Afrezza Real-World Study Protocol titled: Initiating Mealtime Ultra-Rapid Acting Insulin (Afrezza) in Uncontrolled Type 2 Diabetes Patients

Revision 3.5.5 - 02/08/2018

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

INTRODUCTION:

We would like to examine the effects of adding prandial Afrezza inhaled insulin to patients with type 2 diabetes who are not controlled after at least 6 months of other diabetes treatments including oral agents, basal insulin, or GLP-1 use.

Clinical inertia in intensifying treatment of type 2 diabetes patients occurs in the range of 70% in numerous real world database assessments. We propose treating patients with Afrezza who have an index HbA1c between 7.5% and 11.5% despite being treated with diabetes medications for at least 6 months. The response to Afrezza will be assessed with Continuous Glucose Monitoring Systems (CGMS) studies and initial and follow-up HbA1cs. Our goal is to assess how we can rapidly and safely initiate intensification in this patient population, where extensive delays in HbA1c improvement often occur.

OBJECTIVE:

Demonstrate that the addition of mealtime Afrezza can significantly lower HbA1c within 3 months of Afrezza treatment in uncontrolled type 2 diabetes patients initially having HbA1c of 7.5 or higher, despite at least 6 months of prior therapy with diabetes medications.

ENDPOINTS:

Primary
Percentage change from baseline HbA1c

Secondary:
Percentage of patients having HbA1c under 7% after 3 months of Afrezza treatment

Percent of time that Blood glucose (BG) is under 70 mg/dL on CGMS

Percent of time that BG is over 180 mg/dL on CGMS

SELECTION OF STUDY POPULATION:

Enroll 40 type 2 diabetes patients for a 14 week study with 3 months of Afrezza treatment.

INCLUSION CRITERIA:

- Adult type 2 diabetes patients age 18 or older
- HbA1c ≥ 7.5% and ≤ 11.5% after at least 6 months treatment with diabetes medication. Treatment may include oral agents, basal insulin or GLP-1 in any combination.
- Patient and provider agree not to add additional diabetes medications during the 14 weeks of study (unless rescue treatment is indicated).

EXCLUSION CRITERIA:

- History of asthma, COPD or smoking within 6 months
- FEV1 under 70% predicted
- Pregnancy
- Active malignancies and/or life expectancy of < 12 months
- Major surgery planned during study period
- Currently using rapid acting insulins - Novolog, Humalog, Apidra
- Prior use of Afrezza in the last 3 months
- Unwilling to test blood glucose before or after each meal
- Exposure to systemic glucocorticoids within 6 weeks of screening
- Severe hypoglycemia in last 6 months or hypoglycemia unawareness
- Any medical condition which, in the opinion of the PI, would interfere with ability to understand or respond to the administration of inhaled insulin

STUDY VISITS

Visit 1 Week 0**- Office Visit**
Visit 1a Week 1 Follow up Phone Call
Visit 2 Week 2 **Office Visit**
Visit 2a Week 2.5 Follow up Phone Call
Visit 3 Week 3 Phone Visit
Visit 4 Week 4 Phone Visit
Visit 5 Week 6 Phone Visit
Visit 6 Week 8 Phone Visit
Visit 7 Week 10 Phone Visit
Visit 8 Week 12 **Office Visit**
Visit 8a Week 13 Follow up Phone Call
Visit 9 Week 14 **Office Visit- Final Visit**

Visit windows are +/-1 week

STUDY PROCEDURES:

Visit 1- Week 0 **Office Visit**

Informed Consent process

Lung Function Assessment - *FEV1 (Spirometry will be done at Visit 1 UNLESS there is documentation that patient has passed FEV1 with 70% or greater predicted **within 30 days prior to Visit 1)** (If not completed at Visit 1, spirometry **must** be completed before/at Visit 2 before Afrezza can be dispensed) *NOTE: Patient must pass spirometry in order to continue on in study

*Baseline HbA1c (window within 2 weeks prior to Visit 1) *NOTE: Patient must have HbA1c 7.5% - 11.50% in order to continue on in study

For women of childbearing potential - patients will be given a pregnancy test and questioned about birth control methods. Patients who are not surgically sterilized, or not post-menopausal for at least one year must use an approved form of birth control such as birth control pills, intrauterine device, or a barrier method (e.g. diaphragm and condom with spermicide) up to 30 days after the last dose of clinical trial drug. Patients must agree to continue using an acceptable method of birth control during the entire trial.

Patient will be asked about previous and current health
Obtain Medical History, Medications, Clinical assessments
If patient is currently taking a sulfonylurea, patient will be instructed to stop taking all sulfonylurea medications as of day of first study visit and remain off of it for the duration of the study or until being told ok to restart.
Obtain information re: hypoglycemic events in past month
Labs: CMP and CBC (window -labs must be done within 7-10 days if unable to get labs drawn at Visit 1 to receive results before Visit 2)
Obtain vitals (Height, Weight, Blood Pressure, Pulse, Respiratory Rate)
Perform Physical exam (window for physical exam -PE must be completed by Visit 2 if unable to complete at Visit 1 before Afrezza can be dispensed)
Insert CGMS
Activate CGMS with Reader
Place Tegaderm film over sensor
Give patient the CGM brochure/information on how to care for sensor along with extra sheet of Tegaderm (review sensor care with patient)
Discuss interfering substances that could impact sensor with patient. Taking ascorbic acid (vitamin C) while wearing the Sensor may falsely raise Sensor glucose readings so patient will be requested to refrain from taking vitamin C will wearing sensor. Taking salicylic acid (used in some pain relievers such as aspirin and some skin care products) may slightly lower Sensor glucose readings. Patient will be encouraged to minimize use of Aspirin while wearing sensor.
(Bring patient back in for unscheduled visit if there is a problem with the sensor and if it needs to be replaced) Every attempt should be made so patient wears sensor for minimum of 10 days.

Instruct patient to check and record blood glucoses per their doctor's instructions on Diabetes Log Sheet for next 2 weeks
Check with patient that they have sufficient test strips to check blood glucose as frequently as their doctor has indicated.

Visit 1a **Follow up Phone Call**

Week 1 Check how patient is doing with sensor. Remind patient to check and record blood glucoses per their doctor's instructions on the Diabetes Log Sheet
Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before visit.

Visit 2 **Office Visit**

Week 2 Visit 2 should take place 2 weeks after Visit 1 or if necessary, Visit 2 may be postponed for 2 weeks until patient has worn CGMS for total of 10-14 days
Review with patient any clinical issues, medications, hypoglycemic events, serious adverse events
Download CGMS data, review data, and remove CGMS
Review Afrezza safety slide and review side effects of Afrezza with patient
Train patient on how to use Afrezza Inhaler and how to dose Afrezza:

- Patient will be instructed to follow the **Weekly Treat-to-Target BG Testing Regimen** (See appendix 2) and make Afrezza dose changes according to **Afrezza Titration Algorithm** (See appendix 1) and record calculations on Dose Adjustment using Algorithm Worksheet
- Patient will be instructed to record blood glucoses and insulin doses on log sheets provided
- Patient will be instructed to start Afrezza at 4 units (u) / per meal on Treatment Day 1

Dispense study-provided FDA-approved Afrezza medication along with the full Prescribing Information handout (Dispense 12 weeks of study-provided Afrezza (usually 3 combo pac boxes or if needed, Afrezza may be dispensed 1 month at a time and patient can return every 4 weeks to get additional combo pac)
Record Patient Study ID and date dispensed on each box dispensed
Inform patient that all used combo pac boxes and unused Afrezza to be returned to study coordinator at last Office Visit
Ask patient to fax/email/call in BG Log sheet morning of next phone visit so they can be reviewed before phone visit.
Check with patient that they have sufficient glucose tests strips. As part of standard of care, patient will check their blood glucose before meals and as needed and the study will require patients to check 2 hours post meals on 3 days a week.

Visit 2a **Follow up Phone Call**

Week 2.5 Call patient 2-4 days after Visit 2. Confirm date of Treatment Day 1. Check how patient is doing using the Afrezza medication. Review dosing algorithm and remind patient to record dosing and blood glucose on log sheets
Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before phone visit.

Visit 3 **Phone Visit**

Week 3 Review Afrezza use and answer any questions. Review patient dose adjustments and any clinical issues, medications, hypoglycemic events, serious adverse events

- Patient will be instructed to utilize Afrezza titration regimen to increase or reduce meal dosing according to the algorithm and record calculations on Dose Adjustment using Algorithm Worksheet
- Patient will be instructed to follow the Weekly Treat-to-Target BG Testing Regimen as in Week 2 and to **continue this regimen weekly until the conclusion of the study**.
- Patient will be instructed to continue to record blood glucoses and insulin doses on log sheets provided.

Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before phone visit.

Visit 4 **Phone Visit**

Week 4 Review patient dose adjustments and any clinical issues, medications, hypoglycemic events, serious adverse events

Continue to utilize Afrezza titration regimen and record calculations on Dose Adjustment using Algorithm Worksheet.

Continue to utilize Weekly Treat-to-Target BG Testing Regimen unless hypoglycemia (BGs under 70) or **rescue treatment indicated (BG average for prior week over 250 without acute condition to explain high BGs. Investigator judgement if regimen needs transient change for the remainder of study.

Patient will be reminded to continue to record blood glucoses and insulin doses on log sheets provided.

Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before phone visit.

Visit 5 **Phone Visit**

Week 6 Review patient dose adjustments and any clinical issues, medications, hypoglycemic events, serious adverse events. Continue titration regimen and record calculations on Dose Adjustment using Algorithm Worksheet and Weekly Treat-to-Target BG Regimen as clinically indicated.

Patient will be reminded to continue to record blood glucoses and insulin doses on log sheets provided.

Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before phone visit.

Visit 6 **Phone Visit**

Week 8 Review patient dose adjustments and any clinical issues, medications, hypoglycemic events, serious adverse events. Continue titration regimen and record calculations on Dose Adjustment using Algorithm Worksheet and Weekly Treat-to-Target BG Regimen as clinically indicated.

Patient will be reminded to continue to record blood glucoses and insulin doses on log sheets provided.

Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before phone visit.

Visit 7 **Phone Visit**

Week 10 Review patient dose adjustments and any clinical issues, medications, hypoglycemic events, serious adverse events. Continue titration regimen and record calculations on Dose Adjustment using Algorithm Worksheet and Weekly Treat-to-Target BG Testing as clinically indicated.
Patient will be reminded to continue to record blood glucoses and insulin doses on log sheets provided.
Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before office visit.

Visit 8 **Office Visit**

Week 12 Insert CGMS for the 2nd CGMS monitoring period.
Give patient the CGM brochure/information on how to care for sensor along with extra sheet of Tegaderm (review care with patient)
(Bring patient back in for unscheduled visit if there is a problem with the sensor and if it needs to be replaced) Every attempt should be made so patient wears sensor for minimum of 10 days.
Review patient dose adjustments and any clinical issues, medications, hypoglycemic events, serious adverse events
Review patient's average blood glucose testing and continue regimen as clinically indicated.
Patient will be reminded to continue to record calculations on Dose Adjustment using Algorithm Worksheet.
Patient will be reminded to continue to record blood glucoses and insulin doses on log sheets provided.
Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before office visit.
Remind patient to bring all used combo pac boxes and unused Afrezza to next visit

Visit 8a **Follow up Phone Call**

Week 13 Check how patient is doing with sensor. Patient will be reminded to continue to record calculations on Dose Adjustment using Algorithm Worksheet.
Patient will be reminded to continue to record blood glucoses and insulin doses on log sheets provided.
Ask patient to fax/email/call in BG Log sheet morning of next visit so it can be reviewed before visit.
Remind patient to bring all used combo pac boxes and unused Afrezza to next visit

Visit 9 **Office Visit - Final Visit**

Week 14 Download CGMS data, review data, and remove CGMS
Patient will return all unused Afrezza and used Combo pac boxes

Review patient dose adjustments and any clinical issues, medications, hypoglycemic events, serious adverse events
Labs: Final HbA1c (window within 2 weeks prior to Final Visit)
Obtain final vitals (Height, Weight, Blood Pressure, Pulse, Respiratory Rate)
Perform final Physical Exam
Instruct patient to stop study-provided Afrezza
Collect all all used combo pac boxes and unused Afrezza from patient
Instruct patient to discuss with their provider whether to continue Afrezza at the conclusion of this study

STUDY PATIENT WITHDRAWAL:

Participants are free to withdraw from the study at any time. The study coordinator will request a reason for withdrawal. Study patient participation in this study may be stopped if the study doctor or sponsor thinks staying in the study would be harmful, participants need treatment not allowed in this study, participants fail to follow instructions, participants fail to check their blood glucoses or the study is stopped for any reason.

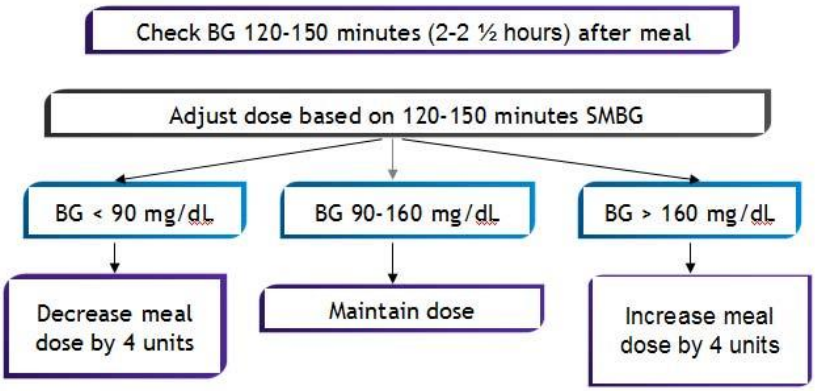
** Rescue Treatment: This treatment is **AT THE DISCRETION OF THE PI** and may be initiated with Humalog replacing Afrezza if:

1. The majority of post prandial and fasting BGs are over 250 after 2 weeks of treatment with Afrezza
2. Clinical symptoms require treatment change

Additionally:

3. Patients' diabetes medications, including basal insulin dose may be changed, as clinically indicated, at the discretion of the PI.
4. The frequency of weekly BG testing regimen may be adjusted, as clinically indicated, at the discretion of the PI.
5. Titration and dosing of Afrezza may be adjusted as needed, for safety reasons, as clinically indicated, at the discretion of the PI.
6. Patients may be requested to return and repeat labs may be drawn, as clinically indicated, at the discretion of the PI.

Afrezza® Titration Algorithm



Appendix 1

Version 12/05/17

Afrezza® (insulin human) Inhalation Powder

For the Treatment of Adults with Diabetes Mellitus

APPENDIX 2

In order to increase patient compliance and minimize burden of daily multiple finger sticks every day of each week, this real-world study requires patients to check pre-meal Blood Glucoses (BGs) and 2 hour post-meal BGs for **two (2)** consecutive days and then use the **results of** Treatment Day **1 and Treatment Day 2** doses as the basis of Afrezza titration. **Patients will review the results of the 2 hour post-meal BGs of the 2 days for each same meal to determine Afrezza Titration for that meal. Patients will be given Titration Algorithm Worksheet.**

WEEKLY TREAT – TO – TARGET BLOOD GLUCOSE (BG) TESTING REGIMEN

Check pre-meal BGs before every meal. When starting Afrezza, take 4 units with each meal for 3 days. On Start Day 1, also check post-meal BGs. On Start Day 4, take 8 units with every meal for the next 3 days. On Start Day 4, also check post-meal BGs. On Start Day 7 and 8, take 12 units with each meal. Start Day 7-8 are considered Treatment Day 1 and 2 and patients will also check post-meal BGs 2 hours after every meal.
Every week on Treatment Days 1 and 2, patients will check pre-meal Blood Glucoses (BGs) and 2 hour post-meal BGs and make the Afrezza dose changes based on modifications to the Titration algorithm.

- Review BGs for all meals for Treatment Day 1 and Day 2, both pre-meal and 2 hour post-meal BGs. On those 2 days, for any meal that BG is over 160 mg/dL on BOTH days for the same meal, increase dose by 4 units.
- If at least one meal is under 90 mg/dL, decrease dose by 4 units for that meal. If BG is 90 mg/DL - 160 mg/dL, then keep dose the same. Continue on calculated dose.
- Dose remains same for the next 7 days. Every week on Treatment Days 3, 4, 5, 6, and 7, patients will check pre-meal BGs only. This will reduce risk of hypoglycemia and catch any excessively high fasting BGs.
- Record and review BGs for all meals for next 2 days (Treatment Day 1 and 2). After those 2 days, review post-prandial BGs for those 2 days (Treatment Day 1 and 2) and for any meal that BG is over 160 mg/dL on Both days for the same meal, increase dose by 4 units. If at least one meal is under 90 mg/dL, decrease dose by 4 units for that meal. If BG is 90 mg/dL - 160 mg/dL, then keep dose the same. Repeat sequence every 7 days with calculating dose on Treatment Day 3 after reviewing Treatment Day 1 and Treatment Day 2 BGs. Continue repeating sequence weekly until end of study.

****Patients will notify study coordinator if pre-meal BGs are under 70** mg/dL **or over 250** mg/dL**. *** Any problems after hours, patients are instructed to call the practice at 410-828-7417, and leave messages for the doctor on call for Dr. Levin.**