




# Expert Opinion on the Therapeutic Use of the Fixed-Ratio Combination of Insulin Glargine 100 U/mL and Lixisenatide: a Central/Eastern European Perspective

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Received: December 23, 2019  
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## ABSTRACT

The fixed-ratio combination (FRC) of a basal insulin and a GLP-1 receptor agonist (GLP-1 RA) has proven to be an effective therapeutic approach. However, physicians face numerous practical questions that cannot be answered by recently published trial results, current guidelines and summaries of product characteristics. In April 2019, a scientific meeting was held with the participation of nine experts from four Central and Eastern European countries to

provide expert consensus on the optimal daily use of the insulin glargine and lixisenatide FRC (iGlarLixi). Topics included the positioning and initiation of iGlarLixi and the management of treatment. This paper summarizes the outcomes of the meeting.

**Keywords:** Expert opinion; Fixed-ratio combination; Insulin glargine and lixisenatide

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## Key Summary Points

The fixed-ratio combination (FRC) of a basal insulin and a GLP-1 receptor agonist (GLP-1 RA) has proven to be an effective therapeutic approach.

Physicians face numerous practical questions when initiating a fixed-ratio combination that cannot be answered by recently published trial results, current guidelines and summaries of product characteristics.

A consensus meeting was held with the participation of experts from four Central and Eastern European countries to provide expert consensus on the optimal daily use of the insulin glargine and lixisenatide FRC (iGlarLixi).

The experts reached consensus in their answers to all of the questions presented; these expert opinions are summarized in this manuscript.

## INTRODUCTION

By the end of the last decade (the 2010s), glucagon-like peptide-1 receptor agonists (GLP-1 RAs) had become important components of standard care for type 2 diabetes mellitus (T2DM). Although GLP-1 RAs are valuable in many aspects for the treatment of diabetes, they do not seem to stop progressive beta-cell failure, a key pathophysiology of this chronic

condition. Thus, an appropriate combination of antidiabetic drugs with different modes of action is necessary to maintain long-term metabolic control.

One very promising and particularly effective therapeutic approach is the fixed-ratio combination (FRC) of a GLP-1 RA and a basal insulin. FRCs have only been used in clinical practice since 2016, so their position in the diabetes therapeutic algorithm is yet to be fully established. The latest Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes (ADA-EASD Consensus Report [1]) indicates the therapeutic position of the combination of a basal insulin and a GLP-1 receptor agonist and the potential benefits of the FRC over the separate use of the GLP-1 RA and the basal insulin, including a decrease in the number of daily injections required. Currently, two FRCs are available: insulin degludec/liraglutide (IDegLira) and insulin glargine/lixisenatide (iGlarLixi).

There is a clear scientific rationale for combining a basal insulin, which mainly reduces the fasting plasma glucose (FPG) by decreasing hepatic glucose production and glucagon secretion but increases body weight, with a GLP-1 RA, which further improves the FPG but also reduces postprandial plasma glucose (PPG) peaks. GLP-1 RAs increase glucose-dependent insulin secretion, decrease glucagon secretion, and reduce the gastric emptying rate, food intake and body weight [2]. The fixed-ratio coformulation of these drugs has several advantages compared to basal-bolus insulin treatment or separate administration of the components, including a less complex and more convenient dosing schedule, fewer injections, easier titration, and lower insulin and GLP-1 RA doses. In addition, the titration of FRCs has been shown to improve the gastrointestinal tolerability of the GLP-1 RA component compared to individual administration owing to slower uptitration than when the GLP-1 RA is administered alone [2].

The efficacy and safety of the two FRCs (iGlarLixi and iDegLira) were investigated and established in the LixiLan and DUAL clinical development programmes, respectively [2]. The

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DUAL programme, which consisted of nine randomized clinical trials, confirmed that once-daily iDegLira generally achieved better glycaemic control than basal insulin or liraglutide alone, was associated with a lower risk of hypoglycaemic events, and had a more favourable patient weight profile than that of basal insulin alone [2].

The iGlarLixi development programme encompassed a proof-of-concept phase 2 [3] and three phase 3 clinical trials (LixiLan-L, -O and -G [4–6]). In LixiLan-L [4], iGlarLixi achieved lower HbA1c levels than titrated insulin glargine in inadequately controlled patients. In LixiLan-O, which included uncontrolled patients treated with oral antidiabetic drugs (OADs) [5], iGlarLixi decreased HbA1c levels more than insulin glargine or lixisenatide alone. The LixiLan-G study included patients who were inadequately controlled with a maximum tolerated dose of a GLP-1 RA, and those who received iGlarLixi achieved a greater reduction in HbA1c levels than those who continued to use the GLP-1 RA [6]. In all trials, iGlarLixi was associated with weight loss or proved to be weight neutral.

A meta-analysis that included studies of both the DUAL and the LixiLan programmes [7] showed that FRCs achieved greater reductions in HbA1c than achieved with various comparators (such as placebo or the individual components of the combination therapies) in different patient populations who switched from using a wide range of antidiabetic treatments. Furthermore, FRCs were associated with weight loss in studies in which patients were switched from basal insulin to a FRC [7].

The results of the development programmes and the recently published ADA-EASD Consensus Report provide a solid base of information for clinicians on how to use FRCs in clinical practice. However, since routine clinical practice involves heterogeneous real-life patient populations, physicians face numerous practical questions (Table 1) that the above data sources cannot provide answers to.

Recognizing the significance of these questions and acknowledging the physicians' need for additional information, Sanofi organized an international expert meeting to discuss these topics and seek expert consensus on the

practical use of iGlarLixi. For some questions, the expert opinion was relevant to the therapeutic class of FRCs in general. The selection of participating countries was based on similarities in routine T2DM clinical practice in the Central and Eastern European region.

Accordingly, the aims of the expert consensus meeting were as follows:

- To collect experts' insights regarding practical questions that arose from the use of iGlarLixi, and
- To answer those questions in a way that could be translated into expert consensus opinions to aid daily clinical practice.

## METHODS

Experts from Czech Republic, Hungary, Romania and Slovakia were invited to discuss these topics and generate consensual opinions regarding specific questions. This involved two main steps:

- First, the experts were asked to validate the list of the questions initially drafted by Sanofi. The experts were given the opportunity to modify the questions and supplement the list with additional topics if they considered that new, clinically relevant aspects should be discussed. Validation and insight collection were performed within individual expert interviews.
- The experts were then invited to a two-day meeting where the questions were grouped into three main categories (positioning of iGlarLixi, treatment initiation of iGlarLixi, and other questions) and discussed in workshops. Discussions in which a consensus was achieved were summarized in a consensus document.

After the meeting, the consensus document was circulated to resolve any disagreements among the experts. The final version of the consensus document was approved by each participating expert. The content of that document is summarized in this publication.

The final set of validated and categorized questions is listed in Table 2.

**Table 1** Important practical questions relating to the use of fixed-ratio combinations

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- Use of GLP-1 RA and basal insulin in combination: simultaneous (FRC approach) or sequential initiation?
  - Is there a HbA1c threshold beyond which it is not recommended to start FRCs?
  - Can FRCs be used as treatment alternatives for select patients treated with basal-bolus therapy?
  - Can FRCs be used for deintensification?
  - Should OADs be continued after starting a FRC? If not, how should OADs be discontinued?
  - Is there an optimal time of the day to use a FRC?
  - Should FRCs be considered as intensification options after GLP-1 RA failure?
  - How should the cardiovascular (CV) benefits of GLP-1 RAs be taken into account when initiating a FRC?
  - What should be done when a FRC is no longer sufficient to provide good glycaemic control?
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The presentation of the expert opinions and their context, limitations and related information follows the structure of the topics and questions listed above. The opinions are listed in bullet points in order to aid lucidity and interpretation.

This article is based on previously conducted studies, published guidelines and opinions of leading experts, and does not contain any studies with human participants or animals performed by any of the authors.

## RESULTS

### Positioning of iGlarLixi Versus Other Treatment Approaches

#### *Sequential Versus Simultaneous Initiation of Insulin Glargine and Lixisenatide After OAD Failure*

- Should the components of iGlarLixi be initiated at the same time or sequentially?

The most important factor that should be considered when choosing iGlarLixi, GLP-1 RA or basal insulin is the level of HbA1c improvement required to achieve the individualized glycaemic target. However, there are other clinical characteristics that should also be taken into account to decide the most appropriate method of intensification:

- Comorbidities (with special consideration of a high/very high risk of CV diseases),
- Risk of hypoglycaemia,
- Level of obesity,
- Significantly increased PPG values (as a root cause of elevated HbA1c levels), and
- History of gastrointestinal adverse events (GIAEs) with previous GLP-1 RA treatment.

The experts generally agreed with the current ADA-EASD Consensus Report [1] that, after OAD failure, GLP-1 RA and basal insulin should be initiated sequentially. However, such an intensification approach should be implemented in a timely manner and ideally within the HbA1c range of 7–8%, with a general recommended HbA1c target of 7%. The single injectable approach (GLP-1 RA or basal insulin) might work for a HbA1c range of 8–9% as well; however, above 9%, HbA1c target achievement may be compromised, especially if the individualized HbA1c target is set at < 7%. The 9% HbA1c threshold resonates well with the current clinical recommendation of the guideline to start a FRC if the HbA1c level exceeds the individual glycated haemoglobin target by 2% (considering that the HbA1c target of 7% is the generally recommended HbA1c target in clinical practice).

The following patient characteristics identify subjects who will potentially benefit more from iGlarLixi initiation than the separate use of a GLP-1 RA or basal insulin:

- HbA1c > 9% (versus any single injection alone),
- Obesity (versus basal insulin alone),
- High risk for hypoglycaemia (versus basal insulin alone),
- High PPG levels (versus long-acting GLP-1 RAs or basal insulin), and

- Gastrointestinal adverse events during the previous GLP-1 RA treatment in the medical history (versus GLP-1 RA alone).

### ***Choosing Between iGlarLixi and Multiple Daily Insulin Injection (MDI) in Patients with a High HbA1c Level After OAD Failure***

The most important factor that should be considered when choosing between iGlarLixi or MDI is the presence of classic symptoms of catabolism (i.e. metabolic decompensation). In the presence of such symptoms, there is no need for the weight loss effect of GLP-1 RAs; only the anabolic effects of insulin are needed. As a consequence, MDI should be the preferred route for intensifying treatment after OAD failure.

The experts could not reach a consensus on a precise HbA1c level which indicates that MDI should be used if there are no signs of metabolic decompensation. Nevertheless, measuring fasting C-peptide can help to elucidate whether a patient with an excessively high HbA1c level but no catabolic symptoms might benefit more from MDI than from iGlarLixi.

Furthermore, there are subgroups of patients with certain clinical characteristics for whom the practical limitations of MDI should be considered and iGlarLixi can be a reasonable treatment alternative:

- Old patients, especially frail subjects and/or those living alone;
- Patients who are not able to cope with the burden of multidose adjustment and/or carbohydrate counting;
- Patients who cannot self-administer insulin (i.e. they need external help to administer insulin) or have a limited adherence to treatment;
- Patients with poor self-management abilities or with limited adherence to the frequent self-monitoring blood glucose tests required in the setting of a MDI regimen; and
- Patients who cannot afford or are not willing to conduct multiple daily self-monitoring of blood glucose (SMBG) tests.

*As a conclusion:*

**Table 2** The final set of questions discussed at the expert meeting

Category	Question
Positioning of iGlarLixi versus other treatment approaches	<ul style="list-style-type: none"> <li>• What is the optimal way of initiating basal insulin and a GLP-1 RA in combination: simultaneously (i.e. iGlarLixi) or sequentially (first GLP-1 RA followed by basal insulin if intensification is needed, or should these be initiated in the opposite order)?</li> <li>• How should we choose between iGlarLixi and basal-bolus therapy in patients with high HbA1c levels after OAD failure?</li> <li>• What are the conditions of and steps involved in deintensification from basal-bolus therapy to iGlarLixi therapy?</li> </ul>
Treatment initiation of iGlarLixi	<ul style="list-style-type: none"> <li>• What aspects should be considered when discontinuing concomitant OADs (other than metformin)?</li> <li>• Is there an optimal time for the daily administration of iGlarLixi?</li> <li>• How does previous GLP-1 RA treatment influence switching to iGlarLixi?</li> <li>• How should iGlarLixi be initiated in patients treated with basal insulin &lt; 20 U/day?</li> </ul>



Table 2 continued

Category	Question
Other questions	<ul style="list-style-type: none"> <li>• How should the established CV benefits of GLP-1 RAs be taken into account when initiating a FRC?</li> <li>• What is the clinical relevance of PPG when deciding to choose a FRC?</li> <li>• What are the scientific rationale and practical steps involved in intensification in the case of disease progression in patients treated with iGlarLixi?</li> <li>• How should the availability of two injection pens of iGlarLixi with different insulin glargine/lixisenatide ratios be appraised?</li> </ul>

- Sequential initiation of a GLP-1 RA followed by basal insulin is generally recommended in patients failing OAD treatment unless the HbA1c level exceeds 9.0%, in which case a FRC is more likely to help the patient to achieve their glycaemic target;
- Both MDI and iGlarLixi can be suitable for treating patients with a highly elevated HbA1c level; and
- The main distinction factor should be the presence of classic catabolic symptoms:

- In the case of catabolic symptoms, MDI is the regimen of choice (at least for a short period; subsequent deintensification to a FRC is an important consideration);

- If a high HbA1c level is not accompanied by catabolic symptoms, iGlarLixi could be a reasonable choice for intensification.

### ***Deintensification of the Complex Basal-Bolus Insulin Regimen with iGlarLixi***

- What are the clinical benefits of deintensification from basal-bolus therapy to iGlarLixi?
- How can we identify the patients who can be switched back safely from basal-bolus treatment?
- What are the practical steps involved in deintensification? How should this be achieved in clinical practice?

In general, treatment deintensification or de-escalation in diabetes care can be defined as switching to a less-complex alternative antihyperglycaemic treatment in order to either reduce treatment burden (without compromising efficacy and safety) or target a less ambitious individualized HbA1c goal due to ageing, the development of significant comorbidities or the presence of a high hypoglycaemia risk. In both cases, FRCs can be considered as treatment alternatives to the complex basal-bolus insulin regimen (Table 3).

Patients cannot be excluded from deintensification based on HbA1c levels or the current insulin dose alone. However, it should be noted that the higher the HbA1c level and the higher the daily insulin dose, the lower the probability of deintensification success. If these two aspects are combined (high daily insulin dose and highly elevated HbA1c levels), the probability of successful deintensification could be markedly reduced.

Due to the potential risk of metabolic deterioration, careful planning of patient re-education, the setting and the practical algorithm for deintensification is required.

- Clinical settings in which deintensification can be carried out include:

- An inpatient setting, which is the preferred option, especially if the total daily insulin dose is > 0.6 U/kg;

**Table 3** Potential clinical benefits and candidates for deintensification from the complex basal-bolus insulin regimen using FRCs

Potential clinical benefits

- Weight loss
- Reduced risk of hypoglycaemia
- Reduced therapy burden
- Better compliance
- Better health-related quality of life
- Lower treatment complexity (e.g. no need for precise carbohydrate counting), and
- Reduced health resource utilization:
  - Reduced need for SMBG
  - Fewer emergency room visits due to hypoglycaemic events, and
  - Less consultation with diabetes specialists.

Potential candidates

Patients:

- Who were intensified to MDI due to metabolic decompensation, acute illness or surgery and then “left” on a MDI;
- For whom the disadvantages of a MDI outweigh the associated benefits and
  - Experienced significant weight gain after basal-bolus initiation or
  - Experienced frequent hypoglycaemic events without any improvement in glycaemic control;
- Who are not compliant with the MDI and/or SBGM due to its complexity; and
- Who are well controlled with the MDI but want to decrease the treatment burden and improve their health-related quality of life.

- An inpatient setting is preferred in Central and Eastern European countries, but
- The outpatient setting might be an option, especially if the local healthcare setting does not allow hospitalization for this treatment

modification, although good patient compliance is essential in this case.

• The mode of deintensification:

- There is currently limited experience on which to base a firm recommendation for how a MDI should be discontinued;
- One-step deintensification (discontinuing MDI and initiating iGlarLixi based on the total daily basal component dose) could be applied if the previous total daily insulin dose was  $\leq 0.6$  U/kg; and
- Gradual discontinuation of basal and/or bolus insulin might be needed if the previous total daily insulin dose was  $> 0.6$  U/kg.

Other aspects that should be considered:

- C-peptide measurement is highly recommended to evaluate residual beta-cell function, which is a prerequisite for safe deintensification, and the fasting C-peptide method is preferred;
- Titration of iGlarLixi can usually be performed by patients, but patient education (e.g. providing an algorithm for titration and structured SMBG plans) and compliance are very important in such cases;
- Treatment compliance should be properly evaluated before deintensification; and
- Detailed analysis of SMBG data by the physician is needed before and during the process of deintensification.

In conclusion, the experts highlighted the need to consider several aspects when choosing iGlarLixi or a monocomponent of a FRC or MDI insulin regimen. An important factor is the presence of classic catabolic symptoms that require MDI treatment.

In the absence of metabolic decompensation, the level of HbA1c and the consideration of different clinical aspects can help to identify patients who may benefit more from initiating iGlarLixi than initiating a GLP-1 RA or basal insulin alone.

Regarding deintensification from MDI, a FRC treatment can be considered in select patients in order to reduce treatment burden/complexity or to decrease the risk of hypoglycaemia or

weight gain, which are the most frequent adverse effects of MDI.

## Treatment Initiation with iGlarLixi

### *Discontinuation of Concomitant OADs (Other Than Metformin)*

- Which OADs should be stopped or continued?
- Should OAD discontinuation be performed gradually or immediately (in one step at FRC initiation)? Are there any safety aspects to consider?

The following aspects should be taken into consideration when discontinuing OADs:

- Dipeptidyl peptidase-4 (DPP-4) inhibitors should be stopped, as they have no additional value to GLP-1 RAs and are not recommended in association with a GLP-1 RA;
- Sulfonylureas should, as a general rule, be stopped (to decrease the risk of hypoglycaemia and weight gain), or the dose should be substantially reduced;
- Acarbose should be used only rarely and should be stopped due to the increased risk of GI side effects;
- Glitazones: a patient-focused decision is key; if safety concerns about combining it with insulin (fluid retention, weight gain) exceed the expected clinical benefit of specifically targeting insulin resistance, discontinuation should be considered;
- Sodium/glucose cotransporter 2 (SGLT2) inhibitors:
  - Although the combination of iGlarLixi with a SGLT2 inhibitor is currently not recommended per the label, the safety profiles and mechanisms of action of iGlarLixi and SGLT2 inhibitors do not suggest any additional safety concerns;
  - The combined use of iGlarLixi and a SGLT2 inhibitor is yet to be formally tested in dedicated clinical trials, but 10% of patients in the iGlarLixi arm of the LixiLan-G study [6] continued treatment with a SGLT2

inhibitor after switching to the iGlarLixi FRC;

- iGlarLixi plus a SGLT2 inhibitor is a potentially beneficial combination due to their complementary mechanisms of action and the insulin-independent effect of SGLT2 inhibitors; this combination may be beneficial in most patients;
- A previous clinical trial investigating the coadministration of SGLT2 inhibitors and iDegLira seems to support the points mentioned above.

Other aspects are as follows:

- When discontinuing OAD medications other than metformin (see the special considerations for SGLT2 inhibitors discussed above), they can be discontinued in one step at the time of iGlarLixi initiation (based on the results from LixiLan-O).
- iGlarLixi dose titration:
  - Titration should be started within a week after initiation based on fasting SMBG levels (inappropriate titration may result in metabolic deterioration); and
  - The titration algorithm can be individualized (it does not need to be the same as that used in clinical trials) and should follow the concept of basal insulin titration.

In conclusion, the Suliqua<sup>®</sup> (Sanofi) SmPC does not provide additional details on OAD discontinuation at iGlarLixi initiation, but it recommends discontinuing all glucose-lowering drugs except metformin. However, this discontinuation of previous drugs raises questions in daily practice: to what extent does immediate discontinuation trigger metabolic instability, and are there any differences when discontinuing different OADs? The experts agreed that most OAD classes could be stopped as (i) the approach does not seem to compromise glycaemic control and (ii) it may have a potential safety benefit (continuing OAD in combination with iGlarLixi may increase the risk of weight gain, GI side effects, and hypoglycaemic events, depending on the OAD). The only drugs that are considered potentially effective and safe to



combine with iGlarLixi are SGLT2 inhibitors, but clinical trial data to support this regimen are currently limited, and it is yet to be included on the label. Whether the previous OADs were discontinued gradually or in one step was not considered to be important by the experts; however, there was an agreement that the strong need to start uptitrating iGlarLixi according to the fasting SMPG immediately after initiation should be highlighted.

#### ***Optimal Time for Daily Administration: Before Breakfast or Dinner?***

- Advantages and disadvantages of breakfast, lunch and dinner administration
- How a patient's lifestyle and the pharmacokinetics/pharmacodynamics of iGlarLixi influence the time of administration

The Suliqua<sup>®</sup> SmPC stipulates that iGlarLixi should be injected within 1 h before a meal, but it does not specify which meal. The following aspects should be considered when choosing the injection time for a specific patient:

- iGlarLixi can be administered with any main meal according to the patient's preference; and
- Once the patient determines the preferred meal, iGlarLixi should be administered each day before the chosen meal.

However, there are some clinical considerations that favour one option over the others:

- Before breakfast:
  - Postprandial glucose levels are typically highest after breakfast in most patients;
  - Trial evidence from the LixiLan-L and LixiLan-O studies [4, 5] is based on administration in the morning;
  - Lixisenatide serum levels are still relatively high at the next meal, leading to a relevant benefit in terms of PPG excursions following two main meals (for pre-breakfast administration, post-breakfast and post-lunch blood glucose levels can be controlled by lixisenatide assuming that there is no more than 4–5 h between the two meals; there is no such benefit of a pre-dinner injection since

the next main meal (breakfast) is taken considerably more than 4–5 h after the pre-dinner injection);

- The risk of nocturnal hypoglycaemia may be lower with the pre-breakfast injection than with the pre-dinner injection (due to the PK/PD characteristics of the basal insulin component, insulin glargine); and
  - Patients who are uncontrolled on basal-supported oral therapy and have nocturnal hypoglycaemia may benefit from a morning injection.
- Before lunch:
    - This is an option when lunch and dinner are the meals to be covered by lixisenatide (again, assuming that no more than 4–5 h elapse between the two meals).
  - Before dinner
    - This is an option when dinner is the main meal.

Other aspects are as follows:

- Data from a randomized controlled trial of lixisenatide [8] demonstrated similar efficacy and safety profiles for administration in the morning and evening.

In conclusion, the experts considered that the patient's lifestyle and the preferred main meal were the most important factors when choosing the timing of the iGlarLixi injection. It was highlighted that iGlarLixi can cover PPG elevations after two meals if no more than 4–5 h elapse between those meals. In addition, data from a clinical trial indicate that the efficacy and safety of lixisenatide do not vary depending on whether it is administered in the morning or evening. However, morning administration is supported by several arguments and may provide the most benefit to patients.

### ***How Does a Medical Treatment History of GLP-1 RA Use Influence the Switch to iGlarLixi?***

- Should either inadequate efficiency or side effects be considered a contraindication?
- Are there any causes that imply an absolute contraindication?

The following aspects should be considered when the physician decides whether to initiate iGlarLixi in a patient formerly treated with any of the GLP-1 RAs:

- iGlarLixi was shown to achieve significantly better glycaemic control than GLP-1 RAs alone in patients inadequately controlled by GLP-1 RA therapy [6];
- The GLP-1 RA class is heterogeneous in terms of glycaemic control (based on either FPG or PPG), weight loss and GI side-effect occurrence;
- If possible, the causes of previous failure(s) should be clarified to determine whether they were related to poor tolerability (e.g. GI side effects), insufficient patient compliance or a lack of efficacy; and
- If GI side effects led to GLP-1 RA discontinuation or compliance problems in the past, initiation of iGlarLixi could be considered based on evidence indicating that it has better GI tolerability than GLP-1 RA alone [5, 9].

In conclusion, depending on the reason(s) for the previous GLP-1 RA failure(s), iGlarLixi can achieve effective glycaemic control in patients who were uncontrolled with previous GLP-1 RA therapy. For those who discontinued previous GLP-1 RA therapy due to GI side effects, iGlarLixi treatment with smaller GLP-1 RA dose increments is likely to be associated with a lower risk of such adverse events, and might therefore result in the successful use of the GLP-1 RA component.

### ***Treatment Initiation in Patients on Basal Insulin < 20 U/Day***

- Which clinical characteristics should be considered (risk of hypoglycaemia, levels of FPG and PPG)?

- What is the recommended starting dose of iGlarLixi when the prior basal insulin dose was less than 20 U/day?

For insulin-treated patients, the starting dose of iGlarLixi is specified in the Suliqua® SmPC and is based on the patients' preceding daily basal insulin dose. The lowest insulin dose for which the iGlarLixi starting dose is specified is 20 U/day, but there is no specified dose for patients treated with < 20 U of basal insulin per day.

In such a scenario, the following aspects should be considered:

- In the Central and Eastern European region:
  - Few patients with T2DM are treated with a basal insulin dose of < 20 U/day; and
  - Insufficient titration of basal insulin is a very common problem in clinical practice.
- Revision of the current basal insulin therapy should be performed, taking FPG, PPG and HbA1c into account.
- If FPG is above the target:
  - When there is no concern about hypoglycaemic events, basal insulin should be uptitrated and optimized before switching to iGlarLixi;
  - When there is concern about hypoglycaemic events, switching to iGlarLixi should be considered instead of increasing the basal insulin dose, which may further increase the risk of hypoglycaemia.
- If PPG is uncontrolled and FPG is at the target (which can be associated with uncontrolled HbA1c levels as well), initiation of iGlarLixi should be the preferred choice due to the mode of action of lixisenatide, which specifically decreases post-meal hyperglycaemia.
- In these treatment scenarios, when the current daily basal dose is below 20 U, the starting dose of iGlarLixi should be 10 U/day, similarly to insulin-naïve patients, due to the better GI tolerance associated with the lowest applicable dose of the FRC. After treatment initiation, iGlarLixi can

potentially be uptitrated with two dose adjustments per week to achieve sufficient overall glycaemic control in a timely manner.

In conclusion, the experts discussed iGlarLixi initiation in patients treated with less than 20 U basal insulin/day. They agreed that steps to optimize glycaemic control in these patients should be determined by interpreting the levels of FPG, PPG and HbA1c and the risk of hypoglycaemic events. When choosing iGlarLixi to improve metabolic control, its starting dose should be the same as that of insulin-naïve patients (10 U/day).

## Other Important Topics

### *Cardiovascular Benefits of GLP-1 RAs*

- How should the established CV benefits of GLP-1 RAs be taken into account when initiating a FRC?

Some GLP-1 RAs reduce the risk of CV events, as has been demonstrated in several long-term cardiovascular outcome trials [10]. Although the results from these trials do not necessarily indicate that the CV benefits of GLP-1 RAs can also be expected when a GLP-1 RA is administered as a component of a FRC, it is reasonable to recommend the following based on the currently available published evidence if the physician has decided to initiate a FRC:

If a patient has established CV disease:

- iDegLira might be considered the first choice based on the results of the LEADER trial [11], although the findings cannot be extrapolated directly to iDegLira, mainly due to the lower GLP-1 RA doses used when a GLP-1 RA is applied as a component of a FRC.

If a patient has no established CV disease:

- Glycaemic control and achieving individual HbA1c target levels are the most important aspects; and
- Either FRC can be used, mirroring the recommendation of the current ADA-EASD consensus.

Additional considerations regarding CV diseases:

- According to the latest ADA-EASD consensus statement, approximately 85% of patients have no established CVD; and
- Some types of CVDs do not always have an atherosclerotic origin (e.g. heart failure).

As the GLP-1 RA component liraglutide had a positive effect on MACE when used at a high dose (whereas lixisenatide had a neutral effect in ELIXA [12]), iDegLira might be considered the first-choice FRC for patients with established CV disease.

For patients with no established CV disease, which corresponds to 85% of all patients with T2DM, there is no preference for either FRC from the perspective of CV risk.

### *Measuring PPG and the Concept of “Residual Hyperglycaemia”*

It should be noted that PPG is rarely measured routinely in patients with T2DM in clinical practice.

- The use of the concept of “residual hyperglycaemia” has been suggested when the level of HbA1c remains suboptimal but the FPG/fasting SMBG levels are at or close to target. PPG is most likely to be the factor behind the elevated HbA1c levels [13]. In such cases, iGlarLixi has a stronger impact on postprandial glucose and should be the first-choice FRC.
- It is recommended that PPG values should be monitored to facilitate an informed choice of FRC.

### *Scientific Rationale and Practical Steps for Intensification in the Case of Disease Progression in Patients Treated with iGlarLixi*

- What are the patient characteristics that should be taken into account when selecting the intensification strategy?
- What are the options to intensify iGlarLixi?

Table 4 summarizes the intensification strategies that can be used when T2DM progresses and iGlarLixi no longer provides

**Table 4** Intensification strategies after the failure of iGlarLixi

Options for intensifying iGlarLixi if FPG is in the target range but HbA1c becomes uncontrolled:

- In general, for patients with long life expectancies (without significant comorbidities):
  - A SGLT2 inhibitor can be added (depending on the estimated glomerular filtration rate);
  - A SU (preferably gliclazide MR/glimepiride based on the ADVANCE and CAROLINA studies [14, 15]) can be added when SGLT2 inhibitors cannot be prescribed (e.g. due to eGFR, access or cost issues); and
  - Prandial insulin can be added, but MDI is not the preferred solution
- For patients with significant coexisting medical conditions or those over 80 years old:
  - The individualized HbA1c target level should be re-evaluated (e.g. relaxed to 8% or even higher) when the patient is:
    - Frail,
    - At high risk of hypoglycaemic events, or
    - Living alone
  - Leaving the treatment regimen unchanged is a reasonable option for these patients (unless severe catabolic symptoms are present).

Options for intensifying iGlarLixi if neither FPG nor HbA1c are in the target range despite reaching 60 U/day basal insulin:

- Switching to the free combination of a GLP-1 RA and basal insulin and uptitrating basal insulin
- Switching to a full-scale MDI, especially if C peptide is low.

\*All of the above are off-label uses according to the current SmPC (except for stopping iGlarLixi and switching to the free combination or full-scale MDI)

acceptable control (i.e. the HbA1c level is not in the target range).

In conclusion, the treatment of patients whose glycaemic status becomes uncontrolled

when they are treated with iGlarLixi should be intensified in accordance with their FPG and HbA1c levels and key patient characteristics such as life expectancy and comorbidities. Adding a SGLT2 inhibitor, SU or prandial insulin, switching to a MDI regimen, or even setting higher individual HbA1c target levels and leaving the treatment unchanged are all possible intensification options.

#### ***Appraising the Two iGlarLixi Injection Pens Available***

- What are the beneficial effects and potential risks of switching between Suliqua<sup>®</sup> pens?

While the availability of two Suliqua<sup>®</sup> pens with different fixed ratios of the compounds provides the opportunity to adapt the drug treatment in a more flexible way, some physicians may feel it increases treatment complexity. The experts were asked to express their opinions regarding the availability and the practical use of the two injection pens of iGlarLixi.

- The availability of two pens with different compound ratios (1:2 and 1:3) is beneficial since it allows better treatment individualization to reflect disease status/progression as follows:
  - In the early disease phase (with relatively well-preserved beta-cell capacity), more GLP-1 RA is typically required and less insulin is needed (the 1:2 ratio pen can be used after OAD failure);
  - In the advanced disease phase (with less residual beta-cell function), more basal insulin (up to 60 U/day) may be needed (the pen with the 1:3 ratio can be used in this case);
- When patients using basal insulin are initiated with iGlarLixi, the availability of the 1:3 ratio pen ensures that the need to reduce the applied basal insulin dose is minimized (patients can even start with 30 U/day depending on their previous basal insulin dose);
- Mixing up the pens should not warrant safety concerns, as patients use only one pen at a particular stage during the course of the iGlarLixi treatment; and

- If needed, it is easy to move from a 1:2 pen to a 1:3 pen using the same basal insulin dose; in such cases, the temporary reduction in the lixisenatide dose (due to the different ratios of the two compounds) will not have a clinically relevant impact on glycaemic control (no deterioration is expected).

In conclusion, the experts considered the availability of the two Suliqua<sup>®</sup> pens with different fixed ratios to be a clinical advantage (over iDegLira), making it possible to flexibly choose between the two ratios according to patient needs. There were no clinically important safety concerns relating to the availability of the two pens.

## CONCLUSIONS

Over the last decade, GLP-1 RAs and fixed-ratio combinations of them with basal insulin have become attractive and important options in the therapeutic armamentarium for people with T2DM. The recent ADA-EASD Consensus Report [1] highlighted the advantages of combined basal insulin and GLP-1 RA therapy over insulin-only regimens. Phase II and III trials [3–6] provided evidence for the efficacy and safety [9] of iGlarLixi FRC when compared to the individual components of this FRC. Similar results for iDegLira are also available.

Although the Suliqua<sup>®</sup> SmPC provides information on how iGlarLixi treatment should be initiated and titrated in patients with T2DM, and the results of the clinical trials and post hoc analyses of them provide evidence on how to use iGlarLixi, numerous questions have arisen in daily clinical practice that could not have been answered by the SmPC and available trial results. These questions were presented by Sanofi in a structured format to a group of leading experts from selected Central and Eastern European countries (Czech Republic, Hungary, Romania and Slovakia) in a consensus meeting. The final set of topics and questions was approved by the experts before the meeting.

The experts reached a consensus for each of the presented questions. Their expert opinions

may therefore help physicians to use iGlarLixi in their daily practice.

However, as with any other expert consensus, it should be noted that the recommendations summarized in this manuscript reflect the professional opinions of experts, which were synthesized from their own practical experiences and the limited evidence available at the time of the expert meeting. With the caveat that these recommendations are not necessarily supported by robust evidence from randomized controlled trials, the authors hope that the expert opinions reported here will guide physicians on how to best use iGlarLixi in routine clinical practice.

## ACKNOWLEDGMENTS

**Funding.** Sanofi Hungary, Sanofi Czech Republic and Sanofi Romania provided financial support to the experts from the given countries who participated in the consensus meeting. Sanofi Hungary funded the medical writing and the Rapid Service Fee.

**Medical Writing and/or Editorial Assistance.** Syreon Research Institute, the contracted partner of Sanofi Hungary, provided assistance with organizing the expert meeting and medical writing. The project did not receive any additional grant or funding.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Authorship Contributions.** Martin Haluzík contributed to forming the expert opinion, participated in the meeting, led the manuscript preparation, and approved the final draft of the manuscript. Milan Flekač contributed to forming the expert opinion, participated in the meeting and manuscript preparation, and approved the final draft of the manuscript. Csaba Lengyel contributed to forming the



expert opinion, participated in the meeting and manuscript preparation, and approved the final draft of the manuscript. Zoltán Taybani contributed to forming the expert opinion, participated in the meeting and manuscript preparation, and approved the final draft of the manuscript. Cristian Guja contributed to forming the expert opinion, participated in the meeting and manuscript preparation, and approved the final draft of the manuscript. Bogdan-Mircea Mihai contributed to forming the expert opinion, participated in the meeting and manuscript preparation, and approved the final draft of the manuscript. Anca Cerghizan contributed to forming the expert opinion, participated in the meeting and manuscript preparation, and approved the final draft of the manuscript. Emil Martinka contributed to forming the expert opinion, participated in the meeting and manuscript preparation, and approved the final draft of the manuscript. Gabor Kovacs drafted the topics to be discussed, facilitated the discussions during the meeting, drafted the manuscript, and approved the final draft of the manuscript. Péter Kempler contributed to forming the expert opinion, participated in the meeting, led the manuscript preparation, and approved the final draft of the manuscript.

**Disclosures.** Martin Haluzík, Milan Flekač, Csaba Lengyel, Zoltán Taybani, Cristian Guja, Bogdan-Mircea Mihai, Anca Cerghizan, Emil Martinka and Péter Kempler received remuneration from country-specific Sanofi affiliates for participation at the consensus meeting. Gábor Kovács is a contracted partner of Syreon Research Institute.

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## REFERENCES

1. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669–701.
2. Blonde L, Anderson JE, Chava P, Dendy JA. Rationale for a titratable fixed-ratio co-formulation of a basal insulin analog and a glucagon-like peptide 1 receptor agonist in patients with type 2 diabetes. *Curr Med Res Opin*. 2019;35(5):793–804.
3. Rosenstock J, Diamant M, Aroda VR, Silvestre L, Souhami E, Zhou T, et al. Efficacy and safety of lixilan, a titratable fixed-ratio combination of lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy: the LixiLan proof-of-concept randomized trial. *Diabetes Care*. 2016;39(9):1579–86.
4. Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, Gonzalez-Galvez G, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. 2016;39(11):1972–80.
5. Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes

- inadequately controlled on oral agents: the LixiLan-O randomized trial. *Diabetes Care*. 2016;39(11):2026–35.
6. Blonde L, Rosenstock J, Del Prato S, Henry R, Shehadeh N, Frias J, et al. Switching to iGlarLixi versus continuing daily or weekly GLP-1 RA in type 2 diabetes inadequately controlled by GLP-1 RA and oral antihyperglycemic therapy: the LixiLan-G randomized clinical trial. *Diabetes Care*. 2019;42(11):2108–16.
  7. Liakopoulou P, Liakos A, Vasilakou D, Athanasiadou E, Bekiari E, Kazakos K, et al. Fixed ratio combinations of glucagon like peptide 1 receptor agonists with basal insulin: a systematic review and meta-analysis. *Endocrine*. 2017;56(3):485–94.
  8. Ahren B, Vorokhobina N, Souhami E, Demil N, Ye J, Aronson R. Equal improvement in glycaemia with lixisenatide given before breakfast or the main meal of the day. *J Diabetes Complic*. 2014;28(5):735–41.
  9. Frias JP, Dex T, Roberts M, Kaplan A. A review of the safety and adverse event profile of the fixed-ratio combination of insulin glargine and lixisenatide. *Diabetes Ther*. 2019;10(1):21–33.
  10. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776–85.
  11. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–22.
  12. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373(23):2247–57.
  13. Raccach D, Chou E, Colagiuri S, Gaal Z, Lavalle F, Mkrtumyan A, et al. A global study of the unmet need for glycemic control and predictor factors among patients with type 2 diabetes mellitus who have achieved optimal fasting plasma glucose control on basal insulin. *Diabetes Metab Res Rev*. 2017;33(3):e2858.
  14. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Advance Collaborative Group, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560–72.
  15. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA*. 2019;322(12):1155–66.