Newsletter No. 3 – November 2021

NEWSLETTER #3

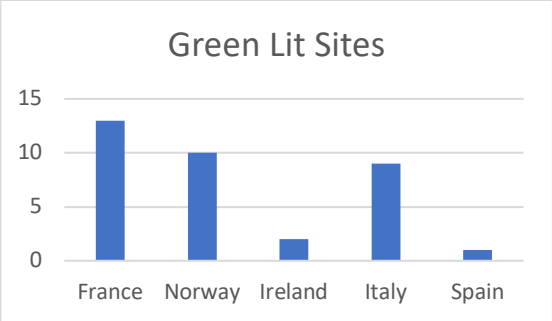
REMEMBER WE HAVE AN INTERNET PAGE: HTTPS://EU-RESPONSE.EU/EU-SOLIDACT/

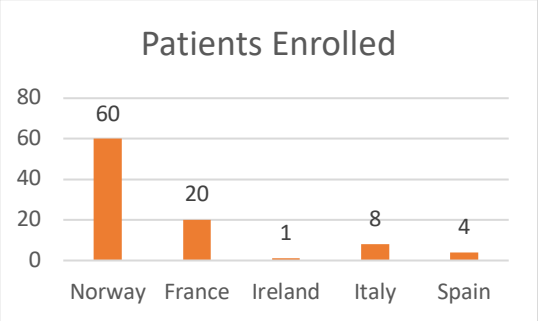
The webpage contains copies of protocols, procedures and training links, so make sure you check it out today!

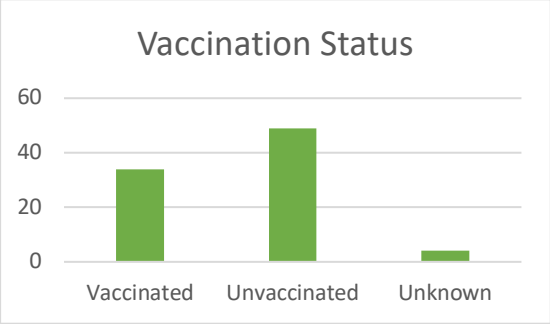
INTRODUCTION

We are steadily increasing the number of countries and sites and have now opened Ireland. Inclusion rates are still slow, mainly because of the epidemiological situation, but we see signs of increased spread. We are focusing on opening Slovakia, Hungary and Czech Republic because we see an increase in these countries. There are now 99 patients included in 21 sites. There are 33 sites with study medication ready to enrol.

STUDY UPDATE AS OF 4TH OF NOVEMBER 2021







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INCLUSION CRITERIA – SOME POINTS ON THE DEFINITION OF "SEVERE DISEASE"

As tocilizumab is increasingly used as rescue therapy in severe and critical COVID, it is important to find a window where randomisation to bariticinib or placebo is possible. Note that the severity criteria in the protocol are the same as in the WHO guidelines for corticosteroid treatment.

1. SpO2<90% on room air, or

2. SpO2 90-94% with a downwards trend and/or signs of respiratory distress*, or

3. Need of oxygen by NIV (CPAP, BIPAP), high flow or non-rebreather mask, or

4. Need of mechanical ventilation/ECMO

*Persistently increased respiratory rate, use of accessory muscles, inability to complete full sentences. Clinical judgement must be applied to determine whether a low oxygen saturation is indicative of disease progression or severity or is habitual for a given patient (i.e., with underlying chronic lung disease).

The range of SpO2 90-94% is on room air, meaning that patients who had SpO2 ≤ 94% and signs of respiratory distress before receiving oxygen will be eligible if other inclusion and exclusion criteria are met.

PROTOCOL AMENDMENT – INCLUSION OF IMMUNOCOMPROMISED PATIENTS

The Bari-SolidAct protocol has now been amended, opening up for inclusion of immunocompromised patients. This will be done with increased pharmacovigilance, including regular evaluation for secondary bacterial, fungal and viral infection. The updated protocol has been submitted as a VHP amendment and is now under evaluation by the regulatory authorities. Indicated feedback time is 16th of November. Following the VHP decision there will be a national phase with submissions to national regulatory authorities and ethics committees. We hope that we will be able to implement the amendment for all countries by late November / early December.

EXCLUSION CRITERIA – CONSIDER eGFR VALUE IN BARI-PROTOCOL

The exclusion criterion SE-16 was not modified in the current amendment.

However, based on available information on **baricitinib**'s safety profile (renal function significantly impacting baricitinib exposure) and the last updated IB dated Sep-2021 – not submitted with the current amendment, **the following exclusion criterion must be applied in BARI-SolidAct trial:**

- **Subjects with estimated glomerular filtration rate (eGFR)** (Modification of Diet in Renal Disease [MDRD]) **<30 mL/min/1.73 m² are excluded (instead of < 15 mL/min/1.73 m²).**

This modification follows the DSMB recommendations as well and will be implemented in the next amendment as of 1st February 2022, when the VHP system allows submissions again. The next amendment will also include the IB of September.

Note that to date no participant with eGFR below 30 mL/min/1.73 m² has been enrolled, highlighting the relevance of the investigators' assessment of the individual benefit/risk ratio.

Note: at the time of this newsletter (and as per protocol), subjects with eGFR between 15-30 will thus still be excluded unless in the opinion of the PI, the potential benefit of participation outweighs the potential risk of study participation.

DOSE ADJUSTMENTS and STOPPING RULES IN CASE OF RENAL IMPAIRMENT DURING THE COURSE OF THE TRIAL

In case of renal impairment during the course of the trial, investigators must consider the eGFR values in order to proceed to a dose adjustment or to IMP discontinuation.

Below is a reminder on these steps, motivated by the occurrence of a fatal renal failure that would have benefited from the dose adjustment mentioned in the protocol.

The trial being blinded, **investigators should assess AEs on the assumption that the participant has received active product**. **Baricitinib** is **predominantly eliminated by the renal route (70%)**, so these **discontinuation rules** are **essential for the safety** of the include patients. **Monitoring of renal function** should be done frequently in all patients with **pre-existing renal damage or significant co-morbidity factors**.

REMINDER ON DOSE ADJUSTMENTS IN CASE OF RENAL IMPAIRMENT (SECTION 6.5 OF THE BARI-SOLIDACT PROTOCOL)

- eGFR **≥ 30 to < 60** mL/min/1.73 m² ⇨ **2 mg once daily**
- eGFR **≥ 15 to < 30** mL/min/1.73 m² ⇨ **withdraw treatment or 2 mg every other day**: according to PI opinion
- eGFR **< 15** mL/min/1.73 m² **or on dialysis** ⇨ **withdraw treatment**

PROTOCOL DEVIATIONS

An information sheet noting how to create a protocol deviation in the eCRF has been created and will be delivered as part of this newsletter.

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WRAP-AROUND LABELS

For the wrap-around labels for France, Norway and Ireland the box is too small for the label, so the label has to be wrapped on top of the label text, see picture below.

We have received concerns about this, given that part of the text is initially covered by the label. However, the wrap-around labels comply with regulations, and are **repositionable** and **specifically designed to be removable** as there are 3 different areas on the labels as following:

Zone 1: has strong glue to stick on the bottle
Zone 2: has no glue
Zone 3: **has light glue to enable the label to be peeled off for reading instructions and stuck back again.**

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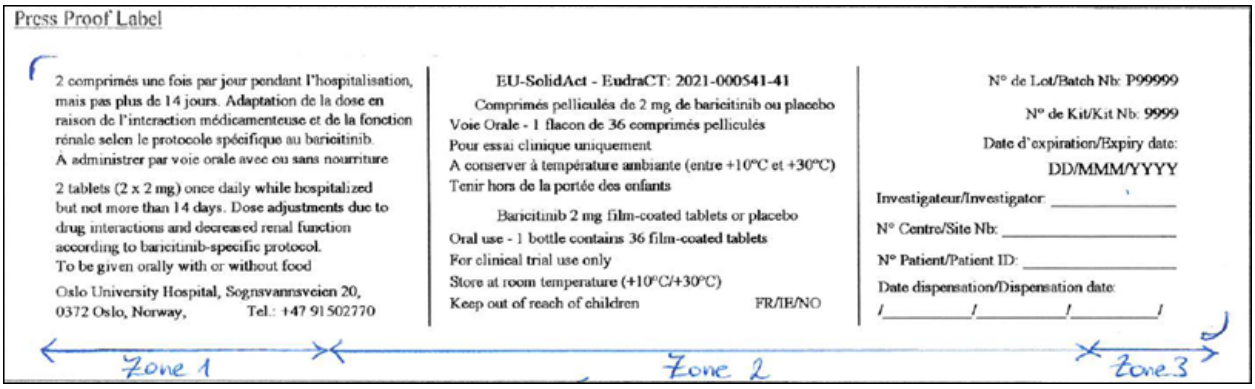

To read any text that is hidden, simply peel off the label and reattach when the text has been read.

PROBLEMS WITH A "LOCKED" ECRF?

The data management team at INSERM has confirmed that only PIs who sign the eCRF can "un-sign" the eCRF. They also state that the CRF should only be signed at the end, when all the patient's data has been entered completely. Please do not to sign the CRFs on an ongoing basis to avoid issues with locked CRFs.

UPDATED AND IMPROVED DRUG ACCOUNTABILITY LOG

Our colleagues in Ireland have very kindly updated the accountability log to make it easier to use. We will include this new form in all the new ISFs, but have attached it here in case anyone would like to change to the new format.

QUESTION & ANSWERS? SEE OUR INTERNET PAGE EU-SOLIDACT - EU-RESPONSE