility is a growing concern in many countries, including the European Union (EU) member states, and fertility rates are steadily declining from the mid-1960s through the turn of the century[2]. The common risk factors include age, smoking, alcohol consumption, obesity, diabetes or thyroid disease, and other occupational and environmental risk factors. It is estimated that about 48.5 million couples worldwide experience infertility[3]. A total of 1.9% of females aging 20-44 years were found to have difficulty in conception worldwide in 2010[4 5]. The prevalence of infertility varies considerably across countries and there is a paucity of reliable data due to the presence of multiple factors which complicate any estimates. Among the EU member states, France recorded the highest fertility rates in 2015[2]. However, its fertility rates fell steadily from 2.01 children per woman in 2012 to 1.93 in 2015 [4 5]. The decreasing trends in fertility can be related to an overall increase in the incidence of infertility due to social, lifestyle, biological, and environmental factors[6]. Furthermore, it estimated that about 20% couples experiencing subfertility or infertility, only 10% seek specialist care [6].

However, various treatment options are available for female fertility in France. Assisted reproductive technologies (ART) comprise one of the most commonly used treatment options for women encountering fertility issues. In ART, gonadotropins are usually administered in order to stimulate the follicular development. Exogenous gonadotropins, including follicle-stimulating hormone (FSH), are universally recognized as the key driver of controlled ovarian stimulation and maturation. Available FSH products include purified urinary-derived human menopausal gonadotropin (hMG), highly purified urinary (HP-uFSH), and recombinant human FSH (r-hFSH).

Gonal-F® (follitropin alfa for injection) was the first FSH preparation of human recombinant DNA origin marketed since 1997 in several indications, including the stimulation of mutifollicular development in women undergoing superovulation for ART[7]. Two biosimilars, namely Ovaleap® (Teva, Castleford, UK), and Bemfola® (Finox AG, Burgdorf, Switzerland), are now marketed in Europe. Ovaleap® was approved by the European Medicine Agency (EMA) in 2013 and recommended by the European guidelines as a biological product containing r-hFSHα[8]. Bemfola® was approved by EMA in 2015 and licensed for all indications of reference products[9]. The biosimilar FSH products have nonclinical pharmacological, pharmacokinetic, and toxicological profiles similar to those of the originator FSH. The clinical safety and efficacy of biosimilars is well documented in literature among women undergoing ART in European countries [10 8]. However, their clinical bioequivalence has been demonstrated on an intermediate criterion that is the number of oocytes retrieved but not on the ultimate objective of interest, which is the number of live births[11] and the secondary end-point of these randomized controlled trials (RCTs)[12 13]. Comparing live birth rates for Gonal-F® versus the biosimilar FSH products for the 1st treatment cycle, results are in favor of Gonal-F®, but with non-statistically significant as the RCTs were not powered for this endpoint. While there is to date no hard-clinical evidence of the superiority of Gonal-F® versus the biosimilar on live birth rates, considering the results observed on existing RCTs and the need to optimize outcomes in relation to limited public resources it is of interest to compare Gonal-F® and the biosimilar FSH products in a cost effectiveness (CE) analysis.

Indeed, currently, the CE of Gonal-F® in comparison to its biosimilars is yet to be demonstrated, considering the lower cost of the biosimilars. Hence, the aim of our study was to perform a CE analysis (CEA) of Gonal-F® in patients undergoing a medically assisted reproduction (MAR) program compared to its biosimilars: Bemfola® and Ovaleap® in a French context.

Material and Method

The analysis was based on previously conducted studies[12 13] and did not involve any new studies with human or animal subjects performed by any of the authors. The study was performed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Practices for Outcomes Research consensus guidance[14] and relevant international and national guidelines for health economics studies. Ethics board approval and informed consent were not required because the study did not involve human or animal participants and the analysis only used publicly available anonymized data.

Model design

A Microsoft Excel-based pharmacoeconomic model was developed to evaluate the CE of Gonal-F® versus its biosimilars in women undergoing ART, focusing on the 1st treatment cycle. The number of cycles used in our model was decided based on the availabilities of the clinical data used to feed the model, knowing that only data for the 1st cycle were available for both treatment comparisons (Gonal-F® versus Bemfola®[12] and Gonal-F® versus Ovaleap®[13]). The CEA was carried out from a National Health Service perspective. To delineate the cost and efficacy of Gonal-F® in patients undergoing an MAR program compared to its biosimilars in a French context, a decision-tree was used. This decision-tree model depicted different relevant outcomes of fertility treatment with r-hFSHα over the 1st cycle. The modeling of decision-tree encompassed the following steps: a) Treatment stimulation; b) Oocyte retrieval; c) Embryo transfer; d) Pregnancy; and e) Live delivery or miscarriage. The probability of having live births/miscarriage was taken as the final outcome of the model. At each step, the probability of succeeding or failing was calculated. Only one reimbursed IVF cycle was considered in the model.

Ovarian hyperstimulation syndrome (OHSS), the most important adverse event of gonadotropin use, was taken into account in the model.

Six treatment arms based on the following three pair-wise comparisons were considered: a) Gonal-F®O versus Ovaleap® using data reported by Strowitzki et al[13]; b) Gonal-F®B compared to Bemfola® using data reported by Rettenbacher et al [12]; c) Pooled Gonal-F® (i.e. Gonal-F®P) versus pooled biosimilars (i.e. BioS) using data from both the clinical trials. The model in Figure 1depicts main steps of ART on which clinical outcomes and costs are based and simulates a patient's journey from the start of IVF therapy through various treatment stages.

Sensitivity analyses were also performed to investigate the stability of CE for the treatment over a range of value variations. For each comparison, one-way sensitivity analysis was performed to assess the impact of different parameters on the ICER. These parameters included the percentage of live birth per woman, mild/moderate OHSS and severe, r-hFSHα dose and the price of the treatment is performed to test the robustness of the results. The variation of each parameter was determined arbitrarily [± 20%], except for r-hFSHα dose, where the confidence intervals of UI dose reported in the two clinical studies have been considered. A tornado diagram was used to analyze the parameters having impact on the ICER.

Clinical studies and evidence details

The choice of clinical outcomes in infertility trials has been debatable owing to the multistage nature of the treatment and a recent review of outcome measures in the *in vitro* fertilization (IVF) clinical trials has indicated very wide diversity in the selection of these outcomes [12]. Live births are the ultimate endpoint of fertility tests and there is a consensus among experts in reproductive medicine to advocate the need to adopt live births as the preferred primary outcome in infertility trials [13]. Hence, the live birth rate was considered as the criterion of interest to assess efficacy of each treatment in our CE model. The

model developed is based on the clinical evidences from head-to-head EMA registration trials of Bemfola® [12] and Ovaleap® [13] which assessed the number of oocytes retrieved as primary end-point and the live-birth rate as secondary end-point: One of these studies was a multinational, multicenter, randomized, assessor-blind phase III study comparing the efficacy (in terms of number oocyte retrieved) and safety of Ovaleap® to Gonal-F® in 299 women undergoing controlled ovarian stimulation with ART [13]. The other study was a multicenter phase III study that compared the efficacy (in terms of number oocyte retrieved) and safety of Gonal-F® to Bemfola® in 372 women undergoing ovarian stimulation for IVF for ART superovulation [12]. We mention that the clinical trials used to feed the model included women according to different criteria (such as age, which range between 20 and 38 years in the Gonal-F® versus Bemfola® clinical trial [12] and between 18 and 37 year for the Gonal-F® versus Ovaleap® clinical trial[13] or body mass index). It is therefore evident that based on other populations the CE model could lead to different results.

Adverse events associated with the use of gonadotropins have been considered in the model. Ovarian hyperstimulation syndrome (OHSS) is one of the most important adverse events of gonadotropin and the severity, management, and costs of OHSS have been considered for all treatment options using data provided in European Public Assessment Reports of Bemfola®[9] and Ovaleap®[8]. No other publication comparing the biosimilars to the originator follitropin alfa was available at the model development date.

The transition probabilities of clinical outcomes, including OHSS rates used in the model were calculated based on the evidence submitted for biosimilars in EMA registrations considering the intent-to-treat (ITT) population data from the two clinical trials. Probability of each treatment arm derived from clinical efficacy outcomes are presented in Table 1.

Costs inputs

The resource pertaining costs associated for each step of the MAR process were retrieved from literature review, PMSI[15] (Programme de médicalisation des systèmes d'information) analysis (a comprehensive French hospital database), and French clinical experts opinions through a management questionnaire[16].

Cost assumptions taken for each step in the model for each treatment were based on a market study based on the responses from 30 gynecologists/endocrinologists and 300 patients using a questionnaire completed by French experts. The ART cost included cost of treatment induction which was separated in three steps: blocking phase, stimulation phase, and trigger phase. Nurse tariffs[17] were applied for one subcutaneous injection each.

Cost analysis also considered monitoring visits, biological hormones dosages[18], and IVF based on French health insurance tariff[19]. The IVF cost is weighted between standard IVF cost (40%) and IVF Intra Cytoplasmic Spermatozoid Injection (ICSI) cost (60%)[16]. Oocyte retrieval costs involved anesthetic visit (10% of patients based on French expert opinion), oocyte retrieval, spermatozoid retrieval (0.09%, based on French Diagnosis-Related Group (DRG) tariff[20]), and spermatozoid preparation.

Embryo transfer involved technical examination, adding a specific fee and one beta-human chorionic gonadotropin (b-HCG) dosage. The management costs were considered similar to normal pregnancy costs from this stage onwards. Pregnancy follow-up costs were based on mensural medical visit and quarterly monitoring. The weighted mean cost of DRG for natural delivery (75%) and caesarian delivery (25%) was applied in case of pregnancy leading to live birth, whereas DRG tariff was considered in case of miscarriage. Costs of mild, moderate, and severe OHSS were used in the model considering the

monitoring costs, unless for the severe OHSS were the cost of the associated DRG ("Autres affections de l'appareil génital féminin" – GHM: 13M041, 13M042, 13M04T, 13M043 and "Interventions sur le système utéroannexiel pour des affections non malignes" _ GHM: 13C071)[20] was added in addition to the monitoring costs. All estimated cost and assumptions made are presented in Table 2.

The total cost per patient was calculated for each treatment group by multiplying the probability of having one of the clinical efficacy outcomes presented in Table 1 with the related costs. The incremental CE ratio (ICER) was calculated by taking the difference in total costs divided by the difference in live birth rate of the two treatment groups in France. All resources are valued in 2017 Euros using official local tariffs sources/database.

Results

Detailed results are presented in Table 3 for each set of pairwise comparisons, presenting the ICER values, cost per live birth, incremental cost, and incremental efficacy either with or without OHSS cases. In all the analyses it was observed that Gonal-F® was found to be cost-effective over its biosimilars, irrespective of the consideration of OHSS.

Base-case analysis

When Gonal-F®O was compared to Ovaleap® after taking OHSS into account, the use of Gonal-F®O resulted in an incremental cost of €259.17 and an incremental efficacy of 0.05 over Ovaleap®. This translated into an ICER of €4,804, which is the additional cost required for Gonal-F®O to gain an additional live birth in comparison with Ovaleap®. The costs of treatment with Gonal-F®O and Ovaleap®, were €3,826 and €3,567, respectively. The cost per live birth was €5,799 with Gonal-F®O and €5,682 with Ovaleap®. Efficacy in terms of live-birth rate was 0.32 and 0.27 for Gonal-F®O and Ovaleap®, respectively, which indicates that there would be 32 live-born children per 100 women treated with the Gonal-F® and 27 live-born children per 100 women treated with Ovaleap®. Similar results were observed when Gonal-F®O was compared to Ovaleap® without taking OHSS into account, with an ICER of €4,878. There was no change in the incremental efficacy (0.05), while the incremental cost was relatively higher without taking OHSS into account (€263) as compared to analysis taking OHSS into account (€259).

For the second set of pairwise comparison between Gonal-F®B and Bemfola®, the incremental efficacy was 0.08 in favor of Gonal-F®B, irrespective of OHSS consideration. The incremental cost of Gonal-F®B over Bemfola® was €279 with OHSS and €299 without OHSS. This resulted in an ICER of €3,275 with OHSS and €3,505 without OHSS.

The third set of pairwise comparison between pooled Gonal-F®P and BioS also showed a similar trend which favored Gonal-F®P over BioS in terms of incremental efficacy (0.06) irrespective of OHSS consideration. The incremental cost of Gonal-F®P over BioS was €260 with OHSS and €278 without OHSS. The observed ICER values are €4,352 with OHSS and €4,668 without OHSS.

Sensitivity analysis

The results of one-way sensitivity analysis are presented in Table 4, and the outcomes for the comparison of Gonal-F®P to BioS are depicted as tornado diagram in Figure 2. This analysis indicates that uncertainty in probability of birth and dosages of r-hFSHα are the most sensitive variables and have the highest impact on ICER values. Gonal-F®O versus Ovaleap® (without OHSS) and Gonal-F®P versus BioS (without OHSS) analyses indicated cost-saving with higher efficacy for Gonal-F®.

Nearly all sensitivity analyses support that Gonal-F® is a cost-effective strategy, even cost-saving when the lower dosage limit is considered for Gonal-F® compared to Ovaleap® or BioS. In case of Gonal-F® probability of live birth decreased by 20%, the Ovaleap® and BioS are observed to be dominant.

Discussion

Cumulative potential savings to health systems in the European Union (EU) and the US, as a result of the use of biosimilars, could exceed €50 billion in aggregate by 2020 and reach as much as €100 billion[21]. The cumulative spending in the EU5 (France, Spain, Germany, Italy and United-Kingdom) alone is expected to reach €47 billion over the period 2016-2020 on different originator biologic medicines. In this regard, Germany and France are leading the addressable biosimilar medicines market in the EU5 with 17 billion euros and 9 billion euros of spending, respectively, for 2016-2020 [21]. France is the first European country to explicitly permit biosimilar substitution, and the drop in price of originator products ranges from 1%-33% in France[22 23]. While biosimilars may offer a less expensive alternative for patients, it is essential to perform CEA to evaluate the cost per course of treatment of biosimilar r-hFSHα with respect to the originator on the base of equivalent therapeutic. However, to the best of our knowledge, there is a lack of published literature on any CEA of the biosimilar gonadotropin in France, and our study is the first CEA comparing biosimilars Ovaleap® and Bemfola® to their originator r-hFSHα Gonal-F® in women undergoing ovarian stimulation for IVF in France.

Previous CEA studies conducted in Italy, Spain, Germany and Portugal have indicated Gonal-F® to be a cost-efficient treatment strategy compared to its biosimilars Bemfola® [24 25] and Ovaleap® [26 27]. The ICER obtained for Gonal-F® versus Ovaleap® was €1,517 per woman with a new-born child in Portugal [26] and between 415.43€ and 2917.47€ for the others countries[27]. The ICER values for Gonal-F® compared to Bemfola® were €3,600 in Italy and €900 in Spain [24]. Yet another recent study in Italy also supported the fact that Gonal-F® provided a lower average cost per live birth than Bemfola® and an ICER of €1,210[25]. This is despite the fact that Gonal-F® had a higher acquisition cost when compared to its biosimilars Bemfola® and Ovaleap®.

In context of extending these CEA results to other countries, our study was able to show that Gonal-F® could remain the cost-effective strategy compared to its biosimilars, owing to its incremental efficacy in terms of the number of live births.

The CE model was fed with data reported in clinical trials and cannot be substituted for the direct real-life comparisons. Also, it should be noted that the methods used in our study were slightly different than other CE models in Portugal, Spain, and Italy, owing to differences in the number of stimulation cycles, stimulation steps and/or costs considered. All patients included in the second cycle of treatment in the Ovaleap® trial were treated with Ovaleap®, irrespective of whether they received Gonal-F® or Ovaleap® during the first cycle of treatment [13]. Furthermore, the objective of the second treatment cycle in the Bemfola® trial was to assess the immunogenicity and safety of Bemfola®. Hence, the CE model was based on only one stimulation cycle since the introduction of second cycle efficacy data could have raised bias not only due to the trial design of the study but also for the small number of patients who underwent the second treatment cycle[12].

The outcomes used to feed the model derive from clinical trials that were designed to compare the number of oocytes retrieved between the biosimilars and Gonal-F®. In our analyze we used the second end-point, which is the live birth rate, to calculate the ICER. Even though the first end-point is the number of oocytes retrieved, the number of live birth represents the most meaningful and relevant clinical outcome for these types of treatments as shown in multiple studies from the literature. In the

French Technology Assessment label[11] for Gonal-F®, multiple sources are presented, such as: the meta-analyses made by Gerli et al (2013)[28] and Al-Inany et al (2009)[29] which involved studies having the live birth rate as first end-point or other study such as Gholami et al (2010)[30] or Sagnella et al (2011)[31], where the first end-point is the pregnancy rate. The recent cost-effectiveness modeling evaluations, such as Gizzo et al (2016)[24] and Gizzo et al (2018)[27], the effectiveness outcome used was also the live birth. Moreover, in order to proof the significance of the used outcome, we analyzed the level where the difference between the two groups was significant for the clinical efficacy outcomes used to feed the model. We observed that the difference become significant at a p-value >25% going up to 50% for some outcomes. However, in our CE model the outcome is the recalculate live birth rate, presented differently than in the original paper. Using the same statistical proportion test (Z test) as above, this difference is significant between the groups at a p-value equal to 13%. By accepting a higher value for the risk of being wrong we can make the hypothesis that our live birth rate difference is significantly different from 0. As mentioned above the studies used for these analyses were not designed to compare the live birth rates and the clinical trials showed that the second end-point was not significantly different between treatment groups. Such results represent an uncertainty for the conclusion. If sufficient data were available with a study design powered to demonstrate the live-birth rate, it might be interesting to analyze the success rate of all the cycles needed to obtain a child and also to confirm our results.

Another potential limitation is that the biosimilar Bemfola® is available only as single-use, fixed-dose, prefilled pens in contrast to Gonal-F®, which is available as multi-dose vials and prefilled pens. As doses need to be individually tailored to response, it is not possible to determine the impact of potential dose wastage on costs arising from the use of the different presentations. Furthermore, dissimilarities in dose reduction were observed between the biosimilar and originator groups, which also could have resulted in a higher incidence of OHSS for the biosimilar [32]. Clinical outcomes data stratified by age groups and types of ART would have access to model sub-populations avoiding biases on treatment-related benefits and potential harms due to different population characteristics.

In our study, treating 100 women with Gonal-F® resulted in nine, six, and five additional live births compared to Bemfola®, pooled biosimilars, and Ovaleap®, respectively, irrespective of OHSS occurrence. The ICER values were €4,804 per live birth for Ovaleap®, €3,275 per live birth for Bemfola®, and €4,353 per live birth when considering OHSS, and the respective ICERs were relatively higher when OHSS was taken into account.

Sensitivity analyses confirmed the robustness of base case model, and the probability of birth was the most sensitive variable followed by Gonal-F® dosage. When the lower dosage limit of FSH was taken into account, Gonal-F® was found to be cost-saving and the dominant strategy. The biosimilars are considered dominant only when Gonal-F® probability of birth is decreased by 20%. Similar results were also observed in two CEA studies conducted in Portuguese women, wherein the probability of birth and lower dosage limits in the sensitivity analyses indicated originator FSH to be the dominant strategy[26 10].

Our study was conducted with a National Health Service (NHS) perspective and eventually, the preferred strategy depends on the NHS willingness-to-pay threshold. However, no national or international thresholds have been defined regarding ICER per live-birth, and hence, no clear implication of our findings on the willingness-to-pay per live-birth can be derived at the moment. Theoretically, the biosimilar r-hFSHα will be preferred if the NHS is willing to pay less than the value of the ICER for one extra live-born child, while the originator Gonal-F® will be preferred if it is willing to pay the value of the ICER or more per extra live-born child.

In conclusion, the results of this CEA indicate that the originator r-hFSHα Gonal-F® could be a cost-efficient treatment strategy from the perspective of French health services in the treatment of infertility, as compared to the biosimilars. Given the limitations of the model, reliability of CEA can be greatly improved over time as evidence continues to grow and long-term data, especially in real-life scenario, are available in the individual patient populations of interest for different geographies.

References

1. Boivin, J., Bunting, L., Collins, J. A. & Nygren, K. G. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum. Reprod.* **22,** 1506–1512 (2007).
2. Macaluso, M. *et al.* A public health focus on infertility prevention, detection, and management. *Fertil. Steril.* **93,** 16.e1–10 (2010).
3. Agarwal, A., Mulgund, A., Hamada, A. & Chyatte, M. R. A unique view on male infertility around the globe. *Reprod Biol Endocrinol* **13,** (2015).
4. Datta, J. *et al.* Prevalence of infertility and help seeking among 15 000 women and men. *Hum. Reprod.* **31,** 2108–2118 (2016).
5. Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S. & Stevens, G. A. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med.* **9,** e1001356 (2012).
6. Magali Mazuy, Magali Barbieri, Didier Breton & Hippolyte d'Albis. Recent Demographic Developments in France: A Decline in Fertility, an Increase in Mortality. (2016).
7. Mazuy M, Barbieri M, d'Albis H. Recent demographic trends in France: The number of marriages continues to decrease. *Population.* (2014).
8. EMA. Ovaleap: EPAR Public Assessment Report. (2013).
9. EMA. Gonal-F: Summary of Product Characteristics. (2010).
10. EMA. Bemfola: EPAR Public Assessment Report. (2014).
11. Haute Autorité de Santé. Avis de la commision de transparence- GONAL-F. Available at: https://www.has-sante.fr/portail/jcms/c_1773269/fr/gonal-f. (Accessed: 16th August 2018)
12. Rettenbacher, M. *et al.* A multi-centre phase 3 study comparing efficacy and safety of Bemfola(®) versus Gonal-f(®) in women undergoing ovarian stimulation for IVF. *Reprod. Biomed. Online* **30,** 504–513 (2015).
13. Strowitzki, T., Kuczynski, W., Mueller, A. & Bias, P. Randomized, active-controlled, comparative phase 3 efficacy and safety equivalence trial of Ovaleap® (recombinant human follicle-stimulating hormone) in infertile women using assisted reproduction technology (ART). *Reprod Biol Endocrinol* **14,** (2016).
14. ISPOR. Good Practices for Outcomes Research. Available at: https://ispor.org/heor-resources/good-practices-for-outcomes-research. (Accessed: 16th August 2018)
15. ATIH. Présentation | Publication ATIH PMSI MCO. Available at: https://www.atih.sante.fr/mco/presentation. (Accessed: 16th August 2018)
16. IQVIA. Questionnaire de prise en charge des patientes ayant recours à une aide médicale à la procréation.
17. AMELI. Actes à domicile. Available at: https://www.ameli.fr/infirmier/exercice-liberal/facturation-remuneration/tarifs-conventionnels/actes-domicile. (Accessed: 16th August 2018)
18. AMELI. Le codage des actes biologiques - NABM. Available at: https://www.ameli.fr/medecin/exercice-liberal/facturation-remuneration/nomenclatures-codage/codage-actes-biologiques-nabm. (Accessed: 16th August 2018)

19. AMELI. CCAM en ligne - CCAM. Available at: https://www.ameli.fr/accueil-de-la-ccam/index.php. (Accessed: 16th August 2018)
20. ATIH. Tarifs MCO et HAD | Publication ATIH. Available at: https://www.atih.sante.fr/tarifs-mco-et-had. (Accessed: 16th August 2018)
21. Aitken, M. Delivering on the potential of biosimilar medicines: The role of functioning competitive markets introduction. *IMS Health.* (2016).
22. GABI. France to allow biosimilars substitution. Generics and Biosimilars Initiative. (2014).
23. Freiberg M, Schwarz R, Khoury C. Biosimilars: Market Access and Market Penetration – A Comparison of France and Germany - Value in Health. Available at: https://www.valueinhealthjournal.com/article/S1098-3015(16)31919-2/abstract. (Accessed: 16th August 2018)
24. Gizzo, S., Garcia-Velasco, J. A., Heiman, F., Ripellino, C. & Bühler, K. A cost-effectiveness evaluation comparing originator follitropin alfa to the biosimilar for the treatment of infertility. *Int J Womens Health* **8,** 683–689 (2016).
25. Ripellino, C., Visentin, E., Gizzo, S. & Bühler, K. A Cost-Effectiveness Evaluation Comparing Biosimilar Bemfola to Gonal-F for the Treatment of Infertility in an Italian Contest. *Value Health* **18,** A735 (2015).
26. Silverio, N., Botica, F. & Batista, A. R. Cost-Effectiveness Of Recombinant Human Follicle Stimulating Hormone Biosimilars In Portugal. *Value in Health* **19,** A402–A403 (2016).
27. Gizzo, S. *et al.* A cost-effectiveness modeling evaluation comparing a biosimilar follitropin alfa preparation with its reference product for live birth outcome in Germany, Italy and Spain. *J Med Econ* 1–6 (2018). doi:10.1080/13696998.2018.1511567
28. Gerli, S., Bini, V., Favilli, A. & Di Renzo, G. C. Clinical efficacy and cost-effectiveness of HP-human FSH (Fostimon®) versus rFSH (Gonal-F®) in IVF-ICSI cycles: a meta-analysis. *Gynecol. Endocrinol.* **29,** 520–529 (2013).
29. Al-Inany, H. G., Abou-Setta, A. M., Aboulghar, M. A., Mansour, R. T. & Serour, G. I. Highly purified hMG achieves better pregnancy rates in IVF cycles but not ICSI cycles compared with recombinant FSH: a meta-analysis. *Gynecol. Endocrinol.* **25,** 372–378 (2009).
30. Gholami, H. *et al.* Pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in women aged < 37, undergoing ovulation induction with human FSH compared with recombinant FSH: a randomised controlled study. *Eur Rev Med Pharmacol Sci* **14,** 97–102 (2010).
31. Sagnella, F. *et al.* A prospective randomized noninferiority study comparing recombinant FSH and highly purified menotropin in intrauterine insemination cycles in couples with unexplained infertility and/or mild-moderate male factor. *Fertil. Steril.* **95,** 689–694 (2011).
32. AMELI. Présentation BdM_IT. Available at: http://www.codage.ext.cnamts.fr/codif/bdm_it/index_presentation.php?p_site=AMELI. (Accessed: 16th August 2018)
33. Financement. Modalités de FINANCEMENT 2016 des activités d'AMP et de CPDPN. (2016).

List of Tables

Table 1: Model input data: clinical background

Clinical efficacy outcomes	Gonal-F®O[a]	Gonal-F®B[b]	Gonal-F®P[ab]	Ovaleap®[a]	Bemfola®[b]	BioS[ab]
Oocytes retrieval	97.9%	100.0%	98.9%	99.3%	100.0%	99.8%
Embryo transfer	93.7%	92.7%	93.2%	92.8%	90.0%	91.0%
Pregnancy	36.6%	44.7%	40.3%	29.8%	37.5%	34.5%
Miscarriage	4.1%	2.0%	3.0%	2.4%	4.8%	4.0%
Birth	95.9%	98.0%	97.0%	97.6%	95.2%	96.0%
Live birth rate per woman	32.0%	41.0%	36.0%	27.0%	32.0%	30.0%
Mild/moderate OHSS	2.1%	12.2%	6.7%	3.9%	21.3%	14.7%
Severe OHSS	0.7%	0.8%	0.7%	0.7%	0.8%	0.7%
r-hFSH mean dose	1614.3	1569.2	1593.7	1535.8	1555.7	1548.1

BioS: Pooled biosimilar data from both clinical trials; Gonal-F®B: Gonal-F® data from clinical trial versus Bemfola®; Gonal-F®O: Gonal-F® data from clinical trial versus Ovaleap®; Gonal-F®P: Gonal-F® pooled data versus both biosimilars; OHSS: ovarian hyperstimulation syndrome; r-hFSHα: recombinant human follicle-stimulating hormone alpha

[a] Source: [13]

[b] Source: [12]

Table 2: All estimated costs with assumptions

Phase	Assumptions	Costs (€)	Sources
Induction stage (without treatment induction)		484.91	Ameli French data base [19]
Blocking phase	LA : 48%, SA : 52%, RN: 100	124.97	KOL
Ovulation trigger phase	Decapeptyl®:10% Ovitrelle® :90%,	33.74	
Monitoring	RN: 30%	110.40	
Bioassays	3 ultrasounds	215.80	
	4 LH, progesterone et estradiol assays		
Oocytes retrieval		1,670.81	Ameli French data base [18]
Pre-anesthesia consultation	10% of patients concerned	27	KOL
Oocyte retrieval		861.87	DRG Tariff: PMSI-MCO[20]
Spermatozoid retrieval	91% by masturbation/9%	918.29	
Spermatozoid preparation	transcutaneous	135.00	
Standard IVF	100% of patients	418.50	
ICSI IVF	40% of patients	702.00	
	60% of patients		
Embryo transfer		131.58	Ameli French data base [19]

Phase	Assumptions	Costs (€)	Sources
Intrauterine transfer	Applied for 100% of patients eligible for embryo transfer	51.25	Modalités de FINANCEMENT 2016 des activités d'AMP et de CPDPN[33]
Transfer fees		58.78	
b-hCG bioassay		21.55	
Pregnancy resulting in miscarriage		1,040.66	Ameli French data base
Bioassays	2 b-hCG bioassays	43.1	DRG Tariff: PMSI-MCO[20]
Consultation>6 months	3,4 and 5 month consultations	55.80	
Ultrasound	11AS, 1T, 2T ultrasounds	135.12	
Miscarriage		806.63	
Pregnancy giving live birth		2,873.40	Ameli French data base
Bioassays	2 b-hCG bioassays	43.1	DRG Tariff: PMSI-MCO[20]
Consultation<6 months	3,4 and 5 month consultations	55.80	KOL (questionnaire)
Ultrasound	11AS, 1T, 2T ultrasounds	235.32	
Consultation>6 months	6, 7, 8 and 9th month consultations	112.00	
Delivery	75% natural delivery - 25% cesarean delivery	2,427.17	
Ovarian Hyperstimulation Syndrome: mild and moderate		235.32	Ameli French data base
Ultrasound	4 ultrasounds performed during gynecologist consultations (as it can occur anytime, this is a mean cost of all ultrasounds performed during pregnancy). As ultrasound costs are more expensive, this tariff will be taken into account instead of consultations	58.83	KOL
Ovarian Hyperstimulation Syndrome: severe		1,391.72	Ameli French data base
Ultrasound	1 ultrasound	58.83	KOL
Hospitalizations	1 hospitalization	1,332.89	DRG Tariff: PMSI-MCO[20]

b-hCG: beta-human chorionic gonadotropin; DRG: Diagnosis-Related Group; ICSI: Intra Cytoplasmic Spermatozoid Injection; IVF: in vitro fertilization; KOL: key opinion leader; LA: Long agonist; PMSI: Programme de médicalisation des systèmes d'information; SA: Short Antagonist; RN: Registered Nurse

Table 3: Results of the base case cost-effectiveness analysis

Strategy	Cost (€)	Incremental Cost (€)	Efficacy	Incremental Efficacy	ICER (€)	Cost per live birth (€)
Gonal-F® versus Ovaleap®						
With OHSS						
Gonal-F®	3,825.90	259.17	0.32	0.05	4,804.41	1,866.82
Ovaleap®	3,566.71	-	0.27	-	-	1,522.53
Without OHSS						
Gonal-F®	3,811.51	263.13	0.32	0.05	4,877.76	1,862.19
Ovaleap®	3,548.39	-	0.27	-	-	1,517.62
Gonal-F® vs Bemfola®						
With OHSS						
Gonal-F®	4,121.81	279.07	0.40	0.08	3,274.80	2,367.76
Bemfola®	3,842.74	-	0.32	-	-	1,857.76
Without OHSS						
Gonal-F®	4,081.80	298.68	0.40	0.08	3,504.89	2,351.50
Bemfola®	3,783.12	-	0.32	-	-	1,838.60
Gonal-F® pooled versus BioS						
With OHSS						
Gonal-F®	3961.50	259.56	0.36	0.06	4,352.17	2,095.56
BioS	3701.94	-	0.30	-	-	1,718.15
Without OHSS						
Gonal-F®	3 935.40	278.39	0.36	0.06	4,667.90	2,086.15
BioS	3 657.02	-	0.30	-	-	1,704.63

ICER: incremental cost-effectiveness ratio; OHSS: ovarian hyperstimulation syndrome

Table 4: Results of one-way sensitivity analyses for the comparison of Gonal-F® with its biosimilars

Reference analyses	Main Variables of One Way Sensitivity Analysis	ICER Lower bound	ICER Upper bound
Gonal-F®O versus Ovaleap®	Birth rate [± 20%]	Gonal-F®O is dominated	4,112.24
ICER with OHSS: 4,804.41	OHSS (mild to moderate) [± 20%]	4,786.49	4,822.34
ICER without OHSS: 4,877.76	OHSS (severe) [± 20%]	4,769.07	4,839.75
	Dosage [663.7; 2,564.9]	**Gonal-F®O** is **dominant**	11,922.79
	Treatment cost [± 20%]	2,501.1	-
Gonal-F®B vs Bemfola®	Birth rate [± 20%]	42,456.71	3,110.34
ICER with OHSS: 3,274.80	OHSS (mild to moderate) [± 20%]	3,207.44	3,342.15
ICER without OHSS: 3,504.89	OHSS (severe) [± 20%]	3,248.24	3,301.35
	Dosage [1061.2; 2,077.2]	1,262.02	5,200.11
	Treatment cost [± 20%]	1,816.79	-
Gonal-F®P versus BioS	Birth rate [± 20%]	Gonal-F®P is dominated	3,884.92
ICER with OHSS: 4,352.17	OHSS (mild to moderate) [± 20%]	4,299.36	4,404.98
ICER without OHSS: 4,667.90	OHSS (severe) [± 20%]	4,317.47	4,386.87
	Dosage [864.4; 2,323]	**Gonal-F®P** is **dominant**	9,043.00
	Treatment cost [± 20%]	2,268.78	--

ICER: incremental cost-effectiveness ratio; OHSS: ovarian hyperstimulation syndrome

List of Figures

Figure 1: Decision-tree

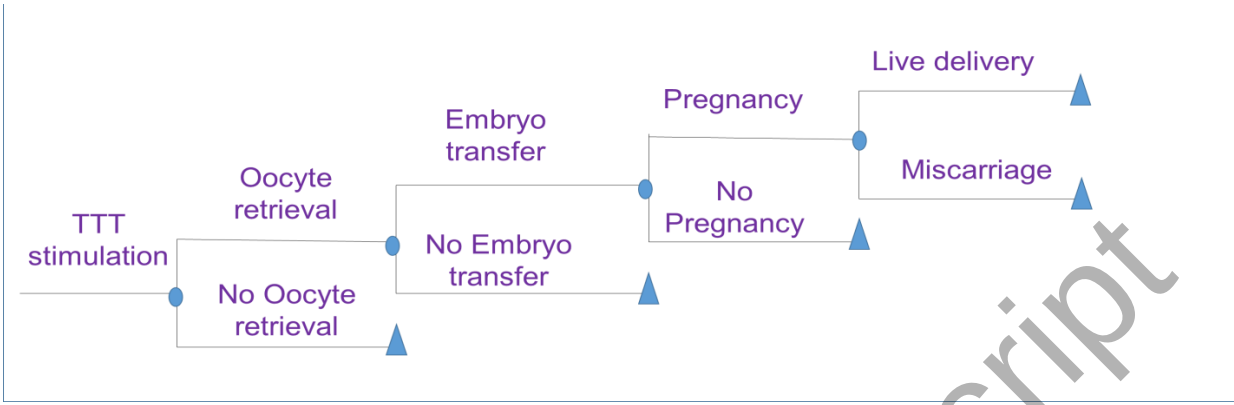

Figure 2: Tornado diagram depicting the sensitivity analysis for Gonal-F®P versus BioS