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Partially Hydrolysed 100% Whey-Based Infant Formula and the Prevention of Atopic Dermatitis: Comparative Pharmacoeconomic Analyses

by Jörg Spieldenner et al.

Key insights

Atopic dermatitis is a common complaint in young children and it is often associated with the development of other allergic disorders. This article investigates the relative health and cost benefits of using partially hydrolysed infant formula (PHF) for preventing atopic dermatitis in at-risk newborns who were not exclusively breastfed.

Current knowledge

Childhood atopic dermatitis places a significant economic burden on healthcare systems, the families of affected children, and on society. Few European economic evaluations have addressed this issue, but a German study found that the annual cost of treating atopic dermatitis was USD 219 per child in 2003, while in Italy the average cost to the family was EUR 1,254 in 2006. It is therefore important to consider the financial, as well as the clinical impact of interventions aimed at preventing or treating atopic dermatitis.

Practical implications

Based upon clinical findings and economic analyses, PHF has been shown to be a suitable alternative to cow's milk-based formulas for preventing atopic dermatitis in at-risk children. European data indicate that from a societal perspective the additional costs associated with using the PHF will be more than compensated for by significantly reduced healthcare costs and time losses for the families. Families with at-risk children will on average save between EUR 624 and 2,200 by using PHF over cow's milk-based formula.

Number of avoided cases of atopic dermatitis (AD) and cost savings from the perspective of the family.

Recommended reading

Iskedjian M, Dupont C, Spieldenner J, Kanny G, Raynaud F, Farah B, Haschke F: Economic evaluation of a 100% whey-based, partially hydrolysed formula in the prevention of atopic dermatitis among French children. *Curr Med Res Opin* 2010;26:2607–2626.

Partially Hydrolysed 100% Whey-Based Infant Formula and the Prevention of Atopic Dermatitis: Comparative Pharmacoeconomic Analyses

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Key Messages

- Atopic dermatitis is a common skin disease in infants and children, and places a substantial economic burden on families and the healthcare system.
- In infants that are not exclusively breastfed, atopic dermatitis can be prevented by using a hydrolysed infant formula to reduce the risk of allergy. A specific 100% whey-based partially hydrolysed formula (PHF-W) has been shown to be more effective than a cow's milk-based standard formula (SF), and comparable to extensively hydrolysed infant formulas (EHF), in the prevention of atopic dermatitis in at-risk infants.
- Based on data from 5 European countries, PHF-W appears to be a feasible option for the prevention of atopic dermatitis, being cost effective from the perspective of public healthcare systems when compared with SF, and associated with substantial cost savings for public healthcare systems and society when compared to EHF.

Key Words

Allergy prevention • Atopic dermatitis • Cost-effectiveness analysis • Cost-minimization analysis • Infant formula • Infant nutrition

Abstract

Clinical trials have demonstrated that the risk of developing atopic dermatitis is reduced when using hydrolysed formulas to feed infants with a documented risk of atopy (i.e. an affected parent and/or sibling) when breastfeeding is not practised. However, little is known about the cost-effectiveness of using hydrolysed formulas. Consequently, economic analyses in 5 European countries (Denmark, France, Germany, Spain and Switzerland) have evaluated the costs and cost-effectiveness of a specific brand of 100% whey-based partially hydrolysed infant formula, NAN-HA[®] (PHF-W) compared with a cow's milk standard formula (SF) in the prevention of atopic dermatitis in at-risk children. This review synthesises the findings of these studies. Cost-effectiveness analyses (CEA) used a decision-analytic model to determine treatment pathways, resource utilisation and costs associated with the management of atopic dermatitis in healthy at-risk newborns who were not exclusively breastfed. The mod-

el had a 12-month horizon and applied reimbursement rates of 60–100% depending on the country. Outcomes were considered from the perspective of the public healthcare system (e.g. the Ministry of Health; MOH), family and society. The final outcome was the incremental cost-effectiveness ratio per avoided case of atopic dermatitis (ICER) for PHF-W versus SF. A cost-minimisation analysis was also performed to compare PHF-W with extensively hydrolysed formulas (EHF). The base-case CEA produced ICERs per avoided case for PHF-W versus SF of EUR 982–1,343 (MOH perspective), EUR –2,202 to –624 (family perspective) indicating savings, and EUR –1,220 to 719 from the societal perspective. The main costs related to formula (MOH and society) and time loss (family). In the cost-minimisation analysis, PHF-W yielded savings of between EUR 4.3 and 120 million compared with EHF-whey when the latter was used in prevention. In conclusion, PHF-W was cost-effective versus SF in the prevention of atopic dermatitis and cost saving compared with EHF when used in prevention.

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Introduction

Atopic dermatitis is one of the most common skin diseases in infants and young children [1]. In addition to having an adverse effect on the quality of life of the child and their family [2], it is often associated with the subsequent development of other atopic disorders [1]. The prevalence of atopic dermatitis among children aged 6–7 years varies from 0.9 to 22.5% in different countries worldwide, with Latin America and Asia having comparatively high rates [3]. In Europe, the prevalence of atopic dermatitis in children is approximately 10–20% [4, 5]. The prevalence of the condition has increased over the last few decades, particularly in developing countries [6–8]. Atopic dermatitis often develops within the 1st year of life; one study found the onset was within 6 months in 45% of affected children and within 1 year in 60% [5]. Infants with a family history of atopy are at increased risk of developing atopic dermatitis [9].

It is recommended that infants are exclusively breastfed for the first 4–6 months of life [10–15]. However, when this is not possible or desired they are given an infant formula instead of, or in addition to, breast milk. Formulas are usually based on cow's milk (standard formula, SF). There is some evidence that early exposure to dietary allergens may increase the risk of developing food allergies and atopic dermatitis [16, 17]. In an effort to reduce the potential risks associated with cow's milk proteins, formulas have been developed that contain proteins which

have been hydrolysed in order to reduce allergenicity. An alternative approach is to use amino-acid-based formulas, but these are considerably more expensive [18]. It has been shown that using hydrolysed formulas can reduce the incidence of allergic manifestations and atopic dermatitis compared with cow's milk formulas [19–21].

Hydrolysed formulas are differentiated by the degree of hydrolysis (extensively or partially hydrolysed) and by the protein source (whey or casein). Partially hydrolysed formulas (PHF) are thought to have hypoallergenic properties similar to extensively hydrolysed formulas (EHF), but a better taste and texture [19]. One specific brand of 100% whey-based partially hydrolysed infant formula (PHF-W) manufactured by Nestlé, NAN-HA[®], and branded under NIDAL HA[®] in France, NAN Excel[®] in Spain, BEBA HA[®] in Germany and Switzerland and NAN HA[®] in Denmark, has been shown to be effective in the prevention of atopic dermatitis in meta-analyses of randomised trials [21, 22]. It was found to be more effective than SF and similar in efficacy to EHF for preventing atopic dermatitis symptoms in infants who were not exclusively breastfed, and who were deemed at risk of allergy because of a family history of atopy [22, 23].

Atopic dermatitis is associated with a significant economic burden for healthcare systems, the families of affected children and for society as a whole [24–31]. Only a few European economic evaluations have focused specifically on children: a German study found that the annual cost of treating atopic dermatitis was USD 219 per child in 2003 [26], while in Italy the average cost to the family

In an effort to reduce the potential risks associated with cow's milk proteins, formulas have been developed that contain proteins which have been hydrolysed in order to reduce allergenicity.

amounted to EUR 1,254 in 2006 [25]. It is therefore important to consider the financial, as well as the clinical, impact of interventions aimed at preventing or treating atopic dermatitis.

Health economics is a discipline that analyses the economic aspects of health and healthcare, including both prevention and treatment approaches [32]. Health economics usually focuses on the costs and the consequences of healthcare interventions, incorporating both medi-

Table 1. Pharmacoeconomic terms

CEA	Alternative interventions are compared in terms of the cost per unit of effectiveness for a specific outcome (e.g. deaths avoided, cases detected).
Cost-minimisation analysis	Assumes the alternative interventions are equally effective in terms of the outcome, and, therefore, only costs are considered.
Decision-analytic modelling	Pharmacoeconomic models combine information on therapeutic strategies, clinical outcomes and/or quality-of-life data, epidemiological data and costs. Decision analytical models reflect a sequence of chance events and decisions over time and are particularly useful for acute episodes of illness.
Discounting	Procedure used to express those costs and benefits that will occur in future years as 'present values'.
Dominance	An intervention is considered dominant if it is more effective and less costly than the alternative intervention. An intervention is dominated if it has a worse outcome and higher costs.
ICER	Ratio of (the difference in the costs of the intervention of interest compared with an alternative) to (the difference in outcomes between the two interventions). Indicates the cost per unit of effect from switching from intervention A to intervention B.
Sensitivity analysis	Performed to examine the effect on the results of uncertainty in some of the inputs. The analysis is repeated while varying the assumptions used.
Time horizon	Time span that reflects the period during which the main differences in effects and use of resources are expected to occur.
Utility	Measure of preference for one health state in relation to another on a numerical scale where 0 = death and 1 = optimal health.

cal and economic information, in order to identify ways of allocating health-related resources effectively [32].

One type of health economic evaluation that is widely used is cost-effectiveness analysis (CEA). In CEA, the costs and consequences of two alternative strategies are compared, with the results expressed as an incremental cost-effectiveness ratio (ICER), representing the difference in costs in relation to the difference in consequences [33]. This can be interpreted as the cost that will be incurred in order to obtain an additional success, if one

treatment is selected over the other (e.g. cost per avoided complication) [33]. Costs that might be considered include direct medical costs associated with the treatment pathway, such as the cost of the intervention (e.g. drug, or in the case of PHF-W, the formula), physicians, hospitalisation and laboratory tests. Indirect costs, such as productivity losses incurred through absence from work, may also be taken into account.

Other terms that are relevant in the field of health economics and the analyses discussed in this paper are summarised in table 1.

Until recently, there has been no research into the cost-effectiveness of PHF-W for the prevention of atopic dermatitis in Europe. However, a series of pharmacoeconomic analyses evaluating the use of PHF-W in 5 European countries has now been performed. These analyses determined the costs, consequences and cost-effectiveness of PHF-W in the prevention of atopic dermatitis in at-risk children when compared with SF. An additional analysis compared PHF-W with EHF. The aim of this article is to summarise and compare the results from these European pharmacoeconomic analyses of PHF-W.

Methods

Pharmacoeconomic analyses exploring the use of PHF-W for the prevention of atopic dermatitis were performed in 5 European countries. CEA were performed as the main analysis in France [23], Germany [34], Spain [35, 36] and Switzerland [37]. In Denmark, a cost-minimisation analysis was performed [36, 38]. Cost-utility assessments (evaluating the relationship between costs and health utility, expressed as quality-adjusted life years) were not performed due to a lack of published data on health utilities for atopic dermatitis in infants.

Similar methodology was applied for each of the CEA. Predictive decision-analytic modelling was used to determine treatment pathways, resource utilisation and costs associated with the management of atopic dermatitis in healthy at-risk children (newborn to 3 years of age) who were not exclusively breastfed. At risk was defined as children with at least 1 parent or sibling with a confirmed medical history of allergies.

The main comparator used was SF for all countries except Denmark, for which EHF-whey (EHF-W) and EHF-casein (EHF-C) were used. For France, Germany, Spain and Switzerland, PHF-W was compared with one or both types of EHF in a secondary analysis.

Three different perspectives were applied to the analyses: those of the public healthcare system (Ministry of

Fig. 1. Decision tree model: atopic dermatitis treatment patterns for newborns to 3-year-olds in France and Spain. Models for Germany, Switzerland and Denmark were similar except that dietary management was not incorporated as a separate treatment approach (i.e. only ‘medical’ and ‘combined’ approaches were included).

Health; MOH), the child’s family and society as a whole (which incorporated both of the other perspectives). The time horizon for the base-case analyses was 12 months, including a 6-month period of formula consumption. Twelve months was chosen because it covered the period during which most cases of atopic dermatitis first develop and also went beyond the usual period of milk consumption.

The structure of the decision-analytic model is summarised in figure 1. The model applied a series of 3-month cycles starting from the birth cohort. Clinical and cost inputs were obtained from medical literature, government publications, official formularies, pharmacy surveys and expert opinions.

The initial cohort entering the model (i.e. at-risk newborns not exclusively breastfed) was determined using the following equation: [(birth cohort of country) × (1 – average exclusive breastfeeding rate) × (rate of at-risk infants)].

The main clinical input, the incidence of atopic dermatitis, was obtained from a meta-analysis of randomised controlled trials, which reported that PHF-W was more effective than SF at preventing cases of atopic dermatitis, and that there was no statistically significant difference in efficacy between PHF-W and

EHF-W or EHF-C [22, 23]. For the CEA, the final clinical outcome of the model was the number of avoided cases of atopic dermatitis when using PHF-W compared with SF.

A panel of expert clinicians was convened in each country in order to define and validate treatment pathways, and to identify and value the resources consumed in the management of atopic dermatitis. Depending on the clinical practice patterns applicable to each country, treatment pathways could encompass dietary management (change in infant formula), medical treatment (topical emollients, corticosteroids or immunosuppressants, depending on the country), or a combination of both approaches.

The costs that were considered are summarised in table 2. The cost of the comparator formula was based on the brand with the largest market share or the average cost of two dominant brands in the relevant country. The base-case CEA assumed that all infant formulas were re-

imbursed at the same rate by the relevant MOH (65% in France, 60% in Spain, 100% in Germany, 90% in Switzerland and 60% in Denmark). This enabled a direct comparison to be made between the different formulas. Costs beyond 1 year were discounted.

The principal analysis for the studies in France, Germany, Spain and Switzerland assessed cost-effectiveness, with the main outcome being

Depending on the clinical practice patterns applicable to each country, treatment pathways could encompass dietary management (change in infant formula), medical treatment (topical emollients, corticosteroids or immunosuppressants, depending on the country), or a combination of both approaches.

Table 2. Costs associated with each perspective

Perspective	Costs
MOH	Reimbursed portion of: <ul style="list-style-type: none">– Formula– Medical visits– Medications– Laboratory tests
Family	Formula (non-reimbursed portion) Medical costs (non-reimbursed portion) Travel costs Indirect costs (productivity and time loss)
Society	All of the above costs

the expected incremental cost per avoided case of atopic dermatitis (ICERs) when comparing PHF-W with SF. ICERs were calculated as the difference in costs between PHF-W and SF divided by the negative value for the difference in the number of cases of atopic dermatitis between PHF-W and SF. The aggregated cost associated with each perspective was an intermediate economic outcome. In these studies, a secondary analysis was performed to compare PHF-W with one or both types of EHF, using a cost-minimisation approach.

The main analysis in Denmark was a cost-minimisation analysis comparing PHF-W with EHF-W and EHF-C. This approach was applied based on the lack of significant difference in efficacy for the prevention of atopic dermatitis between PHF-W and EHF. The analysis assumed that all costs would be similar between comparators with the exception of the acquisition cost for the infant formulas themselves. Even though differences in efficacy were not statistically significant, the nominal differences that existed were taken into account in sensitivity analyses by performing a CEA to produce ICERs for the expected cost per avoided cases of atopic dermatitis when comparing PHF-W with either type of EHF [38].

One-way sensitivity analyses tested the effect of variations in individual key parameters on the outcome of the modelled CEA, and probabilistic sensitivity analyses using a set of 10,000 Monte Carlo simulations (simultaneously varying multiple parameters in a random fashion) tested the robustness of the overall model. The main parameters varied in one-way sensitivity analyses are listed in table 3 [23].

Table 3. Main parameters varied in sensitivity analyses

Infant at-risk rates
Exclusive breastfeeding rates
Risk and incidence of atopic dermatitis
Severity of atopic dermatitis
Quantity of formula consumed
Formula choice after PHF-W discontinuation
Costs of formula, nurses, transportation
Use of laboratory tests
Reimbursement rates
Time lost by family members (medical visits, child care at home, application of creams)
Time horizon
Discounting

Table 4. Atopic dermatitis outcomes for PHF-W versus SF in base-case analyses in cohorts of at-risk newborns who are not exclusively breastfed

Country	Cohort n	Avoided cases of atopic dermatitis using PHF-W vs. SF	
		n	%
France	185,298	13,356	42
Spain	96,614	6,964	42
Germany	142,041	10,238	42
Switzerland	22,933	1,653	42

Results

In the base-case analyses comparing PHF-W with SF for the prevention of atopic dermatitis, the number of avoided cases of atopic dermatitis achieved when PHF-W was used instead of SF ranged from 1,653 to 13,356 among at-risk birth cohorts of 22,933 (Switzerland) to 185,298 (France) infants (table 4) [23, 34–38].

Incremental costs and ICERs for PHF-W versus SF are shown in table 5 [23, 34–36]. From the perspective of the MOH and society, the main driver of overall costs was the cost of the infant formula, while from the family perspective, the main cost driver was loss of time [see table 6 for data from Germany (consistent with data from the other countries studied)]. Expected ICERs (ICER per avoided case of atopic dermatitis for PHF-W compared with SF) ranged from EUR 982 to 1,343 from the MOH perspective, from EUR –2,202 to –624 from the family perspective (indicating savings), and from EUR 1,220 to 719 from the societal perspective (table 5) [23, 34–36]. One-way and probabilistic sensitivity analyses confirmed the robust-

Table 5. Cost and ICERs for PHF-W versus SF in base-case analyses

Setting	Incremental cost, EUR			ICER, EUR		
	MOH	family	society	MOH	family	society
France	17,941,352	-8,338,537	9,602,815	1,343	-624	719
Spain	7,319,916	-7,673,628	-587,489	1,051	-1,102	-84
Germany	11,634,350	-14,910,733	-3,276,383	1,136	-1,456	-320
Switzerland	1,623,775	-3,639,795	-2,016,021	982	-2,202	-1,220

CHF were converted into EUR using the exchange rate from June 24, 2011. Negative values indicate savings.

ness of the model, with most producing ICERs that were consistent with those obtained in the base-case analysis (table 7) [36].

In the analyses comparing PHF-W with EHF-W for the prevention of atopic dermatitis, PHF-W was associated with potential cost savings ranging from EUR 1.3 million (Denmark) to 64 million (France) from the MOH perspective, and savings of EUR 4.3 million (Denmark) to 120 million (Germany) from the perspective of society as a whole (table 8) [23, 34–36, 38].

In the comparisons of PHF-W with EHF-C, PHF-W was associated with potential savings of EUR 1.3 million (Denmark) to 76 million (France) from the MOH perspective, and savings of EUR 3.8 million (Denmark) to 116 million (France) from the societal perspective.

In the Danish study, sensitivity analyses confirmed that PHF-W was dominant over EHF-W, and found that EHF-C showed unattractive ICERs against PHF-W, with no likelihood that EHF-C would dominate PHF-W [38].

As seen in table 7, Monte Carlo simulations indicated probabilities of PHF-W being cost effective against SF (gain in efficacy with a cost increase) of between 45 and 92% and probabilities of it being dominant (cost savings with a gain in efficacy) of between 8 and 55%, with negligible probabilities of being dominated ($\leq 0.2\%$).

Discussion

Atopic dermatitis places a substantial economic burden on the families of affected children and on the health-care system [24–26]. In Germany, it has been estimated that the total annual cost of atopic dermatitis is EUR 1.2–3.5 billion [39]. It has been shown that in infants who are not exclusively breastfed, the use of hydrolysed formulas reduces the risk of developing atopic dermatitis [19–22]. Given the economic impact of the disorder, it is impor-

Table 6. Costs in the base-case analysis for Germany (in EUR)

Item	PHF-W	SF
MOH perspective		
Formula	62,653,435	49,446,691
Physicians	632,178	1,120,485
Treatment	279,597	562,087
Rehabilitation	611,387	1,083,633
Hospitalisation	305,051	540,678
Laboratory tests	121,338	215,062
Total cost	64,602,986	52,968,636
Family perspective		
Treatment	191,701	339,774
Time lost	18,081,614	32,121,375
Travel	930,969	1,653,868
Total cost	19,204,284	34,115,016
Societal perspective ^a		
Total cost	83,807,270	87,083,652

^a Combination of costs from MOH and family perspectives.

Table 7. Probabilistic sensitivity analyses for PHF-W versus SF from the societal perspective^a

Country	Distribution of simulation results per quadrant			
	quadrant 1	quadrant 2	quadrant 3	quadrant 4
France	91.5%	0.1%	0%	8.4%
Spain	78.8%	0.1%	0%	21.0%
Germany	74.8%	0.2%	0%	25.0%
Switzerland	44.6%	0.2%	0%	55.2%

Quadrant 1 = Gain in efficacy but with a cost increase (incremental cost-effectiveness for PHF-W); quadrant 2 = increase in cost and decrease in efficacy (SF dominant); quadrant 3 = cost savings but with a reduction in efficacy; quadrant 4 = cost savings and gain in efficacy (PHF-W dominant).

^a Based on 10,000 Monte Carlo simulations.

Table 8. Cost savings (in million EUR) for PHF-W versus EHF (base-case analysis for Denmark; secondary analyses for other countries)

Country	PHF-W vs. EHF-W		PHF-W vs. EHF-C	
	society	MOH	society	MOH
France	98	64	116	76
Spain	26	26	76	76
Germany	120	120	N/A	N/A
Switzerland	11.4	10.2	N/A	N/A
Denmark	4.3	1.3	3.8	1.3

CHF and DKK were converted into EUR using the exchange rate from June 24, 2011. N/A = Not applicable.

tant to examine the cost-effectiveness of using these formulas for the prevention of atopic dermatitis.

This review discusses the 5 studies, either published as articles or presented as posters, which are the first 5 economic evaluations of Nestlé NAN-HA, the PHF-W used in this study, for the prevention of atopic dermatitis in at-risk infants in Europe. In 4 of the studies, a CEA compared PHF-W with SF, while in the 5th study (and in secondary analyses in the other studies), PHF-W was compared with EHF in a cost-minimisation analysis.

Under the set of assumptions used, and taking into account the robustness of the economic modelling results, PHF-W was shown to be the highly cost-effective option compared with SF for the prevention of atopic dermatitis in infants from the perspective of the MOH in all 4 countries analysed – France, Spain, Germany and Switzerland. From the MOH perspective, incremental costs per avoided case of atopic dermatitis ranged from EUR 982 to 1,343. Furthermore, PHF-W was dominant over SF (more effective and associated with cost savings) in all 4 countries from the perspective of the family, and in 3 countries – Spain, Germany and Switzerland – from the perspective of society. Sensitivity analyses confirmed the robustness of the results, with only 1 scenario providing a notably different outcome from the base case in each study.

Denmark is the only one of the 5 countries studied where EHF are currently approved, and partly reimbursed, for use in the prevention of cow's milk and food allergy in at-risk infants. Therefore, a comparison between PHF-W and both EFH-W and EFH-C formed the basis of the economic evaluation for this particular country. It is also possible that EHF might be used for prevention in some clinical practice situations in other countries studied, and it was appropriate to perform secondary analyses comparing PHF-W to EHF in these settings, too.

Given that there was no significant difference in preventive efficacy between PHF-W and EHF, a cost-minimisation approach was used for all of these analyses.

In the setting of atopic dermatitis prevention, PHF-W was associated with cost savings compared with EHF in all 5 countries studied, including Denmark, both from the perspective of the MOH and from that of society as a whole. In Denmark, the savings with PHF-W were similar in the comparisons with both EHF-W and EHF-C, which was because the acquisition costs of the two types of EHF were almost identical [38]. These data suggest that PHF is preferable to EHF in the preventive setting, which is consistent with guidelines that recommend using PHF (or reduced allergenicity formulas) for the prevention of allergic manifestations in at-risk infants who are not exclusively breastfed [17, 40–42].

Few other economic evaluations of hydrolysed formulas in the prevention of atopic dermatitis have been reported. A study in Germany, which used a longer time frame (6 years) and a fairly low discount rate of 3%, found that from the societal perspective PHF and EHF-C were cost effective or cost saving, while from the perspective of the German statutory health insurance EHF-C was cost effective and PHF was cost saving [39]. The ICER per avoided case for PHF-W compared with SF was EUR –6,358 from the societal perspective and EUR –792 from the German statutory health insurance perspective [39].

Throughout the current analyses, one of the main drivers of cost was that of the infant formulas themselves; loss of time was also an important consideration from the perspective of the child's family. Atopic dermatitis has an adverse effect on the quality of life of both the child and the parents; however, there are few published data on quality of life or health utilities associated with atopic dermatitis in young children, and, consequently, it was not possible to

incorporate a formal cost-utility analysis into the studies discussed here. Nonetheless, a hypothetical cost-utility analysis was performed as a sensitivity analysis in the Spanish study [35]. Utility values of 0.9, 0.8, 0.7 and 0.9 were applied to mild, moderate, severe and relapsing cases, respectively, for 3-month cycles. Applying time horizons of 1 and 3 years, this analysis indicated dominance from the family and societal perspectives and produced ICERs of less than EUR 22,000 per quality-adjusted life year from the MOH perspective, which is well below the commonly accepted threshold of EUR 35,000 per quality-adjusted life year [35].

All economic evaluations have limitations, and the predictive model used in the analyses discussed here is no exception. However, whenever possible the bias was set against the treatment of interest, PHF-W, in the base-case analyses, in order to make the evaluations as conservative as possible.

Incidence rates came from a meta-analysis which included a range of studies of different sizes; however, using a meta-analytic approach to analysis should reduce any bias associated with data from different studies. An equal incidence of atopic dermatitis was assumed for adjoining 3-month intervals in the periods from 0 to 6 and from 6 to 12 months, although, in reality, incidence rates for atopic dermatitis tend to be higher earlier in life. Flare-ups were assumed to occur at 3-monthly intervals, although, in practice, they are likely to happen more frequently. It was assumed that the same quantity was consumed daily for each type of formula, although this may not be the case in reality. In addition, after discontinuing one brand of formula it was assumed that the next brand used was of equal price.

PHF-W generally demonstrated dominance over SF from the family and societal perspectives, and attractive cost-effectiveness from the MOH perspective. PHF-W was also dominant over EHF-W from the MOH perspective.

The effect of altering the assumptions made for these and other parameters was tested individually using one-way sensitivity analyses. In addition, the overall model was tested using probabilistic sensitivity analysis, and the boundaries assigned to parameters in Monte Carlo simulations meant that this probabilistic analysis was more conservative than the base-case analysis.

In summary, a series of European analyses based on predictive modelling have established the cost-effectiveness of PHF-W over SF in the prevention of atopic dermatitis in healthy at-risk infants who were not exclusively breastfed. PHF-W generally demonstrated dominance

over SF from the family and societal perspectives, and attractive cost-effectiveness from the MOH perspective. PHF-W was also dominant over EHF-W from the MOH perspective. These findings should be of interest to public healthcare systems and reimbursement agencies when considering the role of PHF-W in the prevention of atopic dermatitis.

Disclosure Statement

This study was funded by Nestlé Nutrition Institute (NNI). M.I. is employed by PharmIdeas, which performed this study under contract with NNI; J.S. and F.H. are employed by NNI; D.B., C.D., S.N.F. and A.v.B. have received honoraria for their participation. H.S. has participated as a clinical investigator, and/or advisory board member, and/or speaker for Arla, Biocodex, Danone, Nestlé Nutrition Institute, Nutricia, and Mead Johnson.

References

- 1 Spergel J, Paller A: Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003; 112:S118–S127.
- 2 Lewis-Jones S: Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006;60: 984–992.
- 3 Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, ISAAC Phase Three Study Group: Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009;124:1251.e23–1258.e23.
- 4 Schultz Larsen F, Diepgen T, Svensson A: The occurrence of atopic dermatitis in north Europe: an international questionnaire study. *J Am Acad Dermatol* 1996;34:760–764.
- 5 Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG: The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994;30:35–39.
- 6 Asher M, Montefort S, Björkstén B, et al: Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368: 733–743.

- 7 Fennessy M, Coupland S, Popay J, Naysmith K: The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. *J Epidemiol Community Health* 2000;54:581–589.
- 8 Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR, International Study of Asthma and Allergies in Childhood (ISAAC) Phase One and Three Study Groups: Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 2008;121:947–954.
- 9 Böhme M, Wickman M, Lennart Nordvall S, Svartengren M, Wahlgren CF: Family history and risk of atopic dermatitis in children up to 4 years. *Clin Exp Allergy* 2003;33:1226–1231.
- 10 World Health Organization and United Nations Children's Fund: Global Strategy for Infant and Young Child Feeding. Geneva, NLM Classification WS 120 (2003). <http://www.who.int> (accessed Sep 16, 2011).
- 11 European Network for Public Health Nutrition: Networking, Monitoring, Intervention and Training. Infant and young child feeding: standard recommendations for the European Union [http://printfu.org/read/infant-and-young-child-feeding-standard-recommendations-for-the-bb16.html?f=1qeYpurpn6Wih-SUpOGunK2nh7Xd3Mbi3IXR4M2O7dXq28yM0t7O4MyF1tfO0t3U3KeF3-PX09jJ19SS29PX1eLaytrT19nd19Pjks_d5obp1cqMnaSTlqPYqqSjkOjal6jYpqCnn5bS2uPm1t7EttrZyo6q6Z-loofWIKThrpqtp4fU4-rVrpeU5-ngnOfa3tnR0d2k1ObPINXg0Nrd2d2cydvS6ZTZ3dPl5tfT6JTl0cuOqvM (accessed Sep 16, 2011)].
- 12 Société Française de Dermatologie: Prise en charge de la dermatite atopique de l'enfant. Texte des recommandations. *Ann Dermatol Venerol* 2005;132:1S9–1S18.
- 13 Muche-Borowski C, Kopp M, Reese I, et al: Allergieprävention. AWMF Guideline Register 061/16, 2009.
- 14 Lasarte Velillas J: Recomendaciones para la lactancia materna. Comité de Lactancia Materna de la Asociación Española de Pediatría (<http://www.aeped.es/sites/default/files/lacmat-espanol.pdf>).
- 15 Høst A, Koletzko B, Dreborg S, et al: Dietary products used in infants for treatment and prevention of food allergy. Joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology and Nutrition (ESPGHAN) Committee on Nutrition. *Arch Dis Child* 1999;81:80–84.
- 16 Halken S, Høst A, Hansen LG, Osterballe O: Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 'high-risk' infants. *Allergy* 1992;47:545–553.
- 17 Høst A, Halken S, Muraro A, et al: Dietary prevention of allergic diseases in infants and small children. *Pediatr Allergy Immunol* 2008;19:1–4.
- 18 Iskedjian M, Dupont C, Spieldenner J, Kanny G, Raynaud F, Farah B, Haschke F: Economic evaluation of a 100% whey-based, partially hydrolysed formula in the prevention of atopic dermatitis among French children. *Curr Med Res Opin* 2010;26:2607–2626.
- 19 von Berg A, Koletzko S, Filipiak-Pittroff B, et al: The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol* 2003;111:533–540.
- 20 von Berg A, Filipiak-Pittroff B, Krämer U, et al: Preventative effect of hydrolyzed formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). *J Allergy Clin Immunol* 2008;121:1442–1447.
- 21 Alexander DD, Cabana MD: Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. *J Pediatr Gastroenterol Nutr* 2010;50:422–430.
- 22 Szajewska H, Horvath A: Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. *Curr Med Res Opin* 2010;26:423–437.
- 23 Iskedjian M, Szajewska H, Spieldenner J, Farah B, Berbari J: Meta-analysis of a partially hydrolysed 100%-whey infant formula vs. extensively hydrolysed infant formulas in the prevention of atopic dermatitis. *Curr Med Res Opin* 2010;26:2599–2606.
- 24 Emerson RM, Williams HC, Allen BR: What is the cost of atopic dermatitis in preschool children? *Br J Dermatol* 2001;144:514–522.
- 25 Ricci G, Bendandi B, Pagliara L, et al: Atopic dermatitis in Italian children: evaluation of its economic impact. *J Pediatr Health Care* 2006;20:312–315.
- 26 Weinmann S, Kamtsiuris P, Wickman H, et al: The costs of atopy and asthma in children: assessment of direct costs and their determinants in a birth cohort. *Pediatr Allergy Immunol* 2003;14:18–26.
- 27 Su JC, Kemp AS, Varigos GA, Nolan TM: Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 1997;76:159–162.
- 28 Kemp AS: Atopic eczema: its social and financial costs. *J Paediatr Child Health* 1999;35:229–231.
- 29 Verboom P, Hakkaart-Van L, Sturkenboom M, De Zeeuw R, Menke H, Rutten F: The cost of atopic dermatitis in the Netherlands: an international comparison. *Br J Dermatol* 2002;147:716–724.
- 30 Ehlken B, Möhrenschrager M, Kugland B, Berger K, Quednau K, Ring J: Cost-of-illness study in patients suffering from atopic eczema in Germany. *Hautarzt* 2005;56:1144–1151.
- 31 Herd RM, Tidman MJ, Prescott RJ, Hunter JA: The cost of atopic eczema. *Br J Dermatol* 1996;135:20–23.
- 32 Berger ML (ed): Health Care Cost, Quality and Outcomes: ISPOR Book of Terms. Lawrenceville, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 2003.
- 33 Venturini F, Johnson KA: Introduction to pharmacoeconomic principles and application in pharmacy practice. *CJHP* 2002;14:6–15.
- 34 Iskedjian M, von Berg A, Bauer CP, et al: Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among German children: preliminary results (abstracts and poster). Sorrento, 44th Annual Meeting of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition, May 25–28, 2011.
- 35 Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Spanish children. Vevey, Nestlé Nutrition Institute, 2011.
- 36 Iskedjian M, Berbari J, Navarro V, Farah B, Detzel P, Spieldenner J: Pharmacoeconomic analyses of partially hydrolyzed infant formulas in prevention of atopic dermatitis: comparative results from 5 European countries (poster). Madrid, 14th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research, November 2011.
- 37 Spieldenner J, Belli D, Farah B, et al: Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Swiss children: preliminary results (poster). Newcastle, 52nd Annual Meeting of the European Society for Paediatric Research, October 16, 2011.
- 38 Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Danish children. Vevey, Nestlé Nutrition Institute, 2011.
- 39 Mertens J, Stock S, Lungen M, et al: Is prevention of atopic eczema with hydrolyzed formulas cost-effective? An application of results of the GINI-study to the German situation. *Pediatr Res* 2010;(suppl 1):66–67. Copenhagen, Oral presentation at the 3rd EAPS Congress, October 2010.
- 40 Baehler P, Baenziger O, Belli D, et al: Empfehlungen für die Säuglingsernährung 2009. *Paediatrica* 2009;20:13–15.
- 41 Chouraqui J-P, Dupont A, Bocquet A, et al: Alimentation des premiers mois de vie et prévention de l'allergie. *Arch Pédiatr* 2008;15:431–442.
- 42 Host A, Halken S, Muraro A, et al: Dietary prevention of allergic diseases in infants and small children. Amendment to previous published articles in *Pediatric Allergy and Immunology* 2004, by an expert group set up by the Section on Pediatrics, European Academy of Allergology and Clinical Immunology. *Pediatr Allergy Immunol* 2008;19:1–4.