ASL Bari
PugliaSalute
REGIONE PUGLIA
AZIENDA SANITARIA LOCALE DELLA PROVINCIA DI BARI
Lungomare Starita, 6 • 70123 BARI
Partita IVA/Codice Fiscale 06534340721

DELIBERAZIONE DEL DIRETTORE GENERALE

Deliberazione n.ro	Data di Adozione
0001984	06/10/2023

OGGETTO: Autorizzazione studio osservazionale trasversale, multicentrico dal titolo "Profilo del paziente, modelli di trattamento e costi dell'assistenza sanitaria dei pazienti con Idrosadenite Suppurativa (IS): Studio ibrido osservazionale italiano in un setting di pratica clinica – Codice dello studio CAIN457MIT01 (HidraS)" presso U.O.C. Farmacia Territoriale della ASL di Bari

PROPOSTA DI DELIBERAZIONE DEL DIRETTORE GENERALE N.RO 20230002420 DEL 04/10/2023
COMPOSTA COMPLESSIVAMENTE DA 4 (quattro) PAGINE
DI 1 (uno) ALLEGATI SOGGETTI A PUBBLICAZIONE PER UN TOTALE DI 57 (cinquantasette) PAGINE
DI 0 (zero) ALLEGATI NON SOGGETTI A PUBBLICAZIONE PER UN TOTALE DI 0 (zero) PAGINE
DI 1 (uno) DOCUMENTI ISTRUTTORI NON ALLEGATI PER UN TOTALE DI 2 (due) PAGINE

Con la sottoscrizione in calce, i Direttori dichiarano di non versare in alcuna situazione di conflitto di interesse, anche potenziale, ex art. 6-bis, l. 241/90, artt. 6, 7 e 13, c. 3, D.P.R. 62/2013, vigente codice di comportamento aziendale e art. 1, c. 9, lett. e), l. 190/2012 – quest'ultimo come recepito, a livello aziendale nella sezione Anticorruzione e Trasparenza del PIAO – tale da pregiudicare l'esercizio imparziale di funzioni e compiti attribuiti, in relazione al procedimento indicato in oggetto, così come di non trovarsi in alcuna delle condizioni di incompatibilità di cui all'art. 35-bis, D.L.gs. 165/2001.

Parere del Direttore Amministrativo	Parere del Direttore Sanitario
Firmato Digitalmente il 06/10/2023 09:04 Luigi FRUSCIO	*Firmato Digitalmente il 06/10/2023 09:22* Luigi ROSSI

Il Segretario	Il Direttore Generale
Firmato Digitalmente il 06/10/2023 13:22 Raffaele IORIO	*Firmato Digitalmente il 06/10/2023 13:10* Antonio SANGUEDOLCE

ATTESTAZIONE DI AVVENUTA PUBBLICAZIONE

Si attesta che il presente provvedimento viene pubblicato all'Albo pretorio *on-line* della ASL BA, ai sensi dell'art. 32, c. 1, l. 69/2009, per la durata di 30 giorni naturali, decorrenti dal **06/10/2023**

Unità Operativa Affari Generali
L'Addetto alla Pubblicazione
Firmato Digitalmente il 06/10/2023 13:23
Domenico ROVETO

OGGETTO: Autorizzazione studio osservazionale trasversale, multicentrico dal titolo "Profilo del paziente, modelli di trattamento e costi dell'assistenza sanitaria dei pazienti con Idrosadenite Suppurativa (IS): Studio ibrido osservazionale italiano in un setting di pratica clinica – Codice dello studio CAIN457MIT01 (HidraS)" presso U.O.C. Farmacia Territoriale della ASL di Bari

IL DIRETTORE GENERALE

Vista la deliberazione n. 239 del 16/02/2022, con l'assistenza del Segretario, sulla base dell'istruttoria effettuata dal Responsabile del procedimento per le sperimentazioni cliniche, che ne attesta la regolarità formale del procedimento ed il rispetto della legittimità, considera e determina quanto segue.

Premesso che Novartis Farma S.p.A., ha inoltrato una richiesta volta ad ottenere l'autorizzazione a condurre presso la U.O.C. Farmacia Territoriale della ASL di Bari, sotto la responsabilità della dott.ssa Stefania Antonacci, Direttore dell'Area Servizio Farmaceutico dell'ASL Bari lo studio osservazionale dal titolo: "Profilo del paziente, modelli di trattamento e costi dell'assistenza sanitaria dei pazienti con Idrosadenite Suppurativa (IS): Studio ibrido osservazionale italiano in un setting di pratica clinica – Codice dello studio CAIN457MIT01 (HidraS)";

preso atto dalla sinossi che l'obiettivo primario dello studio consiste nel descrivere le caratteristiche demografiche e cliniche dei pazienti affetti da IS al momento dell'arruolamento;

considerato che Novartis Farma S.p.A. (in qualità di Promotore dello studio) si impegna a versare all'Azienda, a titolo di corrispettivo, un importo complessiva di Euro 6.000,00 (seimila/00) + IVA per le attività previste dal protocollo di studio, secondo le modalità indicate nel testo convenzionale, allegato e parte integrante del presente provvedimento;

dato atto che Novartis Farma S.p.A. ha affidato a IQVIA Solutions Italy S.r.l. la conduzione dello studio osservazionale retrospettivo di cui trattasi e che IQVIA ha identificato nella Dott.ssa Franca Heiman il Responsabile scientifico del progetto, nel Dott. Riccardo Cipelli il Responsabile tecnico; inoltre la Dott.ssa Stefania Antonacci è stata individuata quale Referente ASL e la Dott.ssa Grazia Mazzone quale Responsabile per la raccolta dei dati da effettuarsi presso ASL BA;

acquisito il parere favorevole del Comitato Etico Indipendente dell'Azienda Ospedaliero Universitaria Policlinico Consorziale di Bari (parere n. 7265) per la conduzione del suddetto studio presso l'ASL BARI, espresso nella seduta del 17/05/2023 limitatamente ai 18 pazienti di competenza della dott.ssa Stefania Antonacci;

preso atto che per gli studi osservazionali non occorre una copertura assicurativa aggiuntiva rispetto a quelle già previste per la normale pratica clinica;

osservato, altresì, ai sensi dell'art. 13 del Regolamento per lo svolgimento delle sperimentazioni cliniche nell'Azienda Sanitaria Locale di Bari, che per l'attività di sperimentazione deve essere svolta in regime di timbratura in aggiunta alla normale attività istituzionale;

rilevato che dovranno risultare garantite la dignità personale e la qualità della vita dei soggetti coinvolti nello studio anche attraverso il necessario consenso informato, dopo un'adeguata, completa e comprensibile informazione da dare ai soggetti stessi, ai loro familiari, tutori e, se necessario, ai loro rappresentanti legali;

atteso, inoltre, che il Responsabile dello studio ed i suoi collaboratori provvederanno ad ottenere il consenso informato scritto dai soggetti sottoposti alla sperimentazione, prima dell'arruolamento,

previa una completa ed esauriente esposizione dello studio, utilizzando le informative ed i moduli di consenso informato per i pazienti approvati dal Comitato Etico;

considerato che sono state rispettate tutte le procedure per l'autorizzazione;

Acquisito il parere favorevole del Direttore Amministrativo e del Direttore Sanitario

D E L I B E R A

per le motivazioni espresse in narrativa e che qui si intendono integralmente richiamate

1. di autorizzare, per le ragioni illustrate in narrativa, la dott.ssa Stefania Antonacci, Responsabile dello studio, ed i suoi collaboratori, a condurre presso la U.O.C. Farmacia Territoriale della ASL di Bari sotto la sua responsabilità, lo studio dal titolo: "Profilo del paziente, modelli di trattamento e costi dell'assistenza sanitaria dei pazienti con Idrosadenite Suppurativa (IS): Studio ibrido osservazionale italiano in un setting di pratica clinica – Codice dello studio CAIN457MIT01 (HidraS)" secondo le modalità indicate dal Protocollo e approvato dal Comitato Etico Indipendente;
2. di approvare lo schema convenzionale che è parte integrante del presente provvedimento;
3. di disporre che il Responsabile dello studio ed i suoi collaboratori, prima di dare avvio allo stesso, forniscano adeguate e complete informazioni al paziente ed acquisiscano il consenso informato scritto dal medesimo (o dal suo rappresentante legale) utilizzando le Informative e i Moduli di consenso informato approvati dal Comitato Etico;
4. di disporre che il Responsabile dello studio ed i suoi collaboratori, nell'effettuare lo stesso, in nessun caso forniscano al Promotore e/o ad altri soggetti dati personali, ma solo ed esclusivamente informazioni e dati anonimi;
5. di disporre che il Responsabile dello studio trasmetta all'Ufficio Sperimentazioni cliniche dell'ASL BARI la comunicazione di conclusione dello stesso, accompagnata da una relazione dettagliata;
6. di disporre che il Responsabile dello studio trasmetta al Comitato Etico la relazione sull'andamento dello studio;
7. di prendere atto che il presente provvedimento comporta un ricavo ipotizzato di Euro 6.000,00 (seimila/00) + IVA, che verrà imputato al Bilancio dell'Asl Bari, secondo i criteri di riparto stabiliti ai sensi dell'art. 10 del Regolamento per lo svolgimento delle sperimentazioni cliniche, per gli esercizi di competenza;
8. di trasmettere a Novartis Farma S.p.A. e a IQVIA Solutions Italy S.r.l. la presente deliberazione unitamente alla convenzione debitamente sottoscritta;
9. di notificare il presente atto al Responsabile dello studio, al Responsabile per la raccolta dei dati da effettuarsi presso ASL BA, all'Area Gestione Risorse Umane, al Dipartimento del Farmaco, all'Area Gestione Risorse Finanziaria per gli adempimenti consequenziali, nonché al Collegio Sindacale.

Tutti i firmatari del presente atto attestano di non versare in alcuna situazione di conflitto di interesse, anche potenziale, ex art. 6-bis, l. 241/90, artt. 6, 7 e 13, c. 3, D.P.R. 62/2013, vigente codice di comportamento aziendale e art. 1, c. 9, lett. e), l. 190/2012 – quest'ultimo come recepito, a livello aziendale, dalla Sezione Anticorruzione e Trasparenza del vigente PIAO - tale da pregiudicare l'esercizio imparziale di funzioni e compiti attribuiti, in relazione al procedimento indicato in oggetto, così come di non trovarsi in alcuna delle condizioni di incompatibilità di cui all'art. 35-bis, D.lgs. 165/2001.

Il presente provvedimento è esecutivo dalla data di pubblicazione all'Albo Aziendale.

Convenzione per la conduzione della fase retrospettiva dello studio osservazionale "Patient profile, treatment patterns, and cost of care among patients with hidradenitis suppurativa (HS): an Italian hybrid observational study of real-world clinical practice - CAIN457MIT01 (HidraS)"

TRA

L'Azienda Sanitaria Locale della provincia di Bari (C.F. e P.I. 06534340721) di seguito denominata per brevità "**Ente**" o "**ASL BA**"**,** con sede in Lungomare Starita n. 6 - 70132 Bari (BA), legalmente rappresentata dal Dott. Antonio Sanguedolce, nella sua qualità di Direttore Generale,

E

NOVARTIS FARMA S.p.A. (di seguito denominata "**Novartis**"), con sede legale in Milano, Viale Luigi Sturzo n. 43, cap 20154, Codice Fiscale 07195130153 e Partita IVA 02385200122 registro imprese di Milano, n. REA MI- 2668306, in persona dei procuratori Dr. Flavio Caruso, Pharma CCFO IM Europe, e Dr.ssa Paola Coco, Country Chief Scientific Officer & Medical Affairs;

In seguito individuate disgiuntamente e congiuntamente anche come la "**Parte**"/le "**Parti**"

Premesso che:

- Novartis, in quanto azienda farmaceutica presente sul mercato con alcuni prodotti in area terapeutica Dermatologica, risulta interessata alla realizzazione di uno studio osservazionale retrospettivo, dal titolo *"Patient profile, treatment patterns, and cost of care among patients with hidradenitis suppurativa (HS): an Italian hybrid observational study of real-world clinical practice - CAIN457MIT01 (HidraS)"* disegnato per studiare il burden dei pazienti con Idrosadenite Suppurativa, sulla base del Protocollo n. v00 del 23/09/2021 allegato (Allegato1). Rimane inteso che ove il Protocollo sia finalizzato in data successiva alla stipula della presente Convenzione, la stessa avrà piena efficacia tra le Parti, ivi inclusi i rispettivi obblighi e responsabilità, successivamente e subordinatamente a: a) conclusione dell'iter approvativo interno da parte del gruppo Novartis, come precisato al successivo art. 4.1) e b) effettiva notifica al Comitato Etico (CE) di riferimento dello studio in questione e c) ove non vi siano elementi ostativi alla conduzione dello stesso, anche indicati alle Parti dal CE successivamente alla medesima

sottomissione, essendo tali condizioni sospensive ovvero risolutive dell'effettivo avvio dello studio;

- Lo studio CAIN457MIT01 è uno studio osservazionale trasversale, multicentrico, con scopo descrittivo, che si avvale di una raccolta di dati primari (Prima fase trasversale alla visita di arruolamento) e di dati secondari estratti da database amministrativi (Seconda fase retrospettiva estrazione dati amministrativi nei 36 mesi precedenti l'arruolamento). Questo documento disciplina la seconda fase dello studio;

- Per DB amministrativi si intendono i DB estratti dagli archivi sanitari automatizzati Regionali o di una ASL, e contenenti: (i) DB dell'anagrafe, che raccoglie informazioni demografiche di tutti gli assistiti residenti nel territorio di competenza, (ii) DB delle schede di dimissione ospedaliera (SDO), che raccoglie informazioni sui ricoveri ospedalieri presso le strutture pubbliche o private della Regione, (iii) DB delle prestazioni ambulatoriali, che raccoglie tutte le informazioni in merito alla specialistica ambulatoriale, la diagnostica strumentale e le analisi ematochimiche prescritte, (iv) DB delle prescrizioni farmaceutiche, che raccoglie tutte le informazioni in merito alla farmaceutica territoriale (Farmaci in fascia A) e infine (v) File F, che raccoglie le informazioni riguardanti la farmaceutica ospedaliera);

- L'Azienda Sanitaria Locale della provincia di Bari è titolare dei dati raccolti nei propri database ospedalieri e ha preventivamente acquisito il consenso dei pazienti al trattamento dei dati personali e sensibili anche per finalità di ricerca future e di studio retrospettivo quale quello in premessa; **ovvero** ha provveduto alla pseudonimizzazione dei dati per lo studio retrospettivo prima delle analisi relative;

- L'ASL BA è incaricata e autorizzata a gestire i dati dei propri assistiti sul territorio di riferimento. Tali dati ricadono sotto la liberatoria del garante della privacy per dati di popolazione;

- L'analisi di fattibilità condotta in sede di negoziazione della presente Convenzione ha identificato nel database presente presso l'ASL BA una fonte appropriata per rispondere al quesito scientifico di cui all'oggetto;

- Novartis ha affidato ad IQVIA Solutions Italy S.r.l. con sede in Milano via Filzi 29 - P. IVA 00868270158 (di seguito denominata "**IQVIA**"), la conduzione dello studio osservazionale retrospettivo come in premessa;

- IQVIA opera nell'ambito di studi osservazionali ed epidemiologici, ha vasta e documentata esperienza nella gestione di dati secondari per studi osservazionali e riconosciuta esperienza nell'utilizzo di modelli statistici appropriati per l'analisi di suddetti dati; possiede inoltre le competenze tecniche, scientifiche e metodologiche, l'esperienza e l'organizzazione necessarie a garantire l'elaborazione dei dati sopra citati ai fini della realizzazione dello Studio;

- Lo studio verrà effettuato in conformità al Protocollo ed alle normative nazionali e comunitarie applicabili agli studi osservazionali ed ai principi etici e deontologici che ispirano l'attività medica e sarà altresì condotto in conformità ai principi delle "Good Clinical Practices (GCP) of the International Conference on Harmonisation (ICH)" (ref. ICH GCP E6) e delle "Good Epidemiological Practices (GEP)", in osservanza della C.M. n. 6 del 02/09/2002 ed alla determina AIFA del 20/03/2008;

- Novartis ha notificato il Protocollo di Studio, ai sensi delle Linee Guida per gli Studi Osservazionali sui farmaci (Determinazione AIFA del 20 marzo 2008), al Comitato Etico Indipendente di Bari nella seduta del 21/09/2022;

- Il Comitato Etico dell'Azienda, nella seduta del 17/05/2023 ha espresso il proprio parere favorevole definitivo all'esecuzione dello Studio avente n. 7265;

- L'ASL BA si impegna a comunicare a Novartis in forma scritta ogni eventuale comunicazione/riscontro da parte del competente Comitato Etico in merito dello studio oggetto della presente Convenzione, prima che venga avviata ogni attività correlata allo studio; ove la comunicazione o riscontro del CE sia di carattere sospensivo le Parti si impegnano, ciascuna conformemente al proprio ruolo, a dare seguito alle indicazioni del CE e ad attendere l'esito positivo definitivo dello stesso onde avviare lo studio; ove sia di carattere ostativo allo svolgimento dello studio, si fa riferimento a quanto indicato nella precedente premessa e all'art.10, con risoluzione *ipso iure* della presente convenzione, come indicato all'art. 12;

- L'ASL BA e IQVIA in virtù di quanto sopra e delle finalità dello Studio, intendono collaborare con Novartis alla realizzazione dello Studio. A tal fine, le Parti concordano che l'ASL BA si occuperà dell'estrazione della coorte in studio dal database, della verifica e pulizia di tali dati; le Parti concordano inoltre che l'elaborazione ed analisi dei dati per lo Studio si svolgerà presso IQVIA, disciplinando il trasferimento e il trattamento dei dati tra l'ASL BA e IQVIA, in conformità alle finalità dello studio sopra indicate, con separato atto tra le parti interessate, svolgendo IQVIA il ruolo di responsabile del trattamento per tale attività di elaborazione e di analisi;

- Lo Studio sarà condotto secondo i termini e le condizioni specificate nel Protocollo di Studio allegato;

- Lo Studio potrà iniziare a seguito dell'approvazione da parte del competente Comitato Etico, oppure trascorsi 60 giorni dalla data di sottomissione del dossier etico amministrativo al competente Comitato Etico, previa documentata evidenza della presa d'atto da parte del Comitato Etico.

Tutto ciò premesso, si conviene quanto segue:

Art. 1 Premesse

Le premesse costituiscono parte essenziale e integrante della presente convenzione (in seguito "**Convenzione**").

Art. 2 Oggetto

Con la presente Convenzione le Parti intendono disciplinare modalità, termini e condizioni per lo svolgimento dello Studio, ivi incluso la preparazione del report finale che ne illustrerà e sintetizzerà i risultati (in seguito il "**Rapporto Finale**") nonché la pubblicazione scientifica che seguirà (in seguito la "**Pubblicazione**").

2.1 Lo Studio

2.1.1 La presente Convenzione ha per oggetto la realizzazione della fase retrospettiva di raccolta dati dello Studio osservazionale trasversale multicentrico, come descritto in premesse, denominato "Patient profile, treatment patterns, and cost of care among patients with hidradenitis suppurativa (HS): an Italian hybrid observational study of real-world clinical practice - CAIN457MIT01" avente ad oggetto il Protocollo versione n. v00 del 23/09/2021. I referenti individuati da Novartis collaboreranno con quelli identificati rispettivamente da ASL BA e IQVIA per la realizzazione delle attività previste in premessa concordando le attività e le relative tempistiche mediante incontri e aggiornamenti periodici durante la durata della presente Convenzione.

2.1.2 Lo Studio è condotto e realizzato secondo le condizioni e i criteri identificati nella Sinossi e nel relativo Protocollo.

2.2 Modalità di esecuzione

2.2.1 L'ASL BA riceverà dalla A.O., al termine della fase di arruolamento, l'elenco dei pazienti codificato sia con il codice alfanumerico specifico per lo studio CAIN457MIT01 sia con il codice ID univoco (codice fiscale o altro identificativo necessario per la ricerca dei dati amministrativi). La trasmissione e la ricezione del dato dalla A.O. all'ASL BA dovrà avvenire previa adozione di ogni misura in grado di garantire la sicurezza del dato.

2.2.2 L'ASL BA utilizzerà i codici ID univoci per estrarre i dati amministrativi, relativi alle prestazioni sanitarie erogate, associati ai pazienti arruolati nel studio dall'A.O; successivamente tali dati saranno codificati (sarà aggiunto il codice alfanumerico specifico per lo studio CAIN457MIT01 e sarà eliminato il codice ID univoco) e trasmessi attraverso connessione sicura FTP a IQVIA, utilizzando lo strumento "secure tranfer solution" IQVIA, il cui server è di proprietà di IQVIA ed è sito in Europa. IQVIA provvederà ad unire in un unico database, attraverso il codice alfanumerico studio-specifico, i dati provenienti dallo studio trasversale e retrospettivo. I dati codificati di ciascun soggetto partecipante saranno quindi conservati in un database unico.

2.3 Rapporto Finale e Pubblicazione

2.3.1 IQVIA redigerà il Clinical Study Report (CSR) finale, sulla base del template fornito da Novartis, che condividerà prima della finalizzazione, con l'ASL BA e con Novartis al fine di consentire una revisione congiunta dei dati e la valorizzazione in un idoneo contesto clinico. Sulla base del Clinical Study Report, Novartis si occuperà di redigere e sottomettere il manoscritto destinato.

2.3.2 La compilazione del Clinical Study Report e la redazione della Pubblicazione avverranno secondo le condizioni e le specifiche previste nel successivo Articolo 3.

Art. 3 Obblighi e diritti dell'ASL e di IQVIA

3.1 Elaborazione delle informazioni

3.1.1 L'ASL BA si impegna a rendere disponibili a IQVIA i dati di cui è titolare all'utilizzo, relativi ai dati dettagliati nel Protocollo di Studio, ai sensi dell'Autorizzazione n. 9/2016 - Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica del Garante Privacy Si impegna altresì ad occuparsi dell'estrazione dei dati dal database, della verifica e pulizia di tali dati.

3.1.2 L'ASL BA, dichiara, sin d'ora, che la raccolta e il trattamento dei dati personali dei pazienti è stata effettuata in conformità alla normativa in materia di Protezione dei Dati Personali (Regolamento Generale sulla Protezione dei Dati Personali UE 679/2016 e D. Lgs. 196/2003 e successive modifiche e integrazioni.

3.1.3 IQVIA indentifica nella Dott.ssa Franca Heiman il responsabile scientifico del progetto, e nel Dott. Riccardo Cipelli il responsabile tecnico. La Dott.ssa Stefania Antonacci è identificata quale Referente ASL e la Dott.ssa Grazia Mazzone quale responsabile per la raccolta dei dati da effettuarsi presso ASL BA. Novartis identifica come referente scientifico del progetto la Dott.ssa Vita Manfreda per quanto riguarda le attività dettagliate al punto 2.1.1.

3.1.4 IQVIA si impegna a confrontarsi con i referenti dell'ASL BA per l'analisi di veridicità e di validazione dei dati estratti e a stendere congiuntamente con le parti il piano di analisi adeguato agli obiettivi del protocollo di studio.

3.2 Compilazione del Clinical Study Report

3.2.1 A conclusione dello Studio, IQVIA provvederà ad illustrare e sintetizzare gli esiti dell'analisi in un CSR finale, da presentare a Novartis per la condivisione prima della sua finalizzazione, il cui termine è individuato e specificato al successivo punto 3.2.3.

3.2.2 Il CSR finale conterrà soltanto dati di natura anonima e aggregata, non più riconducibili ai singoli soggetti.

3.2.3 All'esito dell'elaborazione dei dati, il CSR finale dovrà essere messo a disposizione di Novartis entro e comunque non oltre 6 mesi dal ricevimento dei dati di ASL BA come dettagliato nell'articolo 3.1.1..

3.3 Pubblicazione

Novartis si impegna a redigere in modo congiunto con IQVIA la pubblicazione scientifica su rivista indicizzata dopo peer-review secondo le modalità e i termini previsti in questa Convenzione e a sottometterle secondo quanto di seguito previsto.

3.4 Modalità esecutive

Lo Studio dovrà essere condotto nel più scrupoloso rispetto del Protocollo, visionato ed accettato dal Responsabile dello Studio, approvato/notificato dal Comitato Etico di riferimento ed in conformità a tutte le normative nazionali e comunitarie applicabili agli studi osservazionali e ai principi etici e deontologici che ispirano l'attività medica.
Lo Studio sarà altresì condotto in osservanza della Circolare Ministeriale n. 6 del 02.09.2002, della Determinazione AIFA del 20.03.2008 e delle procedure descritte nel Protocollo e nei documenti specifici dello Studio. Con la sottoscrizione del presente contratto, l'ASL BA ed il Responsabile dello

Studio dichiarano di conoscere ed impegnarsi ad eseguire le attività inerenti lo Studio conformemente alla regolamentazione sopra richiamata.

IQVIA è responsabile della corretta e adeguata elaborazione dei dati nonché della conformità della redazione e compilazione del Report Statistico e del CSR, che dovrà contenere i risultati di tutte le analisi stabilite nel Protocollo.

Novartis, nel rispetto dell'art. 7 della Determinazione AIFA del 20.03.2008 e della Circolare Ministeriale n. 6 del 02.09.2002, si impegna a garantire la pubblicazione e la divulgazione dei risultati una volta concluso lo Studio, anche in caso di risultati negativi e a darne comunicazione a tutti i soggetti coinvolti.

In considerazione di quanto previsto dal D.M. 12 maggio 2006, art. 5, comma 3 lett. c), le Parti concordano che i risultati della Studio dovranno essere sempre discussi tra le Parti prima della pubblicazione, anche ai fini della tutela brevettuale; in ogni caso nel più rigoroso rispetto delle legislazioni vigenti, italiana ed europea, in termini di protezione dei dati personali e sensibili.

Qualora l'ASL BA e IQVIA intendano divulgare autonomamente i risultati dello studio, si impegna a fornire a Novartis in anticipo la pubblicazione, in modo da garantire a Novartis una appropriata revisione anche al fine di verificare la corretta rappresentare del proprio ruolo conforme a quello rivestito nello studio in questione.

Art. 4 Obblighi e diritti di Novartis

4.1 Novartis collaborerà nella redazione del Protocollo, a sottometterlo al Comitato Etico competente per l'autorizzazione. Ove Novartis si avvalga di un soggetto terzo per le attività di analisi, provvederà a formalizzare con separato incarico tale attività, ivi compresi obblighi e responsabili delle parti, termini e modalità di pagamento dei corrispettivi.

Si precisa che Novartis, nel rispetto delle proprie procedure interne, dovrà provvedere alla valutazione del Protocollo finale d'intesa con la propria Casa Madre, riservandosi sin d'ora di comunicare all'ASL BA un eventuale esito negativo circa l'effettivo avviamento dello studio. Di tale esito negativo Novartis darà tempestivo riscontro all'ASL BA con comunicazione scritta.

In tale ipotesi, Novartis sin d'ora si riserva di recedere unilateralmente dalla presente convenzione, riconoscendo all'ASL BA il corrispettivo per le attività effettivamente prestate fino al momento della comunicazione del recesso.

4.2 A fronte dello svolgimento delle attività oggetto della presente Convenzione, Novartis verserà a titolo di corrispettivo un totale di Euro 6.000,00 (+ IVA) a favore dell'ASL BA. Detto importo verrà fatturato in base alle tempistiche previste al punto 4.4.

4.3 Il pagamento sarà effettuato tramite bonifici bancari ad ambi gli enti sui rispettivi conti a 90 giorni dalla data di ricevimento della fattura.

4.4 Sulla base delle varie fasi di cui si compone lo Studio, delle scadenze attese per ciascuna fase e dei relativi risultati attesi si concorda il seguente piano di fatturazione:

- Euro 6.000,00 (+ IVA) entro dicembre 2023 e comunque non prima della conferma di IQVIA dell'avvenuta ricezione dei dati dell'estrazione.

4.5 Novartis avrà facoltà di recedere dal rapporto in caso di violazione o di mancata o inidonea esecuzione delle obbligazioni da parte dell'ASL BA.

4.6 In caso di ritardata esecuzione delle obbligazioni da parte dell'ASL BA, Novartis avrà facoltà di sospendere il pagamento dei corrispettivi sopra indicati, salvo, in ogni caso, il diritto di recesso alle condizioni di cui al punto che precede.

Art. 5 Riservatezza, divulgazione e titolarità delle informazioni

5.1 Con la stipula della presente Convenzione, le Parti si impegnano a mantenere riservate - per quanto loro compete – e a non divulgare le informazioni e i dati forniti o, comunque, acquisiti e appresi durante lo svolgimento del rapporto ("**Informazioni Riservate**").

5.2 L'obbligo di riservatezza e il divieto di divulgazione delle Informazioni Riservate non cesseranno al termine della presente Convenzione ma obbligheranno le Parti ~~per ulteriori 5 anni~~ anche dopo la scadenza dello studio sine die.

5.3 L'impegno di riservatezza previsto in questo articolo non si estende a quelle informazioni che siano o diventino di pubblico dominio senza responsabilità delle Parti, oppure che siano legittimamente richieste dall'Autorità Amministrativa o Giudiziaria.

5.4 Le Parti si impegnano, per quanto di rispettiva competenza, a trattare i dati dei quali vengano per qualsiasi motivo a conoscenza durante la Convenzione in conformità a quanto disposto dalle vigenti normative comunitarie e italiane in materia di protezione dei dati sensibili e personali.

Art. 6 Trattamento dei dati personali

6.1 Nell'esecuzione della presente Convenzione le Parti si impegnano a ottemperare, ciascuna per gli obblighi di propria competenza, ad ogni prescrizione della normativa vigente in materia di trattamento di dati personali (Regolamento Generale sulla Protezione dei Dati Personali UE 679/2016

e D.lgs. n. 196/2003 e s.m.i.). Esse tratteranno, nelle rispettive qualità di Titolari autonomi del trattamento, i dati personali dei pazienti, in particolare quelli di natura sensibile-sanitaria e altri dati comuni dei soggetti partecipanti allo studio. Si precisa che Novartis tratterà solo dati codificati che non consentono il collegamento ai dati anagrafici del paziente.

Novartis ha designato Responsabile del trattamento dati IQVIA con adeguato atto di nomina, ai sensi del Regolamento Europeo n. 679/2016 e nel rispetto delle disposizioni normative. IQVIA si impegna ad attivare l'estrazione dei dati solo allorchè abbia avuto conferma dall' ASL BA che il paziente in vita abbia sottoscritto il form di consenso relativo alla partecipazione al studio.

6.2 In particolare, l'ASL BA e IQVIA, ciascuno in conformità ai rispettivi ruoli, dichiarano e garantiscono che i dati personali, ivi compresi quelli particolari, che verranno trattati per lo svolgimento dello studio in questione e/o di terzi raccolti o utilizzati in occasione dello studio stesso saranno trattati in conformità a quanto stabilito dalla suddetta normativa.

6.3 A tali fini, esse assicurano che i dati raccolti e trattati saranno conservati e archiviati nel rispetto delle misure di sicurezza previste dalla normativa richiamata, con specifico riguardo a quanto disposto dall'articolo 32 del GDPR, e che non saranno divulgati o resi accessibili salvo a persone, organi e enti che esercitino funzioni di vigilanza su di esse.

6.4 Resta inteso che l'ASL BA e IQVIA, si assumono sin d'ora ogni responsabilità derivante dal trattamento dei dati personali, conforme al rispettivo ruolo, e si impegnano a garantire, manlevare e tenere indenne Novartis da ogni e qualsivoglia responsabilità, spesa e/o danno, estromettendo la stessa da ogni controversia a qualsiasi titolo proposta dai propri dipendenti, collaboratori, dai partecipanti all'evento e/o terzi.

Art. 7 Responsabilità

7.1 Con la stipula della presente Convenzione ciascuna Parte è responsabile del giusto e tempestivo adempimento delle proprie prestazioni e del rispetto dei propri obblighi.

7.2 Ciascuna Parte si impegna a dare diligente esecuzione alle proprie obbligazioni secondo buona fede.

7.3 La presente Convenzione non dà vita ad alcun rapporto di natura associativa e/o societaria tra le Parti, le quali collaborano in qualità di soggetti autonomi e indipendenti.

7.4 Nessuna delle Parti potrà pertanto ritenersi responsabile per le obbligazioni assunte dalle altre Parti, anche nei confronti di terzi.

Art. 8 Modello di Organizzazione Gestione e Controllo ex D. Lgs. 231/2001

Novartis dichiara di aderire alle disposizioni di cui al Decreto Legislativo 231/2001 e successive modificazioni e integrazioni.

A tale proposito essa dichiara di avere adottato un proprio Modello di Organizzazione Gestione e Controllo (di seguito il "**Modello**") conforme alle previsioni del D.Lgs. 231/2001.

Art. 9 Esclusiva

9.1 Per tutta la durata della Convenzione l'ASL BA e IQVIA si impegnano a non utilizzare il Protocollo alla base dello Studio oggetto della presente Convenzione per collaborare in progetti analoghi con altre aziende farmaceutiche diverse da Novartis o da altra società appartenente al medesimo Gruppo della stessa, salvo espressa autorizzazione di Novartis.

9.2 L'ASL BA si impegna a non cedere o condividere con altre aziende farmaceutiche il Rapporto Finale dello Studio in questione.

Art. 10 Durata

Gli effetti della presente Convenzione decorreranno dalla data della sua sottoscrizione fino al completamento delle attività previste dallo Studio, previste presuntivamente per la data del 31/12/23, in cui Novartis finalizzerà e sottometterà per pubblicazione un manoscritto finale. Resta inteso che qualora il competente Comitato Etico dovesse sollevare obiezioni in merito allo svolgimento dello studio, anche successivamente ai 60 giorni dalla sottomissione, la presente Convenzione si intenderà automaticamente risolta e nulla sarà dovuto da parte di Novartis all'ASL BA e a IQVIA, ad eccezione del corrispettivo maturato fino all'anticipata cessazione nonché le relative spese previa idonea documentazione giustificativa, restando esclusa qualsiasi forma di indennizzo o di risarcimento. Le somme eventualmente già corrisposte dovranno quindi essere restituite.

Art. 11 Divieto di cessione della Convenzione

La presente Convenzione non potrà essere in alcun modo ceduto a terzi da alcuna delle Parti, sia parzialmente che interamente, senza previo consenso scritto delle Parti stesse.

Art. 12 Risoluzione

12.1 Ciascuna prestazione delle Parti deve considerarsi essenziale ai fini della corretta e tempestiva esecuzione della Convenzione.

12.2 Fermo e impregiudicato ogni diritto previsto nella presente Convenzione ovvero dalla legge, il rapporto tra le Parti si risolverà *ipso iure* nel caso previsto in premesse e ove la Parte inadempiente non abbia adempiuto le proprie obbligazioni entro il termine di 15 (quindici) giorni dal ricevimento di apposita comunicazione scritta ad adempiere inoltrata dalla Parte adempiente.

Art. 13 Legge applicabile e foro competente

La presente Convenzione è disciplinato dalla legge italiana e per qualsiasi controversia derivante dalla sua interpretazione, esecuzione e risoluzione sarà competente in via esclusiva il foro di Bari.

Art. 14 Miscellanea

14.1 Tutte le clausole della presente Convenzione sono state oggetto di negoziazione tra le Parti e pertanto non necessitano di specifica approvazione.

14.2 Le Parti riconoscono di aver preso parte alla negoziazione della Convenzione in buona fede e di non essere a conoscenza dell'esistenza di cause di invalidità della Convenzione.

14.3 Qualsiasi eventuale modifica della presente Convenzione dovrà essere concordata, accettata e sottoscritta espressamente e in via preventiva dalle Parti.

14.4 La presente Convenzione, stipulata sotto forma di scrittura privata non autenticata, poiché regola prestazioni soggette all'imposta sul valore aggiunto, è soggetta a registrazione fiscale in caso d'uso, ai sensi dell'art. 5 del D.P.R. 26/4/86 n. 131, e prevede l'applicazione dell'imposta di registro in misura fissa, ai sensi dell'art. 40 del precitato D.P.R.

14.5 Le spese di registrazione sono poste a carico della Parte che avrà interesse a chiederla.

14.6 Per tutto quanto ivi non espressamente regolato è fatto richiamo alle disposizioni di legge in materia di accordi con i soggetti pubblici e del Codice Civile.

Art. 15 Allegati

Gli allegati costituiscono parte integrante ed essenziale della presente Convenzione.

Milano, data_____

per **Novartis Farma S.p.A.**

Dr. Flavio Caruso

Pharma CCFO IM Europe

Firmato digitalmente da: CARUSO FLAVIO

Firmato digitalmente da:
COCO PAOLA
Data: 28/09/2023 19:04:13

_____

Dr.ssa Paola Coco

Country Chief Scientific Officer & Medical Affairs

_____

Bari, data_____

per **Azienda Sanitaria Locale della provincia di Bari**

Dr. Antonio Sanguedolce

Firmato digitalmente da: ANTONIO SANGUEDOLCE
Organizzazione: Regione Puglia
Unità organizzativa: REGIONE PUGLIA
Data: 04/10/2023 11:11:00

Si producono i seguenti Allegati:

Allegato 1: Protocollo di Studio

NOVARTIS

Department Patient Access

Non-Interventional Study Protocol (Non-PASS)

CAIN457MIT01

Patient profile, treatment patterns, and cost of care among patients with hidradenitis suppurativa (HS): an Italian hybrid observational study of real-world clinical practice

Authors: Martina Fiocchi Ilaria Peduto Lucia Simoni

Document type: Non-interventional study protocol (non-PASS)

Version number: v00

Release date: 23-September-2021

NIS Protocol Template Primary Data Collection Version 3.0 dated 14-August-2017

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List of abbreviations

ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CRF	Case Report/Record Form
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
DRG	Diagnosis Related Group
eCRF	electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ED	Emergency Department
EphMRA	European Pharmaceutical Market Research Association
GAMP5	Good automated manufacturing practice 5
GPP	Good Pharmacoepidemiology Practices
HEOR	Health Economics & Outcomes Research
HRU	Healthcare Resource Utilization
HS	Hidradenitis Suppurativa
HS-PGA	HS - Physician's Global Assessment Score
HSSI	HS Severity Index
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
LHU	Local Health Unit
MedDRA	Medical Dictionary for Regulatory Activities
NHS	National Health System
PI	Principal Investigator
PRO	Patient-Reported Outcome
QoL	Quality of Life
RWE	Real World Evidence
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDO	Scheda Dimissione Ospedaliera
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
WHO	World Health Organisation

1 Responsible parties

Not applicable.

2 Abstract

Title

Patient profile, treatment patterns, and cost of care among patients with hidradenitis suppurativa (HS): an Italian hybrid observational study of real-world clinical practice

Version and date

v00 – 23 September 2021

Name and affiliation of main author

Martina Fiocchi (Novartis Farma S.p.A.)

Ilaria Peduto (IQVIA Solutions Italy S.r.l.)

Lucia Simoni (MediNeos S.U.R.L, a company subject to the direction and coordination of IQVIA Solutions HQ Ltd)

Rationale and background

Hidradenitis Suppurativa (HS) or "acne inversa" is an uncommon, but not rare, chronic inflammatory disease of the skin that causes recurrent and painful nodules, boils, abscesses, and skin lesions that occur predominantly in the axillary, inguinal, and anogenital regions (Jemec G. B., 2012) .

Due to the variable signs and symptoms exhibited by patients, it remains largely unrecognized and difficult to treat, resulting in a significant diagnostic delay (Napolitano, 2017) (Scuderi, 2017) and inconsistent treatment process. In this regard due to its underdiagnosis or misdiagnosis the prevalence estimates range from 5:10,000 to 4:100 (Miller, 2016).

The present study is designed to provide real-world evidence description of patients with HS in Italy.

Research question and objectives

The aim of the present study is to describe a cohort of Italian patients with HS in terms of demographic and clinical characteristics, quality of life, healthcare resource utilization and associated direct, indirect, and out of pocket costs, utilizing multiple data sources able to provide a multifaceted evaluation of the Italian HS population.

Primary objective

To describe HS patients' demographics and clinical characteristics at enrollment (Visit 1).

Secondary objectives

1. To describe the patient-reported impact of HS on patient's quality of life at enrollment, evaluated by means of the Dermatology Life Quality Index (DLQI) questionnaire.
2. To describe Healthcare Resource Utilization of patients with HS during the 36 months prior to enrollment with administrative database.
3. To estimate direct costs of HS covered by the National Health System (NHS) during the 36 months prior to enrollment with administrative database.
4. To estimate indirect costs of HS in the 12 months prior to enrollment, evaluated by a structured interview between physicians and patients performed during the enrollment visit.
5. To estimate direct costs of HS not covered by NHS in the 12 months prior to enrollment, evaluated by a structured interview between physicians and patients performed during the enrollment visit.

Study design

The current study is an Italian, multicenter, cross-sectional observational study with descriptive aim, involving both a primary data collection (at enrollment visit) and secondary use of administrative data (covering a 36-month period before enrollment).

The study will be conducted in 6 Italian sites.

Setting and study population

Each participating site is expected to enroll consecutively about 15-20 patients during a 12-month enrollment period, for a total number of 100 adult patients.

Inclusion criteria

Patients who meet all the following inclusion criteria can be included in the study at enrollment visit date:

1. Patients aged 18 years or more;

2. Patients diagnosed with HS at least 12 months before enrollment;

3. Patients who signed the informed consent and privacy form at enrollment visit.

Exclusion criteria

Patients meeting any of the following exclusion criteria cannot be included in the study at enrollment visit date:

1. Patients enrolled in clinical trials imposing procedures/interventions which are not part of the site's routine clinical practice (either at enrollment or in the 36 months before);

2. Patients will be excluded if the unique identifier does not allow them to be identified in the Local health Unit (LHU) administrative databases related to the site where they were enrolled (e.g., patients living in another region or in the same region but outside the area of competence of the LHU).

Variables

The following variables will be collected at enrollment visit:

- Patient socio-demographics (age, gender, ethnicity, smoking habits, municipality of residence, domicile (if different from municipality of residence), physical examination (height, weight, Body Mass Index (BMI)) and main clinical characteristics (such as comorbidities, HS history, HS severity, HS phenotypes, symptoms and HS status);
- Assessments of Patient-Reported Outcome (PRO) tools (namely, DLQI questionnaire);
- Resources for estimation of indirect costs and direct costs not covered by NHS, through a structured interview conducted by physicians.

Finally, healthcare resource utilization and direct healthcare costs will be retrieved (claims data) from the administrative databases of the participating LHUs.

Observational methodology will be used in order to capture data, therefore only data available from routine clinical practice will be collected.

Data sources

This study will involve primary and secondary data collection. The data sources will be: 1) Medical records available at the study site for each patient; 2) PRO and physician-patient structured interview collected at enrollment; 3) Data collected from the administrative databases of the participating LHUs where healthcare resource utilization will be retrieved (claims data).

Study size

According to feasibility considerations, during 12 months of enrollment, it is reasonable to expect the inclusion of 100 HS patients in 6 sites. We expect that up to 5% of the enrolled patients could be not evaluable for the primary analysis (due to non-eligibility). Therefore, we expect that 95 patients will be available for the analysis of primary

objective. In case the target sample size is not reached, this will not imply study failure, but it will lead to a lower precision of the estimates of the primary endpoints.

An evaluation of the possible achievable precision of the estimates for the main primary endpoints was performed considering the primary objective of the study and literature data, when available.

In the table below are shown the two-sided 95% confidence interval (CI) for expected frequency of selected categorical primary endpoints for a sample size n=95, using the large sample normal approximation (Dixon, 1983).

Endpoint	Expected estimate	Reference from literature	95% CI (for n=95)
Females (%)	61.5%	(Bettoli V. C., 2019)	51.7% ; 71.3%
Current/former smokers (%)	67.6%	(Bettoli V. C., 2019)	58.2% ; 77.0%
Hurley stage: II/III (%)	66.0%	(Bettoli V. C., 2019)	56.5% ; 75.5%
Affected locations: groin/genitals (%)	44.1%	(Bettoli V. C., 2019)	34.1% ; 54.1%

Data analysis

All analyses will be performed by IQVIA, using SAS software (SAS Institute, Cary, NC, USA).

The study has a descriptive aim, and no a priori hypotheses are defined. All analyses will be mainly descriptive with no planned comparison of patient groups.

Continuous numerical variables will be summarized using mean, standard deviation (SD), median, first and third quartile, minimum, and maximum; categorical variables will be summarized using frequency counts and percentages. Missing data will not be replaced and will be considered a separate category in all analyses and will be described using frequency counts and percentages.

The statistical analyses will be performed considering the set of eligible patients, defined as those subjects meeting all inclusion criteria and not meeting any of the exclusion criteria.

The detailed analysis plan will be provided in the Statistical Analysis Plan.

Primary objective analyses

The analyses that will be performed for the evaluation of demographic and clinical characteristics at enrollment visit are the following:

- descriptive statistics (mean, standard deviation, median, first and third quartile, minimum and maximum, 95% confidence interval) of age at enrollment, time from symptoms' onset to first confirmed HS diagnosis, and disease duration;
- patients' distribution (count and percentage) by gender, ethnicity, BMI classes, smoking habits;
- patients' distribution (count and percentage, and corresponding 95% confidence interval) by presence/absence of comorbidities at enrollment and relevant medical history;
- patients' distribution (count and percentage) by number of HS treatment lines prior to enrollment and by surgery (already received, planned, not planned).
- patients' distribution (count and percentage) by HS severity defined by Hurley staging system, HS-Physician's Global Assessment Score (HS-PGA) and/or HS Severity Index (HSSI) classes.
- patients' distribution (count and percentage) by phenotypes of HS, presence/absence of lesions in various localizations and presence/absence of symptoms.

- patients' distribution (count and percentage, and corresponding 95% confidence interval) by achievement of symptoms control and by presence/absence of flare and remission.

Patients' distribution by presence/absence of comorbidities will be provided also considering only comorbidities retrieved from administrative database. For this analysis, presence of comorbidities will be defined using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and/or exemption codes recorded in the database.

For details about the secondary objectives, please refer to paragraph 7.7.2.

Milestones

Planned dates of study milestones:

Milestone	**Planned date**
Start of primary data collection	March 2022
End of primary data collection	February 2023
Start of secondary (administrative) data extraction	February 2023
Final report of study results	September 2023

3 Amendments and updates

None.

4 Milestones

Table 4.1 Planned dates of study milestones

Milestone	Planned date
Start of primary data collection	March 2022
End of primary data collection	February 2023
Start of secondary (administrative) data extraction	February 2023
Final report of study results	September 2023

5 Rationale and background

5.1 Background

Hidradenitis Suppurativa (HS) or “acne inversa” is an uncommon, but not rare, chronic inflammatory disease of the skin that causes recurrent and painful nodules, boils, abscesses, and skin lesions that occur predominantly in the axillary, inguinal, and anogenital regions (Jemec G. B., 2012). HS is a disease of hair follicles characterized by a perifollicular lymphocytic infiltrate with subsequent sebaceous gland loss. This disease may result from deregulation of the local immune system (Saunte, 2017).

Due to the variable signs and symptoms exhibited by patients, it remains largely unrecognized and difficult to treat, resulting in a significant diagnostic delay (Napolitano, 2017) (Scuderi, 2017) and inconsistent treatment process. In this regard due to its underdiagnosis or misdiagnosis, the prevalence estimates range from 5:10,000 to 4:100 (Miller, 2016) and it occurs more frequently in females than males, and it usually presents after puberty (Zouboulis, 2019). These extremely large variations could be explained by a combination of factors, including different selection procedures, different sources, different diagnostic criteria, geography, and variations in the sex and age distribution of the samples evaluated (Miller, 2016). Moreover, it is estimated that prevalence calculated on clinical dermatologic samples was higher than prevalence based on population-based studies (1.7% and 0.3%, respectively) (Jfri, 2021).

Therefore,the exact prevalence of HS remains unknown; however, there is a high comorbidity burden (e.g., obesity, metabolic syndrome, smoking, depression, arthritis, autoinflammatory syndromes, inflammatory bowel disease, and genetic syndromes), resulting in an increase in hospital visits for patients with HS (Jemec G. B., 2012) (Miller, 2016) (Jemec G. B., 2015).The diagnosis of HS is usually based on the presence of recurrent lesions painful or suppurating lesions more than twice in 6 months in areas of the body considered "typical," including the axilla, genital area, perineum, gluteal area, and, in women, inframammary area (Bettoli V. P., 2016).

Due to the lack of evidence, there is not a therapeutic standard of care. The evaluation of the inflammatory components and the scarring should be at the base of HS treatment. Treatments could include surgery as well as medical treatments (antibiotic topical agents, systemic antibiotics, biologic agents). Since the latter rarely result in lasting cure, surgical treatment, such as deroofing, laser, local excision or wide excisions, is quite common and accepted therapeutic modality for HS (Gulliver, 2016).

To date, there is no consensus for a severity system, but the Hurley staging is most commonly used (van der Zee H. H., 2015). The Hurley system divides HS into three stages according to the most severely affected region: Stage I “Mild”; Stage II “Moderate” and Stage III “Severe”, respectively. Once diagnosed, HS is a challenging disease to treat. Treatment depends on the extent, severity, duration, and chronicity of the lesions. A wide range of therapies are currently used to manage HS. These include topical therapies (antibiotic and nonantibiotic), systemic antibiotics, anti-inflammatory agents, and hormonal therapies. More recently, biologic agents have been included in European guidelines. Because nonsurgical methods are often ineffective in the long term, surgical treatment appears to be a common therapeutic modality for HS (Zouboulis, 2019) (Gulliver, 2016) (Alavi, 2017). Dietary changes, weight loss, and smoking cessation are strongly recommended. Clinical improvement in obese patients after weight loss has been observed (Kromann, 2014).

However, symptom control and lesion resolution are inconsistent and often inadequate, which can lead to increased healthcare costs. Recent studies have shown that patients with HS used health care in high-cost settings (eg, emergency department (ED) and hospital care) more frequently than patients with other chronic inflammatory skin conditions (Jemec G. B., 2015).

A study in Denmark (Jemec G. B., 1996) showed a deterioration of self-reported health in HS. Pain, rash, and the appearance of lesions are described as problems with both work and leisure time by 51% of all patients. In addition, the Hidradenitis Suppurativa Disease Burden in Finland - the HI-FI study identified the economic burden associated with HS, where disease severity and comorbidities are key elements in estimating Healthcare Resource Utilization (HRU) and associated costs in HS (Kosunen, 2018). However, little is known about HS's indirect burden, such as lost income, risk of leaving the workforce, work days lost, and indirect costs.

Finally, HS can have a large negative impact on health-related quality of life (van der Zee H. H., 2012) (Deckers, 2016) (Matusiak, 2010). Indeed, HS patients often experience distress, depression, and other psychological comorbidities, that can lead to feelings of embarrassment, shame, and social isolation and even an increased risk of suicide (Matusiak, 2010) (Thorlacius, 2018). The UNITE, a US registry designed to evaluate the impact of HS on patients in the real-world which collected Patient-Reported Outcomes (PROs) assessment of quality of life, provided a photography of the impact of the disease on the lives of the patients enrolled. The analysis showed that HS affects: psychological well-being (anxiety and depression were reported by a half and a third of patients, respectively), their intimate relationships, the financial well-being of patients (Kimball, 2020) .

5.2 Rationale

Comprehensive data on patients with HS treated according to routine clinical practice in Italy are not yet available. The aim of this study is to generate real-world evidence in order to fill knowledge gaps in disease manifestations, care management and burden of HS in Italy. In particular, the study will be focused on the main characteristics of patients with HS, along with their perceived level of quality of life, care and treatment pathways, and their health/non-health care costs.

An HS hybrid study will be conducted. Specifically, patient-level data from both primary sources and secondary sources from administrative databases of Local health Units (LHUs) will be used. A third item that will further strengthen HS's vision will be PROs data, which will also allow the capture of patients' perspectives on impact of HS on their quality of life (QoL assessment). The strength of this study is that it combines multiple data sources providing a broad overview of HS in Italy.

6 Research question and objectives

The main aim of the study will be to describe a cohort of Italian patients with HS in terms of demographic and clinical characteristics, quality of life, healthcare resource utilization and associated direct and indirect costs, utilizing multiple data sources able to provide a multifaceted evaluation of the Italian HS population.

6.1 Primary objective

To describe HS patients' demographics and clinical characteristics at enrollment.

6.2 Secondary objectives

1. To describe the patient-reported impact of HS on patient's quality of life at enrollment, evaluated by means of the Dermatology Life Quality Index (DLQI) questionnaire.
2. To describe HRU of patients with HS during the 36 months prior to enrollment with administrative database.
3. To estimate direct costs of HS covered by the National Health System (NHS) during the 36 months prior to enrollment with administrative database.
4. To estimate indirect costs of HS in the 12 months prior to enrollment, evaluated by a structured interview between physicians and patients performed during the enrollment visit.
5. To estimate direct costs of HS not covered by NHS in the 12 months prior to enrollment, evaluated by a structured interview between physicians and patients performed during the enrollment visit.

7 Research methods

7.1 Study design

The current study is an Italian, multicenter, cross-sectional observational study with descriptive aim, involving both a primary data collection (at enrollment visit) and secondary use of administrative data (covering a 36-month period before enrollment).

The study will be conducted in 6 Italian sites. Each participating site is expected to consecutively enroll about 15-20 patients during a 12-month enrollment period, for a total number of 100 patients.

Primary data collection will be performed during the enrollment visit, while the retrospective phase will allow to extract administrative data backward from the enrollment visit up to 36 months before.

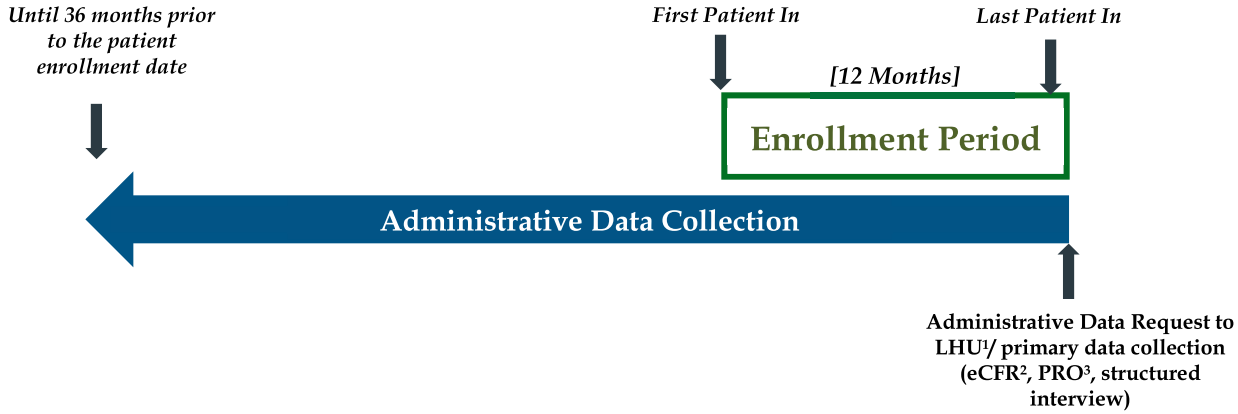
Patients observed in this study will be adult patients diagnosed with HS at least 12 months before enrollment; further details on inclusion/exclusion criteria are available in paragraphs 7.2.1, 7.2.2. The enrollment period will last 12 months (from First Patient In to Last Patient In). Patients will be consecutively enrolled when they spontaneously refer to the dermatological clinic. The enrollment visit will also allow to collect PRO data on patients' quality of life and to conduct a structured interview aimed at investigating direct and indirect cost due to the illness and direct costs not covered by NHS.

The chosen study design allows to address appropriately the primary and secondary objectives (see paragraphs 6.1, 6.2), through the collection of relevant clinical information to describe HS history, disease characteristics, severity and manifestations, as well as impact of HS on the patients in terms of both quality of life and costs; this description will be complemented by secondary use of data on HRU over a 36-month period, which is deemed to be appropriate for describing HS patients management and treatment pathways, as well as estimating direct costs.

The study will be performed on 100 patients and the patients' decision to participate will not, in any way, impact the standard of care they are receiving or any benefits to which they are otherwise entitled. Any treatment decision will be made independently from the patient's inclusion in the study. Finally, all aspects of the clinical management of patients will be in accordance with Italian clinical practice.

HS patients who meet all the inclusion criteria (see paragraph 7.2.1) and none of the exclusion criteria (see paragraph 7.2.2) will be enrolled during a routine visit at the clinical site according to current clinical practice (Visit 1, "Enrollment Visit"). The study design including the administrative data collection and the enrollment period is shown in Figure 1, while the patient scheme is depicted in Figure 2.

Figure 1. Study design and duration.



[1]*LHU - Local Health Unit*
[2]*eCRF- electronic Case Report Form*
[3]*PRO Patient Reported Outcome*

Figure 2. Patient scheme.

Primary data collection phase will be considered complete when data entry in the electronic Case Report Form (eCRF) is concluded for all participating patients. During the enrollment visit, the Principal Iinvestigators (PIs) will also ask the patient to voluntarily complete the PRO (ie. DLQI questionnaire). Additionally, to complete the assessment of the impact of HS on the patient's perspective, patients will be invited to participate to a structured interview conducted by physicians at enrollment, in order to explore relevant domains of HS direct costs not covered by NHS and indirect costs. Also data collected from PRO and physician-patient interview will be entered in eCRF.

Secondary administrative data of HS patients (ie. relevant information regarding resource utilization and direct costs) will be gathered by the LHU of reference and competence of the site where the enrollment visit takes place.

During data entry in the eCRF, each patient will be assigned a study-specific alphanumeric code. The list of enrolled patients, codified with both the study-specific alphanumeric code and patients' unique ID code, will be sent from PI to the reference person designated by the LHU associated with the study site. This process will be conducted by ensuring the security of data transmission and receipt. Then, the Information Technology (IT) department of the LHU will use the unique ID codes to extract administrative data (claims data) associated to the HS patients enrolled in the study. Finally, LHU data will be coded (unique ID code eliminated; study-specific alphanumeric code added) and delivered to the Clinical Research Organization (CRO) through a secure connection system. The study-specific alphanumeric code will then allow to merge into a single database both data collected in the eCRF at enrollment visit and that collected from the administrative database.

7.2 Setting

This study is focused on studying an Italian population of patients suffering from HS, managed according to current clinical practice.

Data collection is scheduled to start in March 2022 and is therefore expected to end in February 2023.

The study will consecutively enroll approximately 100 patients at 6 Italian hospital dermatology clinics (study sites) during a consecutive period of 12 months, according inclusion and exclusion criteria listed at 7.2.1 and 7.2.2.

7.2.1 Inclusion criteria

Patients who meet all the following inclusion criteria can be included in the study at enrollment visit date:

1. Patients aged 18 years or more;
2. Patients diagnosed with HS at least 12 months before enrollment;
3. Patients who signed the informed consent and privacy form at enrollment visit.

7.2.2 Exclusion criteria

Patients meeting any of the following exclusion criteria cannot be included in the study at enrollment visit date:

1. Patients enrolled in clinical trials imposing procedures/interventions which are not part of the site's routine clinical practice (either at enrollment or in the 36 months before);
2. Patients will be excluded if the unique identifier does not allow them to be identified in the Local health Unit (LHU) administrative databases related to the site where they were enrolled (e.g., patients living in another region or in the same region but outside the area of competence of the LHU).

7.2.3 Study exit criteria

Not applicable (no prospective follow-up period foreseen by study design).

7.3 Variables

The following variables will be collected at enrollment visit:

- Patient socio-demographics (age, gender, ethnicity, smoking habits, municipality of residence, domicile (if different from municipality of residence), physical examination (height, weight, Body Mass Index (BMI)) and main clinical characteristics (such as comorbidities, HS history, HS severity, HS phenotypes, symptoms and HS status);
- Assessments of PRO tools (namely, DLQI questionnaire) (see paragraph 7.4);
- Resources for estimation of indirect costs and direct costs not covered by NHS, through a structured interview conducted by physicians (see paragraph 7.4).

Finally, HRU and direct healthcare costs will be retrieved (claims data) from the administrative databases of the participating LHUs (see paragraph 7.4).

Observational methodology will be used in order to capture data, therefore only data available from routine clinical practice will be collected.

7.4 Data sources

This study will involve primary and secondary data collection. The data sources will be:

1. Medical records available at the study site for each patient;
2. PRO and physician-patient structured interview collected at enrollment;

3. Data collected from the administrative databases of the participating LHUs where HRU will be retrieved (claims data).

Primary data (1, 2) will be collected during the enrollment visits which will take place as per normal clinical practice. Retrospective data (3) will be extracted after patient's signature of study informed consent and privacy form. Concomitant or prior medications entered into the database will be coded using the World Health Organisation (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The retrospective data for this study will be retrieved from the administrative databases provided by LHUs. The designated CRO, IQVIA, will perform the analysis according to the contract agreement. Drugs prescriptions comply with the WHO Anatomical Therapeutic and Chemical (ATC) classification system, while medical diagnoses comply with the ninth edition of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of types of assessments performed, and only these data will be collected as part of the study. The physician is asked to complete the appropriate eCRF forms for every patient.

Table 7.1 Data collection

Variables/information to be collected	Time point: Enrollment visit
Inclusion/Exclusion criteria	x
Informed consent and privacy form	x
Socio-demographics: age, gender, ethnicity, smoking habits, municipality of residence, domicile (if different from municipality of residence).	x
Physical examination: height, weight, Body Mass Index (BMI)	x
Comorbidities, including but not limited to: cardiovascular disease(s), metabolic disorder(s), psychiatric disorder(s), gastrointestinal disease(s), autoimmune comorbidity(ies), rheumatologic comorbidity(ies), other skin disorder(s). **Relevant medical history** (*)	x
Hidradenitis suppurativa (HS) history: date of first diagnosis, onset date of symptoms (if available), number of HS treatment lines prior to enrollment and prior surgery for HS (not needed or planned or already received)	x (*)
Current HS severity: Hurley staging system[1], HS Physician's Global Assessment (HS-PGA)[2] and/or HS Severity Index (HSSI)[3], HS phenotype.	x

Variables/information to be collected	Time point: Enrollment visit
Current HS subtypes (genital, axillary-mammary, follicular, gluteal); inflammatory lesions (number and localization of body areas); abscesses, fistulas, nodules, scarring, etc.	x
Current symptoms: Pain, Itching, General discomfort, Fatigue, Restricted/Painful movement of arms/legs, Inflammation/redness of lumps/abscesses, Infected lumps/abscesses, persistent discharge from lumps/abscesses, malodorous discharge, suicidal ideations, other (specify)	x
Current status: symptoms control (yes/no), flare (yes/no), remission status (yes/no)	x
Quality of Life (QoL) questionnaire (Dermatology Life Quality Index -**DLQI**)	x
Variables for the estimation of indirect costs and direct costs not covered by National Health Service (NHS): Working status; out-of-pocket resource consumptions not covered by NHS and related cost; psychological support due to illness not covered by NHS and related cost; weight management not covered by NHS and related cost; smoke cessation counselling not covered by NHS and related cost	x

(*) retrospective clinical data (outside administrative data collection). HRU data of the 36-month period prior to enrollment will be collected outside the eCRF (ie. from administrative database from LHUs).

[1]Hurley stages: Stage I "Mild"; Stage II "Moderate" and Stage III "Severe" (Napolitano, 2017).

[2]HS-PGA (HS Physician's Global Assessment) is a 6-point scale ranging from clear (score = 0) to very severe (score = 5) *(Napolitano, 2017)*.

[3]HSSI (HS Severity Index) score incorporates categorical objective parameters with categorical subjective parameters: body surface area involved, number of skin lesions, pain severity, and drainage. HSSI score can classify disease severity in classes *(Napolitano, 2017)*.

Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index questionnaire is currently the most frequently used method of evaluating quality of life for adult patients with different skin conditions. The aim of this questionnaire is to measure how much the patients' skin problem has affected their life over the previous week. It is self-explanatory and can be simply handed by the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

The DLQI consists of 10 items that cover 6 areas of the patient's life that may be affected by the disease, such as: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment.

The DLQI total score indicates the effect of the disease on patient's life: the higher the score, the more quality of life is impaired (Finlay, 1994) (Basra, 2008) (Hongbo, 2005). The questionnaire will be completed by patients at enrollment visit.

Administrative database (secondary data source)

The study data source will contain anonymized claims data from the administrative database of 5 LHUs. Claims data are collected by LHUs for accounting and healthcare reimbursement

purposes and are therefore an ideal source of data for resource use and direct cost analysis. Structure of the databases may vary between LHUs, yet they generally include all the following data flows:

- Hospitalizations (Hospital discharge forms – SDO)
- Outpatient visits (procedures and exams)
- Emergency Department (ED) access
- Flow of drugs from pharmacies in the area
- Flow of drugs from hospitals in the area (*Diretta* and *per conto)*
- Database of patients' demographics

Patients will be tracked across multiple hospitalizations through a unique anonymous patient identifier, which is conserved until the patient dies.

The following data for each administrative claims data flow are expected to be retrieved:

- Hospitalization (SDO)
  - Patient anonymized ID code
  - Discharge date
  - Type of hospitalization (ordinary, day hospital)
  - Diagnosis Related Group (DRG)
  - Department
  - ICD-9-CM primary code
  - ICD-9-CM secondary codes (from 1 to 5)
  - Cost
- Outpatient visits (procedures and exams):
  - Patient anonymized ID code
  - Date
  - Service
  - Branch
  - Exemption code (if any)
  - Cost
- ED accesses
  - Patient anonymized ID code

  - Date
  - ICD-9-CM primary code
  - ICD-9-CM secondary codes (from 1 to 5)
  - Type of treatment received
  - Type of exams completed
  - Type of pharmacological treatment received
  - Cost
- Flow of drugs from pharmacies in the area:
  - Patient anonymized ID code
  - Date
  - ATC code
  - Quantity
  - Name of the product
  - Exemption code (if any)
  - Cost
- Flow of drugs from hospitals in the area (*Diretta* and *per conto)*:
  - Patient anonymized ID code
  - Date
  - ATC code
  - Quantity
  - Name of the product
  - Exemption code (if any)
  - Cost
- Database of patients' demographics:
  - Patient anonymized ID code
  - Year of birth
  - Gender

Physician-patient structured interview (primary data source)

Enrolled patients will be interviewed by physicians at the enrollment visit in order to investigate the following topics:

- Working status:
    - if employed, annual salary (in class) and number of days lost due to HS during the year preceding the enrollment visit;
    - if retired, in case of early retirement due to HS, most recent annual salary (in class);
    - if unemployed, in case of job loss due to HS, most recent annual salary (in class).
- out-of-pocket resource consumptions not covered by NHS during the year preceding the enrollment visit and related cost;
- psychological support due to illness not covered by NHS during the year preceding the enrollment visit and related cost;
- weight management visit not covered by NHS during the year preceding the enrollment visit and related cost;
- smoke cessation counselling not covered by NHS during the year preceding the enrollment visit and related cost.

7.5 Study size

According to feasibility considerations, during 12 months of enrollment, it is reasonable to expect the inclusion of 100 HS patients in 6 sites. We expect that up to 5% of the enrolled patients could be not evaluable for the primary analysis (due to non-eligibility). Therefore, we expect that 95 patients will be available for the analysis of primary objective. In case the target sample size is not reached, this will not imply study failure, but it will lead to a lower precision of the estimates of the primary endpoints.

An evaluation of the possible achievable precision of the estimates for the main primary endpoints was performed considering the primary objective of the study and literature data, when available.

In the table below are shown the two-sided 95% confidence intervals (CIs) for expected frequency of selected categorical primary endpoints for a sample size n=95, using the large sample normal approximation (Dixon, 1983).

Table 7.2 Estimation for 95% Confidence Interval (CI) of expected estimates (simulations).

Endpoint	Expected estimate	Reference from literature	95% CI (for n=95)
Females (%)	61.5%	(Bettoli V. C., 2019)	51.7% ; 71.3%
Current/former smokers (%)	67.6%	(Bettoli V. C., 2019)	58.2% ; 77.0%
Hurley stage: II/III (%)	66.0%	(Bettoli V. C., 2019)	56.5% ; 75.5%
Affected locations: groin/genitals (%)	44.1%	(Bettoli V. C., 2019)	34.1% ; 54.1%

7.6 Data management

All data required to be recorded at enrollment visit will be collected and entered into an electronic case report form (eCRF). The PI at each site will be responsible for ensuring that the required data for each participant patient are collected and entered into the eCRF.

Subject questionnaires will be collected on paper and data will be entered in the database by the Investigator.

Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

The CRO “IQVIA”, working on behalf of Novartis, will review for completeness and accuracy the data entered into the eCRF by investigational staff and instruct the site personnel to make any required corrections or additions. IQVIA Clinica Data Manager working on behalf of Novartis will perform the cleaning session reviewing the warning messages raised by on-line checks and running post-entry checks by means of validation programs and data listings specific for the study using SAS software (SAS Institute, Cary, NC, USA). During this process, if clarifications are needed, the Clinical Data Manager will raise queries by means of data query forms through the web application. Designated investigator site staff is required to respond to the queries and make the corrections to the database according to the query response.

The PI will review the eCRF for completeness and accuracy. Furthermore, the PI will retain full responsibility for the accuracy and authenticity of all data entered into the eCRF.

If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorized by Novartis.

At the study conclusion, a complete copy of the study data will be created for archival purposes at Novartis facilities.

The validity of data will be granted by all quality control procedures.

The eCRF used for the study is validated according to Good automated manufacturing practice 5 (GAMP5). The IT infrastructure supporting the eCRF solution will be monitored and controlled both in terms of Security (i.e. Intrusion Detection, Antiviruses, etc.) and Operational Performance. Backups and operative controls will be properly managed in order to guarantee the business continuity.

Due to the observational nature of the study no independent review of the data will be performed.

Retrospective data used for the study are collected in the LHU data warehouse. This administrative data is collected for reimbursement purposes and its completeness is implicitly guaranteed by the LHUs. After study approval by the LHU and Ethics Committee, LHU staff will be requested to extract anonymized data.

7.7 Data analysis

All analyses will be performed by IQVIA, using SAS software (SAS Institute, Cary, NC, USA). The study has a descriptive aim, and no a priori hypotheses are defined. All analyses will be mainly descriptive with no planned comparison of patient groups.

Continuous numerical variables will be summarized using mean, standard deviation (SD), median, first and third quartile, minimum, and maximum; categorical variables will be summarized using frequency counts and percentages. Missing data will not be replaced and will be considered a separate category in all analyses and will be described using frequency counts and percentages.

The statistical analyses will be performed considering the set of eligible patients, defined as those subjects meeting all inclusion criteria and not meeting any of the exclusion criteria. For

patients excluded from the statistical analyses, descriptive analysis of the reasons for non-eligibility will be provided.

The detailed analysis plan will be provided in the Statistical Analysis Plan.

Interim analyses are currently not planned. However, depending on the Sponsor's needs, interim analyses might be performed before the conclusion of data collection, in order to perform preliminary evaluations on already collected data (considering both clinical data collected in the eCRF and claims data from the administrative database of LHUs).

7.7.1 Primary objective

The analyses that will be performed for the evaluation of demographic and clinical characteristics at enrollment visit are the following:

- descriptive statistics (mean, standard deviation, median, first and third quartile, minimum and maximum, 95% confidence interval) of age at enrollment, time from symptoms' onset to first confirmed HS diagnosis, and disease duration;
- patients' distribution (count and percentage) by gender, ethnicity, BMI classes, smoking habits;
- patients' distribution (count and percentage, and corresponding 95% confidence interval) by presence/absence of comorbidities at enrollment and relevant medical history;
- patients' distribution (count and percentage) by number of HS treatment lines prior to enrollment and by surgery (already received, planned, not planned);
- patients' distribution (count and percentage) by HS severity defined by Hurley staging system, HS-PGA and/or HSSI classes (to be defined according to (Napolitano, 2017));
- patients' distribution (count and percentage) by phenotypes of HS, presence/absence of lesions in various localizations and presence/absence of symptoms;
- patients' distribution (count and percentage, and corresponding 95% confidence interval) by achievement of symptoms control and by presence/absence of flare and remission.

Patients' distribution by presence/absence of comorbidities will be provided also considering only comorbidities retrieved from administrative database. For this analysis, presence of comorbidities will be defined using ICD9-CM codes and/or exemption codes recorded in the database

7.7.2 Secondary objectives

The analyses that will be performed for the evaluation of the secondary outcomes involve the computation of the following analysis:

1. In order to describe quality of life at enrollment, descriptive statistics (mean, standard deviation, median, first and third quartile, minimum and maximum) of the DLQI score will be calculated, along with patients' distribution (count and percentage) by DLQI classes (to be defined according to the author's scoring instructions).
2. Analysis on HRU in the 36-month period before enrollment will be performed by the description of the following variables (patient distribution with count and percentage):
    a. drugs consumption related to HS (number and types);
    b. ED accesses (number);
    c. hospitalizations due to HS (number and types);
    d. outpatient specialistic visits (number and types);
    e. laboratory tests, instrumental and other diagnostic tests related to HS (number and types).

    This analysis will be also repeated as sensitivity analysis considering the 12-month period before the enrollment, in order to describe HRU of patients who already have been diagnosed with HS.
3. Descriptive statistics (mean, standard deviation, median, first and third quartile, minimum and maximum) of the direct costs covered by NHS per patient in the 36-month period before enrollment will be calculated, as well as patients' distribution (count and percentages) by direct cost classes. Direct costs will be retrieved from administrative

database and will include costs related to: drug consumptions, ED accesses, hospitalizations, outpatients specialistic visits, laboratory tests, instrumental and other diagnostic tests for HS. This analysis will also be repeated as sensitivity analysis considering the 12-month period before the enrollment, in order to describe healthcare resource utilization of patients who already have been diagnosed with HS.

4. Descriptive statistics (mean, standard deviation, median, first and third quartile, minimum and maximum) of the indirect cost per patient in the 12-month period before enrollment will be calculated, as well as patients' distribution (count and percentage) by indirect cost classes. Costs will be calculated based on the data collected during the structured interview performed by the physicians during the enrollment visit and will include the productivity loss due to HS: number of days lost for employed patients, early retirement due to HS for retired patients and job loss due to HS for unemployed patients.
5. Descriptive statistics (mean, standard deviation, median, first and third quartile, minimum and maximum) of the direct cost not covered by NHS per patient in the 12-month period before enrollment, will be calculated, as well as patients' distribution (count and percentage) by cost classes. Costs will be calculated based on the data collected during the structured interview performed during the enrollment visit and will include: out-of-pocket resource consumptions, psychological support due to the illness, weight management visit and smoke cessation counselling not covered by NHS.

7.7.3 Subgroups analyses

Depending on patients' distribution by HS severity and HS duration at enrollment, the primary and secondary analyses might also be repeated in specific and more homogeneous subgroups of HS severity and HS duration at enrollment (specific cut-off to be defined depending on data distribution), if relevant. These subgroup analyses will have a descriptive, exploratory purpose.

7.8 Quality control

7.8.1 Data quality management

The designated CRO "IQVIA" working on behalf of Novartis will assure database quality processes are followed including review of the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

7.8.2 Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file.
The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis (or designee) agree to keep the identity of participating patients confidential. No information reported in source documents about the identity of the patients will be disclosed.

The PI must assure that the patient's pseudonymity will be maintained according to Data Protection Regulation in force. The PI will keep a separate list with at least the initials, the patient's study numbers, names and telephone numbers. The PI will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Novartis.

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Only the patient number will be recorded on the eCRF. Study data of the patient enrolled in the study will be stored in accordance with local data protection laws at the site.

The PIs will maintain a list to enable patients' records to be identified. However, if the results of the study are published, the patient's identity will remain confidential.

Personal data - including sensitive data - collected during the execution of the activities will be processed in accordance with the local laws on data protection.

The PI must maintain adequate and accurate records to enable the conduct of this study and the study data to be subsequently verified. These documents should be classified into two different separate categories: Investigator's Study File and patient clinical source documents.

The Investigator's Study File will contain the observational protocol study/amendments, Independent ethics committees/ Institutional review board (IEC/IRB) and governmental approval with correspondence, sample informed and privacy form consent, patient enrollment log, signed informed consent forms, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

Patient clinical source documents would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, pathology and special assessment reports, consultant letters.

The PI must keep these two categories of documents on file according to local regulations after completion or discontinuation of the study. After that period, the documents may be destroyed accordingly to local regulations.

Should the PI wish to assign the study records to another party or move them to another location, Novartis must be notified in advance.

7.8.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

Monitoring activity will include reviews of the progress of the study and compliance with protocol, Standard Operating Procedures (SOPs), applicable regulation, Good Pharmacoepidemiology Practices (GPP), ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) Guide on Methodological Standards in Pharmacoepidemiology.

On site study monitoring will be performed by designated CRO “IQVIA” working on behalf of Novartis.

It is understood that the Clinical Monitor(s) will visit the PI/site regularly throughout the study, and that they will be permitted to inspect the various study records: eCRFs, filled

questionnaires, PI study file and all available source data, provided that patient confidentiality is respected.

The purposes of these visits are:

- to assess the progress of the study;
- to review signed informed consent forms;
- to evaluate the compliance with the inclusion/exclusion criteria and with the study protocol;
- to discuss any emerging issue;
- to check the eCRFs for accuracy and completeness.
- to support the investigators in queries resolution

In addition, during on-site visits, for a set of variables prior defined by Novartis, the monitor will validate the contents of the eCRFs against the source documents (where they are available as for clinical practice), as specified in section 7.8.2.

Prior to on site monitoring visit, the PI or staff will record all data collected on the eCRFs. The PI and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

The designated CRO “IQVIA” will assure compliance monitoring.

7.9 Limitations of the research methods

Although there are multiple strengths in the design of an enriched study, there are also some limitations to consider.

This study will be conducted in 6 Italian sites, which will not be randomly sampled from the whole Italian territory. Selection bias is present since only patients referring to the selected study sites who meet the inclusion/exclusion criteria will be considered. However, in order to best capture the variability in the current real-world patterns of care, every effort will be made to select sites across a variety of geographic regions.

Moreover, the study will be also based on data from the corresponding five LHUs, and only patients for which the linkage with administrative database is feasible will be enrolled.

Furthermore, extracting from administrative data 36 months of data and considering patients diagnoses at least 12 months before enrollment might imply the risk of analazying an heterogeneous cohort of patients for the retrospective analysis. However, this will reflect the current, actual heterogeneity of HS patient's characteristics. Moreover, to take into consideration this variability, further analyses could be implemented in order to evaluate relevant study endpoints in more homogeneous patient's subgroups (to be defined depending on data distribution in terms of HS severity and duration at enrollment).

As in all studies using secondary data, the risk of information bias derived from incomplete/missing data shall be considered. Moreover, the use of PROs and physician-patient structured interview with a recall period introduces the risk of imprecise/incomplete information due to recall bias. Additionally, administrative data are not standardized across participating sites and some data from clinical practice (e.g. use of medical procedures) may be incomplete or differently adjudicated/reported. Lag-time in the availability of administrative data may vary from LHUs depending on the different data flows. Lastly, no clinical assessments are tracked in the administrative database. Anyway, the analysis on administrative database will be supported and integrated by the clinical assessment provided by the primary data collection.

7.10 Other aspects

Not applicable.

8 Protection of human subjects

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki (World Medical Association, 2013) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of

Observational Studies in Epidemiology) guidelines (Vandenbroucke JP, 2007) and with the ethical principles laid down in the Declaration of Helsinki (World Medical Association, 2013) .

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' *(European Medicines Agency, 2016).*

The PI will perform the study in accordance with the regulations and guidelines governing medical practice and ethics in Italy and in accordance with currently acceptable techniques and know-how.

The final protocol of the study, including the final version of the informed consent form, must be approved or given a favorable opinion in writing by the Ethics Committee.

Patients enrollment will not start before the approval of the Ethics Committee. This study does not include treatments or diagnostic examinations other than those prescribed in the ordinary clinical practice, therefore no insurance agreements are applicable.

The Ethics Committee must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

Informed consent procedures

It is the responsibility of the physicians to obtain written informed and privacy consent from each patient prior to the collection of any data from the patient's records in compliance with European Regulation 679/2016 and local regulation (D.M. 15.7.1997, D.Lgs. 196/2003, D.Lgs. 211/2003, D.Lgs. 200/2007).

The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Each patient's signed informed and privacy consent must be kept on the study's file by the PI.

Novartis will provide physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with regulatory requirements and is considered appropriate for this study.

9 Management and reporting of adverse events/adverse reactions

No solicited safety data capture is required for prospective studies using primary data collection without a Novartis drug of interest.

However, if during the course of the study an adverse reaction (i.e. an adverse event suspected to be associated with the use of a drug) is reported for a patient receiving a Novartis product, the PI will be requested to report this to Novartis as a spontaneous report and to the local Health Authority.

The PI will also be requested to report adverse reactions identified for non-Novartis products to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or poster. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines (International Committee of Medical Journal Editors, 2019).

11 References

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

None.

12.2 Annex 2 – ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Patient profile, treatment patterns, and cost of care among patients with hidradenitis suppurativa (HS): an Italian hybrid observational study of real-world clinical practice

EU PAS Register® number: N/A
Study reference number CAIN457MIT01

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

No progress/interim reports were planned in the design of this study, therefore are N/A

Similarly, no Registration in the EU PAS Register is required for the aim of the study

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5.2
2.1.2 The objective(s) of the study?	☒	☐	☐	5.2/6.1 6.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	5.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

No study hypotheses were described in the protocol as the nature of the study will be descriptive

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.1

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☒	☐	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

Given the design of the study, no population data will be obtained and therefore no measures of occurrence will be calculated This study will be descriptive, therefore no measure of associations will be calculated

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	7.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	7.2
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	7.2
	4.2.4 Disease/indication	☒	☐	☐	7.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	7.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Not applicable. All patients are exposed to HS.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	6.1;6.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	7.5
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	7.7.2

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9

Comments:

As the study nature is descriptive and no hypothesis will be tested, no methods for

confounding calculation was planned.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

As the study nature is descriptive and no hypothesis will be tested, no methods for confounding calculation was planned.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	7.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	7.1/7.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☒	☐	☐	7.7.1-2-3
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	7.7.2

Comments:

As the study nature is descriptive and no hypothesis will be tested, no methods for confounding calculation was planned.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	7.6
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Due to the observational nature of the study no independent review of the data will be performed

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				7.9
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7.2 / 7.5

Comments:

As the study nature is descriptive and no hypothesis will be tested, no methods for confounding calculation was planned.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	8
13.3 Have data protection requirements been described?	☒	☐	☐	8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: Ilaria Peduto

Date: 23/July /2021

Signature: DocuSigned by: Ilaria Peduto 7F4DD06BD8B742B...

12.3 Annex 3 – Additional information

None.

PROFILI CONTABILI

☐ RILEVANTE, a valere su: ☒ NON rilevante

ONERI DI PUBBLICAZIONE OBBLIGATORIA EX D. LGS. 33/2013:

☐ SOGGETTA a pubblicazione ☒ NON soggetta a pubblicazione

ONERI DI RISERVATEZZA:

☐ CONTIENE dati personali da NON pubblicare ☒ NON contiene dati personali

DESTINATARI NOTIFICA/TRASMISSIONE

PROPOSTA N.RO 20230002420 APPROVATA CON DELIBERAZIONE N.RO 20230001984 DEL 06/10/2023

Con la sottoscrizione in calce al presente provvedimento, i firmatari di cui sopra, ciascuno in relazione al proprio ruolo come indicato e per quanto di rispettiva competenza, attestano che il procedimento istruttorio è stato espletato nel rispetto della normativa regionale e nazionale applicabile e che il provvedimento predisposto è conforme alle risultanze istruttorie agli atti d'ufficio.

I medesimi soggetti dichiarano, inoltre, di non versare in alcuna situazione di conflitto di interesse, anche potenziale, ex art. 6-bis, l. 241/90, artt. 6, 7 e 13, c. 3, D.P.R. 62/2013, vigente codice di comportamento aziendale e art. 1, c. 9, lett. e), l. 190/2012 – quest'ultimo come recepito, a livello aziendale, della vigente sezione Anticorruzione e Trasparenza del PIAO – tale da pregiudicare l'esercizio imparziale di funzioni e compiti attribuiti, in relazione al procedimento indicato in oggetto, così come di non trovarsi in alcuna delle condizioni di incompatibilità di cui all'art. 35-bis, D.L.gs. 165/2001.

RUOLO	NOME E COGNOME	FIRMA
Responsabile del Procedimento ai sensi della L. 241/1990	Lepore Marilena	*Firmato digitalmente il 04/10/2023 12:01*
Dirigente PTA	Mangini Francesco Maurizio	*Firmato digitalmente il 04/10/2023 12:04*
Responsabile UOS/UOSD	Fortunato Elisabetta	*Firmato digitalmente il 04/10/2023 12:06*
Direttore/Responsabile di Struttura	Fruscio Luigi	*Firmato digitalmente il 04/10/2023 15:33*